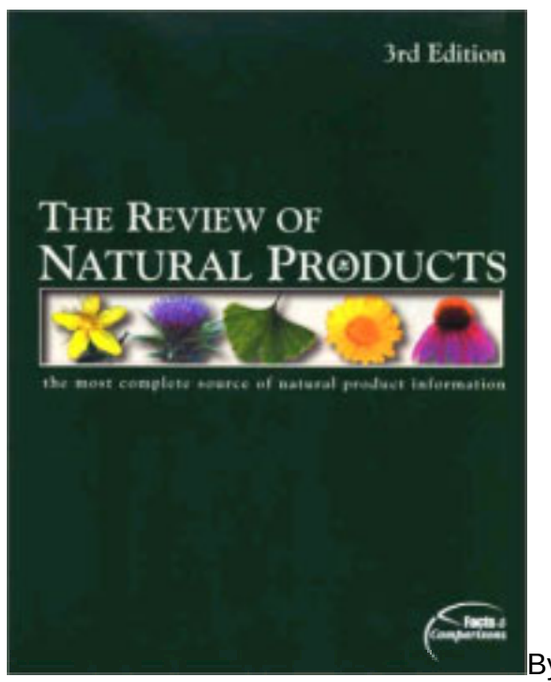
The Review of Natural Products 2004 By Ara DerMarderosian, John A. Beutler By Facts and Comparisons



By OkDoKeY

- CHAPARRAL
- CHARCOAL
- CHASTE TREE
- CHICKEN SOUP
- CHICKWEED
- CHICORY
- CHINESE CUCUMBER
- CHITOSAN
- CHONDROITIN
- CHROMIUM
- CIGUATERA
- CINNAMON
- CITRONELLA OIL
- CLEMATIS
- CLOVE
- COCOA
- COLTSFOOT
- COMFREY
- CORAL
- CORDYCEPS
- CORKWOOD TREE
- CORN COCKLE
- CRAMP BARK
- CRANBERRY
- CREATINE
- CUCURBITA
- CUMIN
- "D" MONOGRAPHS
  - DAMIANA
  - DANDELION
  - DANSHEN
  - DEER VELVET
  - DEVIL'S CLAW
  - DEVIL'S CLUB
  - DEVIL'S DUNG
  - DIACYLGLYCEROL OIL
  - DICHROA ROOT
  - DIGITALIS
  - DOLOMITE
  - DONG QUAI
  - DRAGON'S BLOOD
- "E" MONOGRAPHS
  - ECHINACEA
  - ELDERBERRY
  - ELEUTHEROCOCCUS
  - EMBLICA
  - EMU OIL
  - EVENING PRIMROSE OIL (EPO) (OEP)
  - EYEBRIGHT
- "F" MONOGRAPHS
  - FALSE UNICORN
  - FENNEL
  - FENUGREEK
  - FEVERFEW
  - FISH OILS
  - FLAX
  - FO-TI
  - FORSKOLIN
  - FORSYTHIA
  - FRUIT ACIDS
  - FUMITORY
- "G" MONOGRAPHS
  - GAMMA LINOLENIC ACID
  - GAMMA ORYZANOL
  - GARLIC
  - GELSEMIUM
  - GENTIAN
  - GINGER
  - GINKGO
  - GINSENG, PANAX
  - GLUCOMANNAN
  - GLUCOSAMINE
  - GOAT'S RUE
  - GOLDENSEAL
  - GOSSYPOL
  - GOTU KOLA
  - GRAPE JUICE, PURPLE
  - GRAPE SEED
  - GRAPEFRUIT
  - GREEN TEA
  - GUAR GUM
  - GUARANA
  - GUAYULE
  - GUGGUL
  - GYMNEMA
- "H" MONOGRAPHS
  - HAWTHORN
  - HIBISCUS
  - HOLLY
  - HONEY
  - HOPS
  - HOREHOUND
  - HORNY GOAT WEED

- HORSE CHESTNUT
- HORSERADISH
- HORSETAIL
- HUPERZINE A
- HYSSOP
- "I" MONOGRAPHS
  - IBOGA
  - INDIAN FRANKINCENSE TREE
  - INDIGO
  - IPECAC
- "J" MONOGRAPHS
  - JEWELWEED
  - JIAOGULAN
  - JOJOBA
  - JUNIPER
- "K" MONOGRAPHS
  - KAOLIN
  - KARAYA GUM
  - KAVA
  - KH-3
  - KHAT
  - KINETIN
  - KIWI FRUIT
  - KOMBUCHA
  - KUDZU
- "L" MONOGRAPHS
  - L-ARGININE
  - L-THEANINE
  - LABRADOR TEA
  - LAMINARIA
  - LARCH
  - LATHYRUS
  - LAVENDER
  - LECITHIN
  - LEECHES
  - LEMON
  - LEMON BALM
  - LEMON VERBENA
  - LEMONGRASS
  - LENTINAN
  - LETTUCE OPIUM
  - LEVANT BERRY
  - LICORICE
  - LIFE ROOT
  - LINDEN
  - LOBELIA
  - LORENZO'S OIL
  - LOVAGE
  - LYCOPENE
  - LYSINE
- "M" MONOGRAPHS
  - MA HUANG
  - MACA
  - MACE
  - MAGGOTS
  - MAITAKE
  - MANUKA OIL
  - MARIJUANA
  - MASTIC
  - MATE
  - MEADOWSWEET
  - MELATONIN
  - METHYLSULFONYLMETHANE (MSM)
  - MILK THISTLE
  - MISTLETOE
  - MONASCUS
  - MORINDA
  - MUIRA PUAMA
  - MULLEIN
  - MUSK
  - MUSTARD
  - MYRRH
- "N" MONOGRAPHS
  - NEEM
  - NETTLES
  - NEW ZEALAND GREEN-LIPPED MUSSEL
  - NIGELLA SATIVA
  - NUTMEG
- "O" MONOGRAPHS
  - OATS
  - OCTACOSANOL
  - OLEANDER
  - OLIVE LEAF
  - OLIVE OIL
  - ONION
  - OREGANO
  - OSTRICH FERN
- "P" MONOGRAPHS
  - PAPAYA
  - PARSLEY
  - PASSION FLOWER
  - PAWPAW
  - PECTIN

- PENNYROYAL
- PEPPERMINT
- PERILLA
- PERIWINKLE
- PERU BALSAM
- PINEAPPLE
- PLANTAIN
- PODOPHYLLUM
- POINSETTIA
- POISON IVY
- POKEWEED
- POLICOSANOL
- POPPY
- PORIA
- POTATO
- PRECATORY BEAN
- PRICKLY PEAR
- PROPOLIS
- PULSATILLA
- PURSLANE
- PYCNOGENOL
- PYGEUM

"Q" MONOGRAPHS
- QUASSIA
- QUILLAIA
- QUININE

"R" MONOGRAPHS
- RASPBERRY
- RED BUSH TEA
- RED CLOVER
- REISHI MUSHROOM
- RHODIOLA
- RHUBARB
- ROSE HIPS
- ROSEMARY
- ROYAL JELLY
- RUE

"S" MONOGRAPHS
- SAFFLOWER
- SAFFRON
- SAGE
- SAME
- SANDALWOOD
- SARSAPARILLA
- SASSAFRAS
- SAVORY
- SAW PALMETTO
- SCHISANDRA
- SCULLCAP
- SEAWEED
- SENEGA ROOT
- SENNA
- SHA REN
- SHARK DERIVATIVES
- SHARK LIVER OIL
- SHELLAC
- SLIPPERY ELM
- SMOKELESS TOBACCO
- SNAKEROOT
- SOAPWORT
- SOD
- SOUR CHERRY
- SOY
- SPINACH
- SPIRULINA
- SQUILL
- ST. JOHN'S WORT
- STEVIA
- STILLINGIA
- STORAX
- SWEET VERNAL GRASS

"T" MONOGRAPHS
- TAHEEBO
- TANNING TABLETS
- TANSY
- TEA TREE OIL
- TERMINALIA
- THUNDER GOD VINE
- TINOSPORA CORDIFOLIA
- TOLU BALSAM
- TONKA BEAN
- TRAGACANTH
- TRILLIUM
- TUNG SEED
- TURKEY TAIL
- TURMERIC
- TURPENTINE

"U" MONOGRAPHS
- UBIQUINONE
- UVA URSI

"V" MONOGRAPHS
- VALERIAN
- VANILLA

THE REVIEW OF NATURAL PRODUCTS (2004)

FRONT MATTER

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St. Louis, MO 63146-3098
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ISSN 1089-5302
Printed in the United States of America

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PREFACE

The ongoing publication, *The Review of Natural Products* Monograph System, is the culmination of years of work by professionals interested in providing a continuous update on all natural products and nutraceuticals being used by the public for various health purposes.

Formerly known as *The Lawrence Review of Natural Products*, *The Review of Natural Products* was one of the first and is still the only reference of its kind in medical literature. The editor, consulting editor, and advisory panel, have extensive experience in the field of natural product pharmacy and medicine. *The Review of Natural Products* includes more than 300 monographs published in a single volume loose-leaf format to facilitate monthly updates. Each monograph features scientific names, common names, botany or description of source, history, chemistry, pharmacology, toxicology, patient information, summary and references. The format provides pharmacists, physicians, nurses, and other health professionals with a quick, up-to-date, objective assessment of the latest legitimate medical and scientific studies on numerous natural products, including medically active foods (nutraceuticals). Attempts are made throughout the reference to remain scientifically objective and place weight on legitimate chemical, pharmacological, and clinical studies in reputable journals or Websites.

Other features include a list of natural product Websites, a list of herbal diuretics, a mushroom poisoning decision chart, a list of mushroom societies, national poison control centers, potential herb-drug interactions tables, and scientific and trade organizations related to natural products. There is a primary index (common and scientific names) as well as a comprehensive and useful therapeutic uses index.

Caution is advised in using combination herbal products and single botanical products. *The Review of Natural Products* is intended to provide the reader with scientific data on both the benefits and the risks of various products.

In summer 2004, *The Review of Natural Products* will be reissued. Each monograph will be reorganized into a new easy-to-scan format and will include a new quick-reference clinical overview box that includes uses, dosing pregnancy/lactation, drug-herb interaction, adverse reaction, and toxicology information.

It is hoped that this up-to-date and complete reference will continue to be useful for all whom it is intended. We encourage suggestions and comments to help us improve *The Review of Natural Products* for future editions.

Ara DerMarderosian, PhD
Editior.

Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    FRONT MATTER

"A" MONOGRAPHS

ACACIA GUM

DATE OF ISSUE: MAR 1994

REPLACES MONOGRAPH DATED: OCT 1992

SCIENTIFIC NAME(S): *Acacia senegal* (L.) Willd. (syn. with *A. verek* Guill et Perr.). Other species of Acacia have been used in commerce. Family: Leguminosae or Fabaceae

COMMON NAME(S): Acacia gum, acacia vera,[1] Egyptian thorn,[1] gummi africanum,[2] gum Senegal, gummae mimosae, kher, Sudan gum arabic, Somali gum, yellow thorn

BOTANY: The acacia tree (*A. senegal*) is a thorny, scraggly tree that grows to heights of about 15 feet. It grows most prolifically in regions of Africa, in particular in the Republic of Sudan. During times of drought, the bark of the tree splits, exuding a sap that dries in small droplets or "tears." [3] In the past, these hardened sap tears served as the major source of acacia gum, but today commercial acacia gum is derived by tapping trees periodically and collecting the resin semi-mechanically. At least three grades of acacia gum are available commercially and their quality is distinguished by the color and character in the collected tears. [4] There is considerable variation in gum quality depending on whether it is obtained by natural flow secondary to extreme drought, obtained by tapping or induced by the boring of beetles at sites of branch injury.[5] Gums derived from *Combretum* are readily available at low prices in East and West Africa and are often offered for sale as "gum arabic." Because there is no toxicologic data supporting the safety of these gums, they are not recognized as food additives by most countries. [14] Similarly, trees of the genus *Albizia* are often confused with *Acacia* and should not be used as acacia substitutes. [15]

HISTORY: Acacia gum has long been used in traditional medicine and in everyday applications. The Egyptians used the material as a glue and as a pain-reliever base. Arabic physicians treated a wide variety of ailments with the gum, resulting in its current name. [3] Today, it is used widely in the pharmaceutical industry as a demulcent and in the cooking industry to give body and texture to processed food products. It also is used to stabilize emulsions. The fibers of the bark are used to make cordage.[6]

CHEMISTRY: Acacia gum is a brittle, odorless and generally tasteless material that contains a number of neutral sugars, acids, calcium and other electrolytes. [7] The main component of the gum is arabin, the calcium salt of arabic acid. [4] The structure of the gum is complex and has not yet been fully explained. A comprehensive analysis, including NMR spectra for 35 samples of gum arabic, has been published to serve as the basis for international standardization of acacia gum. [11] The gum is built upon a backbone of D-galactose units with side chains of D-glucuronic acid with L-rhamnose or L-arabinose terminal units. The molecular weight of the gum is large and estimates suggest the weight lies in the range of 200,000 to 600,000 daltons. [7] It is very soluble in water, but does not dissolve in alcohol.

PHARMACOLOGY: Acacia gum has no significant systemic effects when ingested. Although related gums have been shown to be hypocholesterolemic when ingested, there is no evidence for this effect with acacia. When administered to hypercholesterolemic patients for periods ranging from 4 to 12 weeks, acacia gum had no effect on the level of any plasma lipid evaluated. [9,12] Some studies suggest that ingestion of acacia gum may increase serum cholesterol levels in rats. [7] In the past, the gum has been administered intravenously to counteract low blood pressure following surgery and to treat edema associated with nephrosis, but this administration caused renal and liver damage and allergic reactions, and its use was abandoned. [5]

Acacia gum is a demulcent, and soothes irritated mucous membranes. Consequently, it is used widely in topical preparations to promote wound healing and as a component of cough and some gastrointestinal preparations. Whole gum mixtures of acacia have been shown to inhibit the growth of periodontic bacteria, including *Porphyromonas gingivalis* and *Prevotella intermedia* in vitro when added to culture medium in concentrations ranging from 0.5% to 1.0%. [8] At a concentration of 0.5%, acacia whole gum mixture also inhibited bacterial protease enzymes, suggesting acacia may be useful in limiting the development of periodontal disease. In addition, chewing an acacia-based gum for 7 days has been shown to reduce mean gingival and plaque scores compared to a sugar-free gum; the total differences in these scores was significant ($P < 0.05$) between groups suggesting that acacia gum primarily inhibits the early deposition of plaque. [13]

TOXICOLOGY: Acacia is essentially nontoxic when ingested. Allergic reactions to the gum and powdered forms of acacia have been reported and include respiratory problems and skin lesions.[7]

Acacia contains a peroxidase enzyme, which is typically destroyed by brief exposure to heat. If not inactivated, this enzyme forms colored complexes with certain amines and phenols and enhances the destruction of many pharmaceutical products including alkaloids and readily oxidizable compounds such as some vitamins. [5,7] Acacia gum reduces the antibacterial effectiveness of the preservative methyl-p-hydroxybenzoate against *Pseudomonas aeruginosa*, presumably by offering physical barrier protection to the microbial cells from the action of the preservative. [10] A trypsin inhibitor also has been identified, but the clinical significance of the presence of this enzyme is not known.[6]

SUMMARY: Gum acacia has been used in commerce for millennia. Because of its soothing properties, it is included in cough and cold remedies and it is used topically in wound healing preparations. It is used as a stabilizer for foods. Although generally considered safe for internal use, some persons have developed severe allergic reactions following exposure to the gum.

PATIENT INFORMATION— Acacia Gum

Uses: Acacia gum has been used in food as a stabilizer and in pharmaceuticals as a demulcent. It is used topically for healing wounds and has been shown to inhibit the growth of periodontic bacteria and the early deposition of plaque.

Side Effects: Ingestion may raise serum cholesterol. Intravenous administration causes renal and liver damage. Various forms of acacia gum can cause allergic reactions, including respiratory problems and skin lesions.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ACACIA GUM

ACEROLA

DATE OF ISSUE: MAY 2001

REPLACES MONOGRAPH DATED: JAN 1993

SCIENTIFIC NAME(S): *Malpighia glabra* L. and *M. emarginata* (previously *M. punicifolia* L.) Family: Malpighiaceae

COMMON NAME(S): Acerola, Barbados cherry, West Indian cherry, Puerto Rican cherry, Antilles cherry, cereso, cereza, cerisier, semeruco

BOTANY: Acerola is native to the West Indies, but is also found in northern South America, Central America, Texas, and Florida. It grows as small shrubs or trees from 5 to 15 m in height. The branches are brittle and the leaves are glossy and dark to light green. The 5-petaled flowers range from pink to white in color. Acerola fruit is cherry-like, 3-lobed, bright red, and 1 to 2 cm in diameter, containing several small seeds. Mature fruits are soft, pleasant-tasting, and contain 80% juice. The fruits deteriorate rapidly once removed from the tree.[1,2,3]

HISTORY: Acerola is believed to originate from the Yucatan.[3] Traditionally, the fruits have been used to treat dysentery, diarrhea, and liver disorders. Both species of *Malpighia*have been reported to be excellent sources of vitamin C. However, the fruit of *M. emarginata* is known more accurately as acerola and is one of the richest sources of vitamin C known.[1]

CHEMISTRY: Acerola contains from 1% to 4.5% vitamin C (1000 to 4500 mg/100 g) as ascorbic and dehydroascorbic acids in the edible portion of the fruit. This far exceeds the content of vitamin C in peeled oranges (about 0.05% or 50 mg/100 g).[1] The content of vitamin C in acerola varies with ripeness (highest in green and lowest in fully ripened fruit), season, and climate. *M. emarginata* fruit (native to the West Indies) is the richest known source of vitamin C.[1]

Vitamin C analysis regarding acerola storage after picking finds freezing (-18°C) the fruits to be the best way to preserve vitamin C percentage, as compared with room temperature or refrigeration.[4] Older reports evaluating ascorbic acid content in acerola are available.[5,6]

In addition, acerola contains vitamin A (4300 to 12,500 IU/100 g), at about the same level as in carrots. Other constituents include thiamine, riboflavin, niacin, calcium, iron, bioflavonoids, phosphorus, malic acid, pantothenic acid, potassium, magnesium, and sugars dextrose, fructose, and sucrose.[1,2,7] Acerola analysis in another report finds protein, fiber, lipids, fatty acids, zinc, and other minerals present as well.[8]

PHARMACOLOGY: Acerola is used as a source of food and juice. Because of its high concentration of vitamin C, it also is sold as a natural health supplement.[7]

Vitamin C is an essential coenzyme that is required for normal metabolic function. While many animals can synthesize vitamin C from glucose, humans must obtain the vitamin totally from dietary sources. Deficiencies of this water-soluble vitamin result in scurvy, a potentially fatal disease with multisystem involvement. Dietary supplements have traditionally provided adequate protection against the development of this disease.

However, controversy has focused on whether vitamin C derived from "natural" sources is more physiologic than that produced synthetically or semisynthetically (as ascorbic acid). To date, there is no clear evidence that naturally derived vitamin C is superior in its clinical effectiveness than synthetic ascorbic acid. A potential advantage to using acerola as a source of vitamin C is that one receives not only ascorbic acid, but also several other useful vitamins and minerals from the fruit. Whether this is superior to the use of a multiple vitamin preparation has not been determined.

Vitamin C is known to strengthen the immune system, build collagen cells, support the respiratory system, and to be an effective antioxidant.[7] The antioxidative qualities of acerola make it an ideal ingredient in skin care products to fight cellular aging.[2] In another report, acerola extract was shown to enhance the antioxidant activity of soy and alfalfa extracts, acting synergistically, which may be beneficial in coronary artery disease.[9]

Acerola possesses antifungal properties. In one report, *M. glabra* was among the most active antifungal in 26 plants studied. The most susceptible fungi were *E. floccosum*and *T. rubrum*.[10]

Ethnobotanical uses of acerola include use as an astringent and for diarrhea, dysentery, hepatitis, and fever.[2]

TOXICOLOGY: No specific adverse effects have been associated with the ingestion of acerola. Because vitamin C is a water-soluble compound, it is readily excreted by the body, and it is not typically associated with toxicity. However, the ingestion of large doses may induce GI side effects, including diarrhea. Prolonged use of massive doses of ascorbic acid may predispose to the development of renal calculi.[1,7]

SUMMARY: Acerola, or Barbados cherry, is one of the richest sources of vitamin C known. It is high in vitamin A, and contains other important nutrients as well. It is used as a food and in supplementation for its vitamin C content. Vitamin C is an important antioxidant, which also supports the immune system. Acerola also has been found to possess antifungal properties. No specific adverse effects have been associated with acerola.

PATIENT INFORMATION — Acerola

Uses: Acerola provides natural vitamin C and other useful vitamins and minerals. It is used as an astringent and for diarrhea, dysentery, hepatitis, and fever, although clinical trials are lacking.

Side Effects: Large doses may produce GI distress. Prolonged, massive dosage may predispose to formation of renal calculi.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ACEROLA

ACIDOPHILUS

DATE OF ISSUE: SEP 2001

REPLACES MONOGRAPH DATED: NOV 1991

SCIENTIFIC NAME(S): *Lactobacillus acidophilus*

HISTORY: For several decades, health and nutritional benefits have been claimed for products containing *Lactobacillus* cultures. The topical or intravaginal application of yogurt products has been reported to control yeast and bacterial infections, and the ingestion of these preparations has been recommended to reduce the symptoms of antibiotic-induced diarrhea or sore mouth caused by *Candida* infections.[1] Other reports have indicated that the ingestion of acidophilus-containing products can reduce serum cholesterol levels, improve lactose intolerance, and slow the growth of experimental tumors. [2] *L. acidophilus* has been referred to as a probiotic, defined as microorganisms that have a beneficial effect on the host by improving the properties of the indigenous microflora. [3]

PHARMACOLOGY

Replenishment of normal bacterial flora: Products containing live cultures have been investigated for their ability to compete with pathogens in the microenvironment, thereby permitting the reestablishment of normal bacterial flora. Lactobacilli have been shown to inhibit the growth of other vaginal microorganisms including *Escherichia coli*, *Candida albicans*, and *Gardnerella vaginalis*.[4] Several factors may contribute to the possible activity of *Lactobacillus*, including the ability to generate lactic acid, hydrogen peroxide, and exogenous antibacterial compounds, to influence the production of interferon by target cells, [5] and to alter the adherence of bacteria. Lactacin F, an antibacterial compound produced by *L. acidophilus*, has been isolated and partially characterized as a heat-stable protein with at least 56 amino acid residues.[6,7]

Lactobacillus has long been considered to be a component of the protective flora in the vagina. Recently, *Lactobacillus* species that produce hydrogen peroxide have been found in normal vaginal flora. Consequently, the therapeutic benefits of *Lactobacillus* products have been investigated in women with vaginal and urinary tract infections. Women who used acetic acid jelly, an estrogen cream, a fermented lactobacillus-containing milk product, or metronidazole (eg, *Flagyl*) were evaluated to determine the effects of intravaginal therapy on bacterial vaginosis. Clinical cures were obtained for 13 of 14 women receiving metronidazole but for only 1 of 14 using the fermented milk product. This latter intervention did not influence the predominance of lactobacilli in the vagina. [8] An evaluation of 16 commercially available products containing *Lactobacillus* in the form of capsules, powders, and tablets (in addition to yogurt and milk) found that all 16 products contained lactobacilli, of which 10 strains produced hydrogen peroxide. At least one contaminant was detected in 11 of the products, including *Enterococcus faecium*, *Clostridium sporogenes*, and *Pseudomonas* species. Only 4 of the products contained *L. acidophilus*and, therefore, the authors concluded that most commercially available products may not be appropriate for recolonization of the vagina. [4] The American Medical Association proposed guidelines for manufacturers to state on yogurt containers the number of viable *L. acidophilus* organisms contained therein.[9] Vaginal tablets containing *L. acidophilus* and estriol were shown to cure bacterial vaginosis.[10] A study showed decreased candidal vaginitis after ingestion of yogurt containing *L. acidophilus*.[11] However, ingestion of yogurt containing *L. acidophilus* increased colonization of the vagina and showed a reduction in the episodes of bacterial vaginosis but not in episodes of candidal vaginitis when compared to pasteurized yogurt. [12]

*Lactobacillus*species that are strong producers of hydrogen peroxide and are highly adherent to vaginal epithelial cells effectively treat bacterial vaginosis. [13,14] Specific isolates of *Lactobacillus* with these characteristics are potential probiotics for vaginal recolonization. [14] The weekly instillation of *Lactobacillus* has been shown to reduce the recurrence rate of uncomplicated lower urinary tract infections in women, and the use of a strain that is resistant to nonoxynol-9, a spermicide that kills protective vaginal flora, may have potential for use in women with recurrent cystitis using this contraceptive agent. [15]

L. acidophilus is normally found in the human alimentary tract. Because of its acid-resistance, it persists in the stomach much longer than other bacteria do. Consequently, the oral administration of products containing *L. acidophilus*may be useful in the management of a variety of conditions associated with altered GI flora. Their beneficial effects may be related to the ability to suppress the growth of pathogens. In vitro, *L. acidophilus* has been shown to suppress the growth of *Campylobacter pylori*, a pathogen implicated as a causative factor in acid-peptic disease, although the therapeutic implications of these findings are not clear. [16,17] In vivo, inactivated *L. acidophilus* added to the triple regimen of an acid-suppressor plus two antibiotics increased eradication rates of *Helicobacter pylori*, another pathogen implicated in myriad upper GI diseases. Larger clinical trials are necessary to validate this finding. [18]

No consensus has been reached regarding the effectiveness of *Lactobacillus*-containing products in ameliorating antibiotic-induced diarrhea. When *Lactinex* granules, a combination of *L. acidophilus* and *L. bulgaricus*, were given 4 times daily for 10 days to children concomitantly with amoxicillin (eg, *Amoxil*) therapy under double-blind conditions, 70% of the patients receiving placebo and 66% of those taking *Lactinex* experienced diarrhea. Closer analysis suggested that the incidence of diarrhea diminished during the last 4 days of therapy for the *Lactinex* patients, while it remained constant for those given placebo. [19] However, in a study of 40 children who received amoxicillin concomitantly with fermented *Lactobacillus* milk products, the treated group showed a lower frequency of stool passages and more fully formed feces compared with no treatment.[20] In a study of 27 patients randomized to amoxicillin/clavulanate (eg, *Augmentin*) with or without *Lactinex*, there were fewer episodes of diarrhea reported in the *Augmentin*-only group, although the addition of *Lactinex* resulted in reduction of nausea, cramping, flatulence, and yeast superinfection.[21]

Addition of lyophilized, heat-killed *L. acidophilus* LB to oral rehydration therapy decreased duration of diarrhea in a randomized clinical trial of children not on antibiotic therapy.[22] However, *L. acidophilus*did not prevent traveler's diarrhea. [23]

The ingestion of these products has been associated with decreases in the concentration of several fecal enzymes that have the capacity to convert procarcinogens to carcinogens in the colon. This suggests that consumption of *Lactobacillus*-containing products may have beneficial health effects, although no further data are available to support this hypothesis. [24] The combination of *L. acidophilus* and lactulose appears beneficial in the therapy of radiotherapy-related intestinal side effects.[25]

Effect on cholesterol levels: It has been suggested that appropriately selected strains of *Lactobacillus* may be useful adjuncts for the control of hypercholesterolemia in humans, by virtue of the bacteria's ability to assimilate cholesterol and to grow well in the presence of bile. [26] The results of one study, in which 354 subjects took *Lactinex* tablets or placebo 4 times a day for 3 weeks in a crossover fashion, found no clinically significant changes in lipoprotein concentrations for either group. [27] Serum LDL-cholesterol was lowered in a study of healthy male patients consuming low-fat milk fermented with 2 strains of *Lactobacillus* and fructo-oligosaccharides (which could have contributed to the results). [28] Yogurt enriched with *L. acidophilus* did not lower serum cholesterol in another study of men and women.[29] Conflicting results remain concerning *Lactobacillus*species' effect on serum cholesterol levels.

Consumption of yogurt containing *L. acidophilus*in 15 asthmatic patients showed trends in decreased eosinophilia and increased interferon gamma, however, without improving clinical parameters.[30] Viability might be a prerequisite for effects on the immune system. [31] Further studies are necessary to ascertain if *L. acidophilus* has an effect on immunity.

Effect on lactose intolerance: Acidophilus milk containing *L. acidophilus*has been used in hospitals to treat patients with lactose intolerance, although controversy remains regarding effectiveness on lactose digestion. [32] In a randomized trial of 18 patients, symptoms were not significantly improved after ingestion of *L. acidophilus*.[33]

TOXICOLOGY: Endocarditis caused by *Lactobacillus*species, including *L. acidophilus* has been reported.[34] This is a rare infection seen in patients with abnormal heart valves who have recently experienced dental manipulation. [34] Neurological sequelae from D-lactic acidosis, caused by consumption of acidophilus tablets and yogurt containing *L. acidophilus*, was observed in a child with short-bowel syndrome.[35] Complete avoidance of *L. acidophilus* in children with short-bowel syndrome may help prevent episodes of D-lactic acidosis.[35]

SUMMARY: Preparations containing *L. acidophilus*include yogurt, milk, tablets, capsules, and granules. They are used most frequently to restore normal flora to the GI tract and vagina. However, the data supporting the efficacy of these products for these uses are conflicting. Use of *L. acidophilus* is generally considered safe. Rare adverse events include endocarditis in susceptible patients and lactic acidosis in children with short-bowel syndrome.

PATIENT INFORMATION— Acidophilus

Uses: *L. acidophilus* has been used to restore normal oral, GI, and vaginal flora in those affected by antibiotics or by *Candida* and bacterial infections. Its value in treating these infections, lower urinary tract infections, and lactose intolerance remains unclear. In vitro, it suppresses growth of *C. pylori*, implicated in acid-peptic disease. In vivo, it suppresses growth of *H. pylori*, also implicated in upper GI diseases.

Side Effects: *L. acidophilus* is generally considered safe, as it is normally found in the human alimentary tract. However, in patients with abnormal heart valves who have recently experienced dental manipulation, endocarditis caused by *Lactobacillus* species has been reported. Complete avoidance of *L. acidophilus*in children with short-bowel syndrome may help prevent episodes of D-lactic acidosis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ACIDOPHILUS

ACKEE

DATE OF ISSUE: DEC 2003

REPLACES MONOGRAPH DATED: OCT 2002

SCIENTIFIC NAME(S): *Blighia sapida*, K. Konig. Family: Sapindaceae

COMMON NAME(S): Ackee, akee, aki, arbre a' fricasser,[1] seso vegetal,[2] yeux de crabe,[1] merey del diablo,[1] ris de veau,[1] fruto de huevo,[1] arbol de seso,[1] pero roja,[1] pan y quesito[1]

BOTANY: Ackee is the national fruit of Jamaica and is widely found throughout the West Indies and has been naturalized to parts of Central America, Florida, and Hawaii. This tall, leafy tree grows to approximately 12 meters and produces fruit 2 times/year, between January and March, and June and August. [1] Its oval, compound leaves have 5 pair of leaflets, the longest of which is approximately 15 centimeters at the tip. The plant produces small, greenish-white flowers. The red fruit pods split open at maturity, exposing 3 shiny, black seeds embedded in a white, waxy aril. [2]

HISTORY: The ackee tree was imported to Jamaica from West Africa in the late 1700s and is often grown as an ornamental. [3] Although the unripened walnut-like seeds are toxic, the ripe fruits are used in traditional island cooking. [2] The ackee is a major food in Jamaica and is noted for its high protein and fat content. [4] Fresh ackee berries are available in season in markets and canned fruit is available throughout the year. Poisonings have long been associated with the use of the ackee, and published reports of Jamaican intoxications date back to 1904. [5] In South America, the fruit is used to treat colds, fever, and diseases as varied as edema and epilepsy.[3]

CHEMISTRY: Hypoglycin A and hypoglycin B are potent hypoglycemic compounds.[1] The most toxic is the cyclopropyl amino acid hypoglycin A and its metabolite methylenecyclopropylacetic acid, found in the aril and the seeds of the unripe ackee fruit. [1,6,7] The unripe ackee fruit contains hypoglycin A at concentrations 100 times higher than those in ripe ackee fruit.[7,8] In addition, other hypoglycemic compounds, including hypoglycin B and cyclopropanoid amino acids, are found in the seed. CNS active carboxycyclopropylglycines found in the unripened fruit are reported to be potent group II metatrophic glutamate receptor agonists. [9]

PHARMACOLOGY: Hypoglycin A is a water-soluble liver toxin that induces hypoglycemia by inhibiting gluconeogenesis by limiting the activity of cofactor mimics (CoA and carnitine) that are required for the oxidation of long-chain fatty acids. [5] Methylenecyclopropylacetyl-CoA also causes secondary inhibition of gluconeogenesis by inactivating several acyl-CoA dehydrogenases involved with the oxidation of fatty acids and several amino acids. [10] The pink raphe (the portion of the seed that attaches to the ovary wall) and the aril in the immature plant are poisonous because of the presence of the hypoglycins. The arils become edible when the fruit ripens; hypoglycin A is efficiently removed from the edible arils when the ackee fruit is boiled in water for approximately 30 minutes. [7] Hypoglycin A appears to be approximately twice as toxic as hypoglycin B.[6] The powdered fruits are used in Africa as a fish poison.[3]

More than 5000 people have died from ackee poisoning since 1886.[6,10] In the past, large-scale poisonings appeared to be limited to the island of Jamaica where they reached epidemic proportions during the winter months under the name of "Jamaican vomiting sickness." [2] In Jamaica, 28 patients who had symptoms of ackee poisoning were identified during the period between January 1989 through July 1991. Six of these patients died. The most common symptoms were vomiting, coma, and seizures. Seven of the patients had confirmed hypoglycemia. Most of the cases occurred between January and March. [5]

A case-control, retrospective study of health-service records and interviews with family members, village chiefs, and local healers in a rural area in west Africa identified 29 cases of fatal encephalopathy in preschool children (2 to 6 years of age) during January to May 1998. All children died within 48 hours of onset of symptoms. The clinical presentation was similar to that of Jamaican vomiting sickness and toxic hypoglycemic syndrome; most common symptoms included hypotonia, convulsions, and coma.[8]

Eighty cases with symptoms consistent of ackee poisoning (ie, continuous vomiting, abdominal pains, loss of consciousness, convulsions within 24 hours) were recorded in 2 districts of Haiti's Northern Province between November 2000 and March 2001. [1] Retrospective analysis confirmed 31 of the 80 cases were related to consumption of ackee. The mean age of the victims ranged from 6 months to 88 years, with a median of 7 and an average of 16. The case fatality rate was 52%. [1]

Poisonings may be present in 1 of 2 distinct forms. In the first case, vomiting is followed by a remission period of 8 to 10 hours, followed by renewed vomiting, convulsions, and coma. The second type is characterized by convulsions and coma at the onset. Additional symptoms associated with chronic fruit ingestion include cholestatic jaundice, abdominal pain, and elevated liver function values. [11] Diarrhea and fever are usually absent. Six to 48 hours may elapse between ingestion of the fruit and the onset of symptoms.[12] Severe hypoglycemia develops[2] and blood glucose levels as low as 3 mg/dL are observed in many cases.[5]

Management of ackee intoxication consists of fluid therapy and the administration of glucose and electrolytes. Because patients with preexisting nutritional deficits and children may be more sensitive to the toxic effects of the fruit, vitamin and nutritional supplements should be administered. [2,5,12]

SUMMARY: The ripe ackee fruit is traditionally used in Jamaican cooking. However, the unripened fruit is toxic, causing severe hypoglycemia often accompanied by convulsions and death.

PATIENT INFORMATION — Ackee

Uses: The ackee is a major food in Jamaica. In South America, the fruit has been used to treat colds, fever, and diseases as varied as edema and epilepsy, although there are no clinical trials to support these uses.

Side Effects: Six to 48 hours may elapse between ingestion of the unripened fruit and the onset of symptoms. Symptoms of ackee poisoning include cholestatic jaundice, vomiting, hypoglycemia, convulsions, coma, and potentially death.

Drug Interaction/Disease-State Concerns: Hypoglycemia caused by ackee may be masked in patients on beta-blockers because these suppress epinephrine-mediated warning signs of imminent hypoglycemia; monitor patients with diabetes.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ACKEE

ACONITE

DATE OF ISSUE: FEB 2002

REPLACES MONOGRAPH DATED: FEB 1993

SCIENTIFIC NAME(S): *Aconitum napellus* L. *A. columbianum* Nutt. also is described in cases of aconite toxicity. Family: Ranunculaceae

COMMON NAME(S): Aconite, monkshood, friar's cap, helmet flower, soldier's cap, wolfsbane[1]

BOTANY: These erect perennial plants grow to a height of 0.6 to 1.5 m (2 to 6 feet). In general, they resemble delphiniums. The characteristic helmet-shaped blue flowers grow in a raceme at the top of the stalk in summer or fall. Occasionally, the flowers may be white, pink, or peach. The seed pods dry and contain numerous tiny seeds.[1] More than 100 species of *Aconitum* are distributed throughout the temperate zones of the United States and Canada. These plants also are found throughout many parts of Asia, Africa, Europe, and Russia.

HISTORY: Aconite is well known because it is extremely toxic. The tuberous root has been used in traditional medicine, although all parts of the plant are considered to be toxic. While the extracts of the plant are used rarely in American medicine today, they continue to find use in liniments as rubifacients for external application. Extracts of the plant are used in homeopathic and traditional medicine as hypotensives, to decrease fever, as cardiac depressants, and to treat neuralgia.[2] In traditional Asian medicine, extracts of the root are typically mixed with other ingredients (eg, licorice, ginger) for ailments ranging from sciatica to nephritis. Extracts also have been used as arrow poisons.

CHEMISTRY: Alkaloids account for up to 1.5% of the dry weight of the plant. These consist primarily of the related alkaloids aconitine, picraconitine, aconine, and napelline.[3] Aconitine is hydrolyzed to picraconitine, which hydrolyzes to aconine. A wide variety of minor alkaloids have been isolated from the various species of aconite. Some examples include the following: Species *A. sinomontanum* contains norditerpenoid alkaloids sinomontanitines, lappaconitine, and ranaconitine. [4] Hypaconitine is found in roots of *A. coreanum*.[5] Other plants, such as delphinium, may have similar alkaloids such as methyl-lycaconitine. [6]

PHARMACOLOGY: Some *Aconitum* species have been reported to exert antitumor activity in vitro and in animals, while others possess antibacterial and antifungal activity.[3] In animal models, aconitine and related compounds have been shown to possess anti-inflammatory and analgesic properties. [7]

TOXICOLOGY: Aconite is a fast-acting toxin. The active principles are aconitine and related alkaloids. As little as 2 to 5 mg of aconitine (˜ 1 teaspoonful of the root) may cause death from paralysis of the respiratory center or cardiac muscle.

Toxicity from the wild plant has resulted when the plant was mistaken for wild parsley or the root for horseradish. [2]

Aconitine's toxicity is characterized by a burning sensation of the lips, tongue, mouth, and throat almost immediately following ingestion. Numbness of the throat may ensue with difficulty in speaking. Salivation, nausea, and vomiting may occur along with visual blurring or yellow-green color vision distortion. A single dose of 0.6 mg/kg of aconitine administered intraperitoneally to rabbits has been shown to cause histopathologic damage to the myelin sheath of the visual pathway, spinal cord, and peripheral nerves.[8] Similarly, aconitine has demonstrated arrhythmogenic and cardiotoxic effects on myocardium in anesthetized cats. [9] Weakness, dizziness, and incoordination may occur. Gastric lavage or induction of emesis following the injection of atropine has been recommended. [10] Some experiments have used aconitine to artificially induce arrhythmias in laboratory animals to study the antiarrhythmic effects of other drugs. [11,12]

Cardiac arrhythmias of unusual electrical characteristics have been observed following aconite poisoning. [13] These arrhythmias may not respond to procainamide and may worsen following verapamil administration. Putrescine, a compound used experimentally as a molecular probe, has been shown to attenuate aconitine-induced arrhythmias.[14] Death may ensue secondary to cardiac arrhythmia,[1] which may occur unpredictably within minutes or days.[2] Several case reports describe poisonings with aconite or its constituents, including ventricular tachycardia, other arrhythmias, and death. [15,16,17,18] One homicide attempt with the plant has been reported.[19] Self-medication with aconite tincture resulted in severe bradycardia, sinus inactivity, hypotension, and other cardiotoxicities, all of which were reversible. [20] Life-threatening ventricular tachycardias were successfully treated with amiodarone. [21] Resuscitation and percutaneous cardiopulmonary bypass were instituted in a 41-year-old male who mistakenly consumed the plant. He was discharged ˜ 3 months after the incident.[22] A postmortem evaluation of aconitum alkaloid distribution following a suicidal ingestion of the tuber parts has been reported. High alkaloid content was found in the kidneys, liver, and ileum. Elimination of the alkaloids were via urine and feces.[23]

Aconitine is classified as a neurotoxin, which can induce severe neurological symptoms and cardiovascular collapse. Alkaloid lappaconitine blocks voltage-gated sodium channels in heart tissue.[24]

Aconitine is known to shift voltage-dependence of voltage-dependent sodium channels toward the hyperpolarized direction, resulting in permanent activation of the channel. Structurally related alkaloids in rat hippocampi have been studied for their effects. [25]

Aconitine produces tingling and numbness when applied to the skin and significant toxicity may develop following percutaneous absorption.

There is evidence to suggest that aconite may lose potency after undergoing certain manufacturing procedures; therefore, processed aconite may not have a similar toxicity profile to the crude plant material.[26]

SUMMARY: Aconite and several of its related species are recognized as highly toxic. Some traditional or homeopathic uses include employment of the plant for external liniments, hypotensives, or treatment of neuralgias. Several case studies regarding tachycardia and other cardiac toxicities have been reported.

PATIENT INFORMATION— Aconite

Uses: Aconite extracts have been used externally and homeopathically in Europe and Asia, but rarely in the United States. Research suggests a variety of possible applications. Use is not recommended because of its toxicity.

Side Effects: Aconite is highly toxic. As little as 2 to 5 mg may cause death from paralysis of the respiratory center or cardiac muscle. Significant toxicity also may develop following percutaneous absorption.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ACONITE

AGRIMONY

DATE OF ISSUE: AUG 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Agrimonia eupatoria* L. Family: Rosaceae

COMMON NAME(S): Cocklebur, stickwort, liverwort

BOTANY: Agrimony (of British Herbal Pharmacopoeia) is a perennial herb with small, star-shaped yellow flowers. The plant possesses a short rhizome and is supported by a firm, hairy stem. The basal leaves are arrayed in a rosette and they, as well as the alternate sessile stem leaves, are pinnate, serrate and glabrous. [1] The flowers and fruit (achene) grow at the top of the stem in a long, terminal spike. Agrimony is common in grasslands throughout Europe. It is imported from Bulgaria, Hungary and the former Yugoslavia.[2]

HISTORY: The name Agrimonia may have its origin in the Greek "agremone" which refers to plants which supposedly healed cataracts of the eye. The species name *eupatoria* probably relates to Mithradates Eupator, King of Pontres, who is credited with introducing many herbal remedies. Its ancient uses include treatment for catarrh (mucous membrane inflammation with discharge), bleeding, tuberculosis and skin diseases. [1] In folk medicine, it has been reported, without verification, to be useful in gallbladder disorders. Numerous other reported uses include use as a dye, flavoring, gargle for performers and speakers, antitumor agent, astringent, cardiotonic, coagulant, diuretic, sedative, antiasthmatic and for corns or warts. [3]

CHEMISTRY: The aerial parts of the plant contain 4% to 10% condensed tannins, small amounts of ellagitannins and traces of gallotannins. [2,4] Also reported are some 20% polysaccharides.[4] A triterpenoid, urosolic acid, has been isolated. Silicic acid and traces of essential oil are listed as constituents.The flavonoids, luteolin and apigenin 7-0-ß-D-glucosides, are present. [4] Organic acids, vitamin B_1, vitamin K and ascorbic acid are also listed as components. The fresh herb contains agrimoniolide, palmitic and stearic acids, ceryl alcohol and phytosterols. Seeds contain 35% oil which contains oleic, linoleic and linolenic acids. [2,3]

PHARMACOLOGY: Agrimony is used widely in Europe as a mild astringent (externally and internally), particularly against inflammation of the throat, gastroenteritis and intestinal catarrh. Studies of ethanolic extracts display the anti-viral properties. This plant is often included in phytomedicine mixtures for "liver and bile teas," again without true scientific verification. Agrimony extracts are often used in small amounts in prepared European cholagogues and stomach and bowel remedies (eg, *Neo-Gallonorm*®-Dragees) and urological products (eg, *Rhoival*®). Agrimony is also a component of the British product *Potter's Piletabs*®.[2,4,5,6]

TOXICOLOGY: Agrimony has been reported to produce photodermatitis in man.[3]

SUMMARY: Agrimony is used as a tea and gargle for sore throats, in compresses or poultices for skin rashes and cuts, and in various bath preparations. It does appear to have justifiable use as a mild antiseptic and topical astringent. Internal uses of this herb require further verification.

PATIENT INFORMATION — Agrimony

Uses: Agrimony is used as a tea and gargle for sore throat, and externally as a mild antiseptic and astringent.

Side Effects: Agrimony reportedly can produce photodermatitis.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AGRIMONY

AGROPYRON

DATE OF ISSUE: APR 2002

REPLACES MONOGRAPH DATED: FEB 1996

SCIENTIFIC NAME(S): *Agropyron repens* (L.) P. Beauv., *Elymus repens*, *Graminis rhizoma*, *Triticum repens*. Family: Gramineae

COMMON NAME(S): Couch-grass root, dog grass, quack grass, triticum, twitchgrass

BOTANY: Agropyron is a weed that is widely distributed throughout the northern hemisphere. The grass grows up to 1.5 m tall with spikes up to 15 cm long containing many flowered spikelets.[1] The leaves alternate with sheaths, the blades are long and narrow, and the veins are parallel.[2] The grass also contains shiny, pale yellow, hollow pieces of rhizome and longitudinally grooved stems that are 2 to 3 mm thick. Thin roots and short fiber-like cataphylls are present at the unthickened nodes. Agropyron has an almost bland but slightly sweet taste. The rhizomes, roots, and stems are used to formulate the product.[1]

HISTORY: In folk medicine, agropyron has been used as a diuretic in cases of bladder catarrh and bladder/kidney stones, and as a cough medicine to alleviate bronchial irritation. It has been used to treat gout, rheumatic disorders, and chronic skin disorders. The drug products are typically imported from Romania, Hungary, the Yugoslavian region, and Albania.[1]

CHEMISTRY: The major constituent of agropyron is triticin (3% to 8%), a polysaccharide related to inulin. Upon hydrolysis, triticin releases the following: fructose; mucilage (10%); saponins; sugar alcohols (mannitol, inositol, 2% to 3%); essential oil with polyacetylenes or carvone (0.01% to 0.05%); small amounts of vanilloside (vanillin monoglucoside), vanillin, and phenolcarboxylic acids; silicic acid; and silicates.[1,3,4] Extraction of silicon species from agropyron has been studied.[5] Lectins found in the seedlings and leaves also may be present in the rhizome.[1] However, the lectin content of the leaves varies from season to season.[6] Other constituents found in agropyron include agropyrene (volatile oil constituent, 95%), mucilage, thymol, menthol, iron, and other minerals.[3,4] Albumin content in agropyron and other wheat related plants has been evaluated.[7] Breeding potential of agropyron also has been reported.[8]

PHARMACOLOGY: In addition to the folk uses of agropyron, it has been indicated for irrigation therapy in inflammatory disorders of the urinary tract, in the prevention of renal gravel, and to supplement treatment in catarrh of the upper respiratory tract. Agropyron is said to be useful as a diuretic.[1] One study reports the effects of agropyron on calcium oxalate urolithiasis risk in rats, finding antilithiasic effects to be more dependent on diet.[9] Agropyron leaf lectin exhibits specificity for N-acetylgalactosamine and agglutinates, preferentially blood-group-A erythrocytes.[6] Nutritive value of the plant has been studied in sheep.[10] The essential oil has shown antimicrobial effects, and extracts of the drug are used as a dietary component for diabetic patients.[1] Broad spectrum antibiotic activity has been documented for agropyrene and its oxidation product. Agropyron may have weak anti-inflammatory effects.[4] Despite these indications, pharmacological and clinical studies are lacking.

TOXICOLOGY: There are no known side effects or drug interactions associated with the use of agropyron. One study reports on allergans in canine atopic dermatitis. Intradermal skin tests in 1000 dogs revealed 33% reacting to the house dust mite and 15% reacting to agropyron, suggesting these to be common allergens.[11] Agropyron can be consumed safely when used appropriately.[12] The limited amount of toxicological data requires cautious use during pregnancy and lactation.

SUMMARY: Agropyron has been used in folk medicine for a variety of GU ailments and as a cough remedy to alleviate bronchial irritation. It has been used to treat gout, various rheumatic disorders, and chronic skin conditions. Extracts of the drug are used as a dietary component for diabetic patients. However, no clinical studies to date have proven any of these indications for agropyron; further investigation is needed.

PATIENT INFORMATION— Agropyron

Uses: Agropyron has been used to treat gout, rheumatic disorders, chronic skin conditions, and urinary tract, bladder, and kidney disorders. Various extracts have been used as a dietary component for diabetic patients. There is a lack of clinical studies that have proven these uses.

Side Effects: There are no known side effects.

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Document Bibliographic Information:
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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AGROPYRON

ALCHEMILLA

DATE OF ISSUE: AUG 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Alchemilla xanthochlora* Rothm. (Syn. *Alchemilla vulgaris* auct. non L.). Family: Rosaceae

COMMON NAME(S): Lady's mantle

BOTANY: Lady's mantle is a perennial herb with a short rhizome carrying ascending or sprawling stems, and a rosette of basal leaves with dentate lobes of a circular or kidney-shaped outline. The inflorescence is a compound terminal cyme made up of dense clusters of small hellow-green flowers. Sepals are seen in two rings of four without petals. The fruit is of the achene type. Overall, the plant is softly pubescent. It is found throughout Europe in meadows, woodland clearings, pastures and in the lowland areas of the British Isles. Currently, it is distributed in Europe, North America and Asia. [1,2]

HISTORY: *Alchemilla* is one of an aggregate of species collectively referred to as lady's mantle, all possessing similar medicinal properties. Many are cultivated. Medieval alchemists collected rain water or dew collected in the leaf center and used it for its purported magical and medicinal powers. This custom derived from the plant's generic name, *alchemilla*, which is from the Arabic word, "alkimiya" (universal cure for disease). In medieval tradition, it was used to treat wounds and female ailments. It has long been dedicated to the Virgin Mary, since the leaf lobes resemble the edges of a mantle. Among lady's mantle's historical uses are as a mild astringent, anti-inflammatory, diuretic, menstrual cycle regulator, treatment for digestive disorders and relaxant for muscular spasms. Externally, it was widely used in bath preparations, wound healing, skin bruises and as an herbal cosmetic. [1,2]

CHEMISTRY: Lady's mantle contains 6% to 8% tannins (elligiannins, such as pedunculagin and alchemillin) and flavonoids (quercetin 3-0-ß-D-glucuronide). [2,3]

PHARMACOLOGY: The historical uses of lady's mantle as an astringent against bleeding and as a treatment for diarrhea seem justified on the bases of its tannin content.[2] Newer studies show that the water extract of *A. xanthochlora* possesses lipid peroxidation and superoxide anion scavenging activity. [4]

Several rosaceae species, including *A. xanthochlora*, have high tannin content and elastase inhibitin activity. [5] In a similar vein, flavonoids extracted from *Alchemilla* inhibit the activity of the proteolytic enzymes elastase, trypsin and alpha-chymotrypsin. [6] These results suggest a possible role by these inhibitors in the protection of conjunctive and elastic tissues.

A number of traditional plant treatments have been studied for diabetes in normal and streptozotocin diabetic mice, but no useful effects for lady's mantle have been found in this disorder.[7]

A study on the mutagenic potencies of several plant extracts (including Tinctura Alchemillae) containing quercetin in *Salmonella typhimurium* TA98 and TA100 found that the mutagenic potential of the plant extracts correlates well with their quercetin content. [8] The cytostatic activity of a lactone fraction from Alchemilla pastoralis has also been reported.[9]

TOXICOLOGY: No significant toxicological studies appear to have been carried out on lady's mantle and long use for various purposes (internal and external) seem to bear out the fact that it is safe in low doses. The warning in the Standard License about possible liver damage appears to be exaggerated. [2]

SUMMARY: The use of lady's mantle for its local astringent and anti-diarrheal properties are mildly justified by the known tannin content of the plant. Newer chemistry and pharmacological studies are sparse, revealing only possible usefulness for its anti-oxidant properties and vague protective effects as well as mutagenic potential and cytostatic activity. More human clinical data are needed to justify its use for its historical medical applications.

PATIENT INFORMATION — Alchemilla

Uses: Alchemilla has been used topically and internally, as a treatment for wounds, gastrointestinal complaints and female ailments. Its tannin content appears to justify astringent and antidiarrheal uses. It may protect conjunctive and elastic tissues and possibly be useful as an antioxidant.

Side Effects: None known for low doses, with the possible exception of liver damage.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALCHEMILLA

ALETRIS

DATE OF ISSUE: SEP 2003

REPLACES MONOGRAPH DATED: OCT 1993

SCIENTIFIC NAME(S): *Aletris farinosa* L. Family: Liliaceae

COMMON NAME(S): Unicorn root, stargrass, whitetube stargrass, crow corn, Ague grass, Aloerot, Devil's-bit, colic root, ague root, starwort, blazing star, mealy starwort, huskwort. Some of the common names are also used in connection with Helonias (*Chamaelirium luteum* [L.] A. Gray).[1,2,3,4,5]

BOTANY: Aletris (of NF VII) is a perennial herb with linear leaves that grow in a rosette. These leaves surround a slender stem that reaches 1 m in height. These are grasslike, of a yellowish green color, and from 5 to 15 cm long. They surround the base of the stem in the form of a star, in this respect differing distinctly from another starwort (*Chamailirium luteum*) with which it is sometimes confused. The plant is native to North America and is distributed widely throughout the continent. Three other species of aletris, *Aletris aurea* Walt., *A. lutea* Small, and *A. obovata* Nash, bear much resemblance to *A. farinosa* and are frequently collected with the latter.[2]

HISTORY: Aletris is a North American plant that is now recognized worldwide in traditional folk medicine. Aletris occurs in dry, generally sandy soil from Maine to Minnesota, Florida, and Tennessee. It had been used by American Indians in the Carolinas as an antidiarrheal tea and in Appalachia for the management of rheumatismsand as a tonic and a sedative.[1] Aletris is used in the preparation of herbal remedies designed to ameliorate discomfort. The fabled *Lydia Pinkham's Vegetable Compound*, which was touted as a cure-all for female discomforts, contained aletris, among other plant derivatives.[6] It has been included in laxatives and has been used as an antiflatulent (hence the name "colic root") and antispasmodic.

The roots and rhizomes are collected in the fall and dried for preservation.

CHEMISTRY: Little is known about the chemical composition of *A. farinosa* with diosgenin being the only significant compound. Diosgenin has also been isolated from it, along with gentrogenin from the related Japanese species *A. foliata* and *A. formosana*.[7] An oil derived from *A. farinosa* is reported to have pharmacologic activity, but this has not been well defined.[1] The plant also contains a resin and a saponin-like glycoside that may yield diosgenin on hydrolysis.[1]

PHARMACOLOGY: Aletris has been reported to have estrogenic activity, although estrogenic compounds have not been isolated nor have detailed studies confirmed this activity. The potential estrogenic properties of aletris may be due to a diosgenin-derived steroid that has not yet been characterized. Studies have indicated the drugs examined act on the strips of the isolated human uterus in the same manner as on the guinea pig uterus, but to a much lesser degree. *Aletris farinosa*, *Pulsatella pratensis*, and oil of valerian depress the activity of the strips.[8] Another pharmacological study shows similar results of *Aletris farinosa* on the isolated uterine tissue of the rat, the guinea pig, and the rabbit. Studies were also conducted on the in vivo uterus of the rabbit and the cat. It exerted a definite action of depression on the isolated uterus of the rat. The antagonistic action of aletris against the stimulating effect of the oxytocic principle of the posterior lobe of the pituitary (pitocin) was also studied on the isolated uterus of the rat. The results using the isolated uterine tissue of the guinea pig and of the rabbit and the in vivo rabbit uterus were inconsistent, the predominant action being stimulation. The effect of aletris on the decerebrate cat and the cat that was estrus induced by the injection of a compound estrogenic preparation, was mainly pronounced sedation.[9]

TOXICOLOGY: No adverse events have been reported with the use of aletris. The plant has been reported to have narcotic properties, and in small doses can induce colic, stupefaction, and vertigo.[10]

SUMMARY: Aletris is a common plant in nutrient-poor locations that has been used widely in folklore for the management of female discomforts. The pharmacologic activity of the plant has not been well defined, but steroidal compounds identified in the plant may form the basis of its purported estrogenic activity.

PATIENT INFORMATION— Aletris

Uses: Aletris has been used as a sedative, laxative, antiflatulent, antispasmodic, and as a treatment for diarrhea and rheumatism. Its potential estrogenic properties may account for its use in treating female disorders. However, there are no clinical trials to support these potential uses.

Side Effects: None are known, but aletris reportedly has narcotic properties and can induce colic, stupor, and vertigo.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALETRIS

ALFALFA

DATE OF ISSUE: MAR 2001

REPLACES MONOGRAPH DATED: MAR 1991

SCIENTIFIC NAME(S): Medicago sativa L. Common cultivars include Weevelchek, Saranac, Team, Arc, Classic, and Buffalo. Family: Leguminosae

COMMON NAME(S): Alfalfa

BOTANY: This legume grows throughout the world under widely varying conditions. A perennial herb, it has trifoliate dentate leaves with an underground stem that is often woody. Alfalfa grows to ˜ 1 m and its blue-violet flowers bloom from July to September.

HISTORY: Alfalfa has played an important role as a livestock forage. Its use probably originated in Southeast Asia. The Arabs fed alfalfa to their horses, claiming it made the animals swift and strong, and named the legume "Al-fal-fa" meaning "father of all foods." The medicinal uses of alfalfa stem from anecdotal reports that the leaves cause diuresis and are useful in the treatment of kidney, bladder, and prostate disorders. Leaf preparations have been touted for their antiarthritic and antidiabetic activity, for treatment of dyspepsia, and as an antiasthmatic. Alfalfa extracts are used in baked goods, beverages, and prepared foods, and the plant serves as a commercial source of chlorophyll and carotene.[1]

CHEMISTRY: Dried alfalfa leaves are ground and sold as tablets or powder for use as nutritional supplements. Leaf tablets are rich in protein, calcium, trace minerals, carotene, vitamins E and K, and numerous water-soluble vitamins.[2] A steroidal saponin fraction composed of several factors (eg, soyasapogenols, hederagenin, medicagenic acid)[3,4] is believed to play a role in the hypocholesterolemic and hemolytic activity of the leaves and sprouts.[5] Alfalfa seeds contain the toxic amino acid L-canavanine, an analog of arginine. Sprouts of certain cultivars of alfalfa contain up to 13 g/kg canavanine (dry weight). Canavanine levels decrease as the plant matures. The alkaloids stachydrine and l-homo-stachydrine found in the seed possess emmenagogue and lactogenic activity.[6] Seeds contain up to 11% of a drying oil used in the preparation of paints and varnishes. The chemistry of alfalfa has been well characterized.[1]

PHARMACOLOGY: There is no evidence that alfalfa leaves or sprouts possess effective diuretic, anti-inflammatory, antidiabetic, or antiulcer activity in humans. Alfalfa saponins are hemolytic in vitro.[7]

Several studies indicate that the ingestion of alfalfa reduces cholesterol absorption and atherosclerotic plaque formation in animals.[8,9,10,11] Alfalfa plant saponins and fiber[12] bind significant quantities of cholesterol in vitro; sprout saponins interact to a lesser degree. In vitro bile acid adsorption is greatest for the whole alfalfa plant, and this activity is not reduced by the removal of saponins from the plant material. In 1 study, the ability of alfalfa to reduce liver cholesterol accumulation in cholesterol-fed rats was enhanced by the removal of saponins. Therefore, alfalfa plant saponins appear to play an important role in neutral steroid excretion, but are not essential for increasing bile acid excretion.[13] In a study with prairie dogs, the lowest incidence of cholesterol gallstones was obtained with the diet of the higher fiber content (85% alfalfa).[11] In a study of 15 patients, alfalfa seeds added to the diet helped normalize serum cholesterol concentrations in patients with type II hyperlipoproteinemia.[14] *Cholestaid*, a product available in the US containing 900 mg of Esterin patented process alfalfa extract with 100 mg citric acid, is said to neutralize the cholesterol in the stomach before it reaches the liver, thus facilitating the excretion of cholesterol from the body with no side effects or toxicity.[15,16] There is no evidence that canavanine or its metabolites affect cholesterol levels.

INTERACTIONS: The vitamin K found in alfalfa can antagonize the anticoagulant effect of warfarin, resulting in decreased anticoagulant activity and lowered prothrombin time.[32] Based on the potential immunostimulating effect of alfalfa, it has been theorized that alfalfa may interfere with the immunosuppressive action of corticosteroids (eg, prednisone) or cyclosporine.[33]

TOXICOLOGY: Changes in intestinal cellular morphology were noted in rats fed alfalfa; these effects were more extensive in animals fed whole plant material compared with sprouts. The interaction of saponins with cholesterol in cell membranes may only be partly responsible for these changes.[13] The importance of the changes in animal intestinal morphology is not clear; it is known that these changes, when observed concomitantly with changes in steroid excretion, may be related to an increased susceptibility to colon cancer.[17]

A disease similar to systemic lupus erythematosus (SLE) has been observed in monkeys fed alfalfa seeds.[18] The disease was characterized by hemolytic anemia, decreased serum complement levels, immunologic changes, and deposition of immunoglobulins in the kidney and skin. Alfalfa ingestion has resulted in pancytopenia and hypocomplementenemia in healthy subjects.[19] L-canavanine has been implicated as the possible causative agent. The toxicity of L-canavanine is mainly due to its structural similarity to arginine. Canavanine binds to arginine-dependent enzymes interfering with their action. Arginine reduces the toxic effects of canavanine in vitro.[20] Further, canavanine may be metabolized to canaline, an analog of ornithine. Canaline may inhibit pyridoxal phosphate and enzymes that require the B_6 cofactor.[14] L-canavanine has also been shown to alter intercellular calcium levels[21] and the ability of certain B or T cell populations to regulate antibody synthesis.[22,23] Alfalfa tablets have been associated with the reactivation of SLE in at least 2 patients.[24]

A case of reversible asymptomatic pancytopenia with splenomegaly has been reported in a man who ingested up to 160 g of ground alfalfa seeds daily as part of a cholesterol-reducing diet. His plasma cholesterol decreased from 218 mg/dL to 130 to 160 mg/dL.[19] Pancytopenia was believed to be due to canavanine.

A popular self-treatment for asthma and hay fever suggests the ingestion of alfalfa tablets. There is no scientific evidence that this treatment is effective.[25] Fortunately, the occurrence of cross-sensitization between alfalfa (a legume) and grass pollens appears unlikely, assuming the tablets are not contaminated with materials from grasses.[26] One patient died of listeriosis following the ingestion of contaminated alfalfa tablets.[27]

Alfalfa seeds and sprouts can be contaminated with such pathogens as *Salmonella enterica* and *Escherichia coli*.[28,29,30,31] Most healthy adults exposed to salmonella or *E. coli* will have symptoms such as diarrhea, nausea, abdominal cramping, and fever that are self-limiting. The *E. coli* infection can lead to hemolytic uremic syndrome with kidney failure or death in children or the elderly. In 1995, 4 outbreaks of *Salmonella* infection occurred in the US because of the consumption of contaminated alfalfa sprouts. In 1995 to 1996, 133 patients in Oregon and British Columbia developed salmonellosis from ingesting alfalfa sprouts contaminated with *S. enterica*(serotype Newport).[28] Also in 1995, 242 patients in the US and Finland developed salmonellosis from ingesting alfalfa sprouts contaminated with *S. enterica* (serotype Stanley).[29] In June and July 1997, simultaneous outbreaks of *E. coli* 0157:H7 infection in Michigan and Virginia were independently associated with eating alfalfa sprouts grown from the same seed lot.[30] The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts.[31]

SUMMARY: Alfalfa is a nutritious legume of importance as animal forage. Leaf preparations have been used in the treatment of kidney and bladder disorders and as an antirheumatic agent. There is no evidence supporting these uses in humans. Evidence from animal studies suggests that alfalfa saponins may lower cholesterol levels. *Cholestaid*, a product available in the US containing 900 mg of Esterin patented process alfalfa extract with 100 mg citric acid, is said to neutralize the cholesterol in the stomach before it reaches the liver, thus encouraging the excretion of harmful cholesterol from the body with no side effects or toxicity. Ingestion of alfalfa preparations is generally without significant side effects for healthy adults, but these may reactivate latent SLE and have caused reversible pancytopenia. Alfalfa seeds and sprouts can become contaminated with such pathogens as *S. enterica* and *E. coli*. The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts.

PATIENT INFORMATION— Alfalfa

Uses: No evidence supports the use of various parts of the alfalfa plant for diuretic, anti-inflammatory, antidiabetic, or antiulcer purposes. Results from 1 small human study showed that the plant might reduce cholesterol levels.

Side Effects: Alfalfa ingestion, especially of the seeds, has been associated with various deleterious effects, and alfalfa seeds and sprouts can be contaminated with bacteria such as *S. enterica* and *E. coli*. The FDA issued an advisory indicating that children, the elderly, and people with compromised immune systems should avoid eating alfalfa sprouts. Ingestion of alfalfa preparations is generally without important side effects in healthy adults.

Dosing: Alfalfa seeds are used commonly as a supplement to lower cholesterol at doses of 0.75 to 3 g/day; however, clinical trials have not been performed to validate this dosage.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALFALFA

ALKANNA ROOT

DATE OF ISSUE: APR 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Alkanna tinctoria* (L.) Tausch Family: Boraginaceae

COMMON NAME(S): Alkanet, alkannawurzel (German), alkermeswurzel (German), anchusa, Dyers's Bugloss, henna, orchanet (English), racine d'alcanna (French), racine d'orcanette(French), radix anchusea (tinctoriae) (Latin), rote ochsenzungenwurzel (German), schminkwurzel (German)

BOTANY: Alkanna is typically a biennial or perennial herbaceous plant growing from 1 to 2 feet in height with pubescent lanceolate leaves. It bears blue to purple trumpet-shaped flowers arranged in loose, one-sided scorpiorid racemes. The root is usually seen as a cylindrical, fissured rhizome with exfoliating, brittle and dark purple bark on the outside and remains of bristly leaf and stem pieces near the crown region. [1] While native to southern Europe, the plant is also grown in and imported from Albania, India and Turkey.[1]

Alkanna should not be confused with another plant also known as alkanet, but which is in the related genus *Anchusa officinalis*(L.) of the same family (Borage).[2] *A. officinalis* has had some use in the form of a decoction (tea) of the leaves and roots for coughs and chest disorders in older herbals. [2]

HISTORY: Alkanna and related plants have long been referred to as "henna" and used as a dye for cloth. Alkanna has also been used to impart a red color to fats, oils and waxes. It also has medicinal historical uses as an astringent. Currently, alkanna has no medicinal importance, and many countries have prohibited its use as a food dye.[1]

CHEMISTRY: Alkanna root contains a mixture of red pigments in the bark at levels up to 5% to 6%. These consist mainly of fat soluble naphthazarin (5,8-dihydroxy-1, 4-naphthaquinone) components such as alkannin and related esters. [1],[3] The red pigments are soluble in fatty oils which make them useful for the detection of oily materials in microscopic powders during histological examination. Like some of the other members of the Borage family, pyrrolizidine alkaloids have been found in *Alkanna tinctoria*, but levels have not been determined.[1] The alkannin esters of beta, beta=dimethylacrylic acid, beta-acetoxy-isovaleric acid, isovaleric acid and angelic acid have also been isolated from the root. [4]

PHARMACOLOGY: Currently, alkanna root has no recognized medical uses except for its older use as an astringent. Even its use as a pigment is minimal and many countries have prohibited its use as a food coloring. Today, it is used almost exclusively as a cosmetic dye. [1] The esteric pigments, however, displayed excellent antibiotic and wound-healing properties in a clinical study on 72 patients with ulcus cruris (indolent leg ulcers). [1],[4]

TOXICOLOGY: No toxicological data on alkanna root are available in the current medical literature.

SUMMARY: Alkanna root has historically been used for its mild astringent properties and as a source of pigments for coloring purposes. However, except for little use as a red color in cosmetics, it is not a major pigment source or a particularly useful drug by today's standards. One study indicates some potential for its esteric pigments in wound healing in patients with ulcus cruris (indolent leg ulcers). [1]

PATIENT INFORMATION — Alkanna Root

Uses: Alkanna is an astringent and a source of red pigment used in cosmetics. It appears to have antibiotic and wound-healing properties.

Side Effects: Unknown.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALKANNA ROOT

ALLSPICE

DATE OF ISSUE: DEC 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Pimenta dioica* (L.) Merr. synonymous with *P. officinalis* and *Eugenia pimenta*. Family: Myrtaceae

COMMON NAME(S): Allspice, pimenta, Jamaica pepper, clove pepper, pimento.[1,2,3]

BOTANY: Pimenta is a sturdy tree that grows to 13 meters. It has leathery, oblong leaves and is native to the West Indies, Central America and Mexico. The parts of the plant used medicinally are the dried, full-grown but unripe fruit and leaves. [1] Allspice powder available commercially consists of the whole ground dried fruit. [2]

HISTORY: The plant has been used as a carminative. Besides its use in cosmetics and toothpastes, it is used as a food flavoring. Its odor is reminiscent of a combination of cloves, cinnamon and nutmeg. Allspice has been used medicinally as a tonic, purgative, carminative and antidiarrheal [3] and for rheumatisms, neuralgia and stomachache.[2]

CHEMISTRY: Allspice berries contain from 1% to 4% of a volatile oil, which contains from 60% to 80% eugenol and eugenol methylether (40% to 45%). [1,2,3] The leaf oil contains more eugenol (up to 96%) and bears many similarities to the composition of clove leaf oil. [1] The oil is known as pimenta or allspice oil, and also contains cineole, levophellandrene, caryophyllene and palmitic acid. [3] Enzymes released after harvesting appear to be responsible for producing many of the volatile components from chemical precursors.[1] More than three dozen chemical constituents have been identified in the plant. [1] In addition, small amounts of resin, tannic acid and an acrid fixed oil are present. [1]

PHARMACOLOGY: Any pharmacologic activity associated with the plant is most likely due to the presence of eugenol. Eugenol has local antiseptic and anesthetic properties. Eugenol also has antioxidant properties and allspice may serve as a potential source of new natural antioxidants. [1,4] Furthermore, allspice appears to have in vitro activity against yeasts and fungi. [5,6]

Eugenol, aqueous extracts of allspice and allspice oil, has been shown to enhance trypsin activity and to have larvicidal properties. [1]

TOXICOLOGY: Allspice and extracts of the plant can be irritating to mucous membranes. Although allspice generally has not been associated with toxicity, eugenol can be toxic in high concentrations. Ingestion of more than 5 ml of allspice oil may induce nausea, vomiting, central nervous system depression and convulsions. [3]

When pimento oil and eugenol were applied to intact shaved abdominal skin of the mouse, no percutaneous absorption was observed. [1]

SUMMARY: Allspice is a popular spice and fragrance. The oil may induce topical irritation and ingestion of the oil may result in toxicity.

PATIENT INFORMATION — Allspice

Uses: Apart from use for spices and fragrance, allspice has been used for various gastrointestinal ills, rheumatism and neuralgia. Extracts have antiseptic, anesthetic, and antioxidant properties and efficacy in vitro against yeasts and fungi.

Side Effects: Allspice can irritate mucosa. Ingestion of extracts may produce toxicity and affect the CNS.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALLSPICE

ALOE

DATE OF ISSUE: OCT 2001

REPLACES MONOGRAPH DATED: APR 1992

SCIENTIFIC NAME(S): *Aloe vera* L., *A. perryi Baker* (Zanzibar or Socotrine aloe), *A. barbadensis* Miller (also called *A. vera* Tournefort ex Linne or *A. vulgaris*Lamark; Curacao or Barbados aloe), or *A. ferox*Miller (Cape aloe). *A. vera* Miller and *A. vera* L. may or may not be the same species. Family: Liliaceae

COMMON NAME(S): Cape, Zanzibar, Socotrine, Curacao, or Barbados aloes, aloe vera

BOTANY: Aloes, of which there are ˜ 500 species, belong to the family Liliaceae.[1] The name, meaning "bitter and shiny substance," derives from the Arabic "alloeh." Indigenous to the Cape of Good Hope, these perennial succulents grow throughout most of Africa, southern Arabia and Madagascar, and are cultivated in Japan, North and South America, and in the Caribbean and Mediterranean regions. They do not grow in rain forests or arid deserts. Often attractive ornamental plants, their fleshy leaves are stiff and spiny along the edges and grow in a rosette. Each plant has 15 to 30 tapering leaves, each up to 0.5 meters long and 8 to 10 cm wide. Beneath the thick cuticle of the epidermis lies the chlorenchyma. Between this layer and the colorless mucilaginous pulp containing the aloe gel are numerous vascular bundles and inner bundle sheath cells, from which a bitter yellow sap exudes when the leaves are cut. [2]

HISTORY: Drawings of aloe have been found in the wall carvings of Egyptian temples erected in the fourth millennium BC. Called the "Plant of Immortality," it was a traditional funerary gift for the pharaohs. *The Egyptian Book of Remedies* (ca. 1500 BC) notes the use of aloe in curing infections, treating the skin, and preparing drugs that were chiefly used as laxatives. *The Bible* (John 19:39-40) says that Nicodemus brought a mixture of myrrh and aloes for the preparation of Christ's body. Alexander is said to have conquered the island of Socotra to obtain control of it. The Greek physician Dioscorides, in 74 AD, recorded its use to heal wounds, stop hair loss, treat genital ulcers, and eliminate hemorrhoids. In the 6th century AD, Arab traders carried it to Asia. From the Mediterranean region, it was carried to the New World in the 16th century by the Spaniards. In the modern era, its clinical use began in the 1930s as a treatment for roentgen dermatitis. [2]

CHEMISTRY: The aloe yields 2 commercially important products. "Aloe resin" is the solid residue obtained by evaporating the latex obtained from the pericyclic cells beneath the skin.[3] The bitter yellow latex contains the anthraquinone barbaloin (a glucoside of aloe-emodin) and iso-barbaloin in addition to a series of O-glycosides of barbaloin, called aloinosides, chrysophanic acid, and up to 63% resin. Filtering out resins from the exudate and concentrating the remaining anthraglycoside material (which is up to 25% barbaloin) into crystalline form produces aloin. Aloin is a mixture of water-soluble glycosides obtained from aloe.

A second product, aloe gel, is a clear, thin, gelatinous material obtained by crushing the mucilaginous cells found in the inner tissue of the leaf. The gel is the product used most frequently in the cosmetic and health food industries. It is generally devoid of anthraquinone glycosides. The gel contains a polysaccharide glucomannan, similar to guar gum. It is this component that is believed to contribute mostly to the emollient effect of the gel. "Aloe vera gel extract" is not actually an extract, but rather the pulverized whole leaves of the plant.

Allantoin is a primary mucilaginous substance in aloe and is an important proliferating agent.

Other compounds such as tannins, polysaccharides, organic acids, enzymes, vitamins, and steroids have been identified. [4] Aloe contains bradykininase, which relieves pain and decreases swelling and redness. Magnesium lactate, by blocking histamine production, may contribute to the antipruritic effect of aloe. An antiprostaglandin that reduces inflammation also has been isolated. The anthraquinones are local irritants in the GI tract and have been used in treating certain skin diseases such as psoriasis.

Chemical composition differs among the species of aloe. For example, *A. barbadensis* Miller may contain 2.5 times the aloe-emodin of *A. ferox* Miller, and the time of harvest is a further factor in composition.

PHARMACOLOGY: Aloe latex has been used for centuries as a potent cathartic. The aloinosides exert strong purgative effects by irritating the large intestine.

The most common use of the gel remains in the treatment of minor burns and skin irritation. Early studies of its use generally were poorly controlled, and the data were incomplete and conflicting. These reports described the use of aloe in the treatment of radiation-induced dermatitis. [5] *A. barbadensis* extracts, in a murine model, have been shown to prevent ultraviolet radiation-induced suppression of contact and delayed hypersensitivity by reducing the production of interleukin-10. [6,7] However, a small study in 10 healthy volunteers did not support this observation. [8] Subsequent reports of the use of topical aloe in treating human and animal radiation burns suggested that although healing occurred, a clear advantage over aggressive wound care could not be established. However, in a study of 27 patients, aloe vera gel-treated partial thickness burn wounds healed in an average of 12 days as opposed to the vaseline-gauze-treated area of the same burn, which healed in an average of 18 days.[9]

The activity of aloe in treating burns may stem from its moisturizing effect, which prevents air from drying the wound. [10] Its activity also has been ascribed to its chlorophyll content and that of other minor components, but this has not been adequately substantiated. Current theory suggests that healing is stimulated by mucopolysaccharides in combination with sulfur derivatives and nitrogen compounds. Topical aloe treatment for burns has not been adequately documented. Two FDA advisory panels found insufficient evidence to show that *A. vera* is useful in the treatment of minor burns and cuts or vaginal irritations.

Other studies have generally found preparations containing aloe to accelerate wound healing. In patients who underwent dermabrasion, aloe accelerated skin healing by about 72 hours compared with polyethylene oxide gel dressing, [11] and aloe has been found to accelerate wound healing in patients with frostbite. [12] Aloe vera applied to debrided white or clear blisters and to intact hemorrhagic blisters every 6 hours, is part of the treatment protocol for frostbite. [13,14] Addition of oral pentoxifylline, in a study with rabbits, showed additional improvement in tissue survival after frostbite injury. [15] However, at least 1 study found that aloe applied as standard wound therapy delayed wound healing significantly (83 vs 53 days). [16]

Studies of the antibacterial activity of aloe have yielded conflicting results. One study using *A. vera* gel[17] found no activity against *Staphylococcus aureus*and *Escherichia coli*. Other tests found that *A. chinensis* inhibited growth of *S. aureus*, *E. coli*, and *Mycobacterium tuberculosis*, but that *A. vera* was inactive.[18] Further, these extracts lost their in vitro activity when mixed with blood. The latex has shown some activity against pathogenic strains. [19] Two commercial preparations exerted antimicrobial activity against gram-negative and gram-positive bacteria as well as *Candida albicans*when used in concentrations > 90%.[20] Aloe has been found to be more effective than sulfadiazine and salicylic acid creams in promoting wound healing and as effective as silver sulfadiazine in reducing wound bacterial counts. [21]

A double-blind, randomized, placebo-controlled trial demonstrated effectiveness of an aloe vera crude extract emulsion in reducing scaliness, pruritus, and the number of involved sites in 44 patients with seborrheic dermatitis.[22]

A double-blind, randomized, placebo-controlled trial demonstrated effectiveness of topical *A. vera* extract 0.5% in a hydrophilic cream in curing 25/30 vs 2/30 placebo-treated patients with psoriasis.[23]

Aloe-emodin is antileukemic in vitro[24] and has exhibited selective activity in vitro and in a murine model against neuroectodermal tumors (eg, neuroblastoma, Ewing sarcoma).[25] Other studies showed *A. vera* gel to be less cytotoxic[26] than indomethacin or prednisolone in tissue cultures. In vitro study of diethylhexylphthalate isolated from *A. vera*Linne demonstrated antileukemic and antimutagenic effects; however, results are conflicting when studied in rats. [27,28] The National Cancer Institute concluded that *A. vera* latex was not worthy of further study as a cancer cure. However, the US Department of Agriculture has approved *A. vera* as an adjunctive treatment for fibrosarcomas in dogs and cats.[29]

Other health claims are generally poorly documented. An emulsion of the gel was reported to cure 17 of 18 patients with peptic ulcers, but no control agent was used in this study.[30] Additionally, pretreatment with an *A. vera* extract reduced aspirin-induced injury in a study with rats.[31] Further human studies are needed to establish this potential protective property.

A. vera extract 0.5% in a hydrophilic cream was shown in a placebo-controlled study to shorten time to healing in male patients with first episodes of genital herpes.[32]

A gel containing *A. vera* extract 0.125%, allantoin 0.35%, and silicon dioxide was found effective in decreasing the duration of lesions associated with aphthous stomatitis.[33]

Lyophilized *A. barbadensis* combined with zinc acetate has been studied in rabbits for use as a vaginal contraceptive.[34]

In 1 laboratory experiment, rats injected with 1, 10, or 100 mg/kg SC doses of *A. vera* (without anthraquinones) daily for 7 days showed improved circulation and wound healing.[35] Arthritic mice were injected SC with a 150 mg/kg suspension of anthraquinones once a day for 13 days. This aloe extract caused a 48% inhibition of inflammation, caused by anthraquinone and cinnamic acid, and a 72% inhibition of arthritis, caused by anthranilic acid, which also had an anti-inflammatory effect. *A. vera* extracts have bradykininase activity in vitro.[36] Topical administration of aloe extracts reduced swelling in an animal model of inflammation by 29%.[37] Investigations have established that certain components of aloe inhibit the complement system, thereby reducing inflammatory responses.[38,39]

A small study has found that parenteral administration of aloe extract protects the liver from chemical injury and has been shown to ameliorate ALT levels dramatically in patients with chronic hepatitis.[40]

Only the dried latex is approved for internal use as a cathartic. In some cases, *A. vera* is sold as a food supplement, allegedly with FDA approval. FDA has only approved *A. perryi*, *A. vera*, *A. ferox*, and certain hybrids for use as natural food flavorings.[41]

TOXICOLOGY: Because aloe is used extensively as a folk medicine, its adverse effects have been well documented. Except for the dried latex, aloe is not approved as an internal medication. Anthranoid laxative (aloe-emodin) use has not been shown to be a risk factor for the development of melanosis coli, colorectal adenomas, or carcinomas.[42] Aloe-emodin and other anthraquinones may cause severe gastric cramping and aloe has been associated with congenital malformations,[43] thus its use is contraindicated in pregnant and nursing women,[44] children < 12 years of age,[45,46] patients with inflammatory bowel disease,[46] and elderly patients with suspected intestinal obstruction.[46] The external use of aloe has not been associated with severe adverse reactions. The majority of adverse effects are relatively mild and reversible upon cessation of application.[47] Reports of burning skin following topical application of aloe gel to dermabraded skin have been described.[48] Contact dermatitis from the related *A. arborescens*has been reported.[1] Erythema, edema, urticaria, and eczematous rash have also been reported following *A. vera* application.[49,50]

There has been 1 report that using the gel as standard wound therapy delayed healing. The gel may cause burning sensations in dermabraded skin, and redness and itching can also occur. Use caution with cosmetic products containing *A. vera* gel.[51]

SUMMARY: Aloe products derived from the latex of the outer skin are strong cathartics to be used with caution. Compounds derived from the inner gel intended for internal administration have not been shown to exert any consistent therapeutic effect. The effective topical use of the gel in the treatment of minor burns and wounds has not been established, although several human trials indicate a potential therapeutic benefit. Use of *A. vera*cream has been placed in the protocol for frostbite treatment.

PATIENT INFORMATION — Aloe

Uses: Aloe appears to inhibit infection and promote healing of minor burns and wounds, frostbite, and possibly of skin affected by diseases such as psoriasis and seborrheic dermatitis. Dried aloe latex is used, with caution, as a drastic cathartic.

Side Effects: There has been 1 report that using the gel as standard wound therapy delayed healing. The gel may cause burning sensations in dermabraded skin, and redness and itching can also occur. Use caution with cosmetic products containing *A. vera* gel.

Dosing: As a gel, *A. vera* may be applied externally ad lib. The resin product is cathartic at doses of 250 mg and is not recommended for internal use.[52]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALOE

ALPHA LIPOIC ACID

DATE OF ISSUE: OCT 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): 1,2-dithiolane-3-pentanoic acid; 1,2-dithiolane-3-valeric acid; 6,8-thioctic acid; alpha-lipoic acid; 5-(1,2-dithiolan-3-yl) valeric acid.

COMMON NAME(S): Alpha-lipoic acid, lipoic acid, thioctic acid, acetate replacing factor, biletan, lipoicin, thioctacid, thioctan.

PRODUCT(S): eg, Alpha Lipoic Acid Extract (Pharmacist's Ultimate Health, et al.).

SOURCE: Lipoic acid is a fat-soluble, sulfur-containing, vitamin-like antioxidant. It is not a true vitamin because it can be synthesized in the body and is not necessary in the diet of animals. Lipoic acid functions in the same manner as many B-complex vitamins. Good sources of lipoic acid are yeast and liver. [1,2] Other sources include spinach, broccoli, potatoes, kidney, heart, and skeletal muscle. [3]

HISTORY: In the 1930s, it was found that a certain "potato growth factor" was necessary for growth of certain bacteria. [3] In 1951, a fat-soluble coenzyme factor was discovered from work done on lactic acid bacteria. Reed et al, isolated this naturally occurring d-form and found it to be an important growth factor for many bacteria and protozoa. This compound was isolated and identified as "alpha lipoic acid." [4]

CHEMISTRY: Alpha lipoic acid is a molecule with 2 sulfur high-energy bonds. It functions as a coenzyme with pyrophosphatase in carbohydrate metabolism to convert pyruvic acid to acetyl-coenzyme A (Kreb's cycle) to produce energy. [1]

PHARMACOLOGY: Pharmacokinetics and bioavailability of different enantiomers of alpha lipoic acid (ALA) have been performed in 12 subjects. [5] Pharmacology of ALA has been studied in the areas of oxidation, diabetes, AIDS, cancer, and liver ailments.

Oxidation: ALA's antioxidant properties have been demonstrated. It has the ability to chelate metals and to scavenge free radicals. [6] ALA is easily absorbed and transported across cell membranes; thus, free radical protection occurs both inside and outside of cells. It is also water- and fat-soluble, which makes it effective against a broader range of free radicals than vitamin C (water-soluble) and vitamin E (fat-soluble) alone. [2] ALA administration also increases intracellular levels of glutathione, an important antioxidant. [7] ALA regenerates or recycles antioxidant vitamins C and E [3] but in one report, had no effect on vitamin E tissue concentration in animals, contradicting this effect. [8]

The body routinely converts ALA to dihydrolipoic acid, an even more powerful antioxidant. Both forms "quench" the dangerous peroxynitrite radicals, which are responsible in part for heart, lung, and neurological disease and inflammation as well. [9] In oxidative stress models such as ischemia, reperfusion injury, and radiation inury, ALA has been shown to be beneficial. [10,11]

Diabetes: ALA has been shown to be beneficial in type 1 and type 2 diabetes. ALA has prevented various pathologies associated with this disease, such as reperfusion injury, macular degeneration, cataracts, and neuropathy. [2,3,10,12] ALA reduced diabetic neuropathy in rats, which was improved in a dose-dependent manner. In part, the mechanism was suggested to be caused by reduction of the effects of oxidative stress. [12] ALA is approved in Germany to treat diabetic neuropathy. High doses (600 mg/day) improve this condition. [2]

ALA also improves the diabetic condition by improving blood sugar metabolism. It facilitates better conversion of sugar into energy. [2] In 13 non-insulin-dependent diabetes mellitus patients, ALA increased insulin-stimulated glucose disposal. Metabolic clearance rate for glucose rose by 50% compared with the control group. [13]

ALA improves blood flow to peripheral nerves and stimulates regeneration of nerve fibers. [2] A German study evaluating 800 mg/day ALA in diabetics with damaged autonomic nervous systems was compared against placebo. After 4 months, sympathetic systems showed improvement and autonomic nerve disorder decreased in the ALA group. [14]

Antioxidants in general may lead to regression of diabetic complications. When ALA was compared with antioxidant vitamin E, results failed to justify the higher cost of ALA over less-expensive and equally effective nutritional antioxidants. [2]

AIDS: Patients with HIV have a compromised antioxidant defense system, which may benefit from ALA's role as an effective antioxidant. [2] A small pilot study was conducted administering 150 mg ALA 3 times daily to HIV patients. It increased glutathione in all 10 patients and increased vitamin C in most patients as well. In addition, it improved the T-helper lymphocyte to T-helper suppressor cell ratio in 6 of 10 patients. [2]

ALA significantly inhibits replication of HIV by reducing the activity of reverse transcriptase, the enzyme which makes virus from DNA of lymphocytes. [2] In another report, ALA was found to also inhibit activation of "nuclear factor kappa-B," a substance involved in AIDS progression. [15]

Cancer: There is limited information available concerning ALA's role in cancer. Its mechanism of action and anticarcinogenic and cytoprotective effects have been addressed. [16] ALA administration, in conjunction with cyclophosphamide, lowered the toxic effects of this anticancer drug when tested in animals. [17]

Liver ailments: ALA has been used as an antidote to *Amanita* mushroom poisoning. [4] A review on mushroom intoxications employing ALA and other antidotes is available. [18]

Various: Various reports on ALA pharmacology include the following: Suppression of T-4 metabolism, exerting a lipid-lowering effect in rats, [19] treatment in Wilson's disease, [4] and cardiovascular disease. [3]

TOXICOLOGY: No adverse effects from ALA supplementation have been reported in either animal or human studies, even with large doses or extended use. [2] Its use in diabetes may warrant a reduction in dose of insulin or other oral diabetic medications. Close monitoring of blood sugar levels must be performed. In addition, ALA use may spare vitamins C and E, as well as other antioxidants. [2]

SUMMARY: ALA is a vitamin-like, "universal antioxidant." It functions to produce energy and has been studied in a number of areas. Its ability to scavenge free radicals has been clearly demonstrated. Its use in diabetes, AIDS, cancer, and liver ailments offer promising results such as reduction of pathologies associated with these diseases. No adverse events from ALA supplementation have been reported.

PATIENT INFORMATION — Alpha Lipoic Acid

Uses: Alpha lipoic acid has been used as an antioxidant for the treatment of diabetes and HIV. It also has been used for cancer, liver ailments, and various other conditions.

Side Effects: No adverse effects have been reported.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALPHA LIPOIC ACID

ALPINIA

DATE OF ISSUE: JUL 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Alpinia officinarum* Hance

COMMON NAME(S): China root, Chinese ginger, East Indian root, galangal, rhizoma galangae

BOTANY: Galangal is a reed-like perennial herb bearing stems that grow up to 3 feet high and that are covered by sheaths of narrow lanceolate leaves. Its inflorescence is a short raceme of white flowers which are veined and shaded in dull red. The plant has been cultivated for the rhizomes in the idland of Hainan off Southern China, and in coastal areas around Pak-hoi. Galangal rhizomes appear on the market as branched or simple rhizome fragments and show wavy annulations of the leaf bases. These are reddish-brown in color and have an aromatic, spicy and pungent odor and flavor. [1]

HISTORY: The rhizomes of galangal and its derivatives have long been used for its aromatic stimulant, carminative and condiment properties much like ginger (the dried rhizome of *Zingiber officinale*). Galangal oil is used to flavor French liqueurs and in some tobaccos. [1] The "ginger" of Thailand is obtained from *Alipinia galanga* Willd., a species related to galangal. Likewise, the large, ordinary, preserved ginger of China is also from *A. galanga*.[2] *A. galanga* (greater galangal), containing the volatile oil essence d'Amali, is used in China and northern India for various respiratory complaints in children, particularly bronchial catarrh (mucous membram inflammation).[3]

CHEMISTRY: Galanga contains a greenish-yellow volatile oil containing cineol, eugenol, sesquiterpenes, isomerides of cadinene, a resin containing galangol, kaempferide, galangin, as well as starch and other constituents.[1] Recent studies reveal sevel flavonoids,[4] acetoxychavicol acetate (*A. galanga*),[5] a cardiotonic principle (*A. oxyphylla*),[6] catecquic tannins, phenols, alkalokds and essential oils (*A. speciosa*),[7] nootkatone (*A. oxyphylla*),[8] dehydrokawain derivatives (*A. speciosa*),[9] diterpenes (*A. galanga*),[10] essential oils (*A. speciosa*),[11] nootkatol (*A. oxyphylla*),[12] starch (*A. galanga*),[13] monoterpenes (*A. galanga*),[14] the pungent principle 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone (*A. officinarum*).[15] The constituents in the essential oil of *A. khulanjan* M. Sheriff are 38.42% methylcinnamate, 20.21% cineol 1:8, 9.15% l-camphene, 8.75% l-borneol, 7.97% methylchavicol, 7.34% DELTA3-carene and 2.69% alpha-pinene. [16]

PHARMACOLOGY: Although the major uses of Alpinia involve its use as a carminative and condiment, there have been a number of recent interesting medical applications. Antifungals are found in *A. galanga*[5,10] and *A. officinarum*.[17] *A. speciosa* oils are also effective anitfungal agents, inhibiting 80% of the dermatophyte strains tested in a recent in vitro study. [18]

A. oxyphylla (bitter cardamon) significantly inhibits gastric lesions by 57% in rats; susquiterpenois nootkatone is suggested as the active principle. [8] Guaiacol, a cardiotonic principle, has been found in *A. oxphylla*.[6] Anti-ulcer activity is found in the seeds of *A. galanga*.[19]

A. speciosa extracts have shown diuretic and hypotensive properties.[7,20,21] The dehydrokawain derivatives from *A. speciosa*, 5,6-Dehydrokawain (DK) and dihydro-5,6-dehydrokawain (DDK), are antiplatelets due to their inhibition of thromboxane A2 formation. [9]

A. Galanga shows antitumor activity in mice.[22] and has been found to be moderately effective as an anthelmintic against the human *Ascaris lubricoides*.[23] Alpinia fructus (the fruit of *A. oxyphylla*) is effective as an anti-diuretic, anti-ulcerative and anti-dementia agent in rats. [24]

A. officinarum and ginger (*Zingiber officinalis*) roots contain potent inhibitors against prostaglandin biosynthesizing enzyme (PG synthetase). Gingerols and diarylheptanoids were identified as the active constituents. The structure of these components indicates that they might also be active again arachidonate 5-lipoxygenase, an enzyme of leukotriene (LT) biosynthesis. [25]

A. officinarum, used as an antirheumatic in Saudi traditional medicine, does not produce significant inhibition of carrageenan-induced inflammation. [26]

TOXICOLOGY: A hydroalcoholic extract of *A. speciosa*, injected intra-peritoneally (I.P.) in rats at a dose range of 100 to 1400 mg/kg, caused writhing, psychomotor excitation, hypokinesis and pruritus. The LD-50 by I.P. injection was 0.760 ± 0.126 g/kg, and 10.0 ± 2.5 g/kg by the oral route. Subacute toxicity studies in rats revealed an increase in transaminases and lactate dehydrogenase. Blood glucose, urea and creatinine were normal; a histopathological study of the liver, spleen, gut, lung and heart showed no changes. The extract caused a prolongation of sleeping time and a dose-dependent fall in blood pressure in doses of 10 to 30 mg/kg. [7]

Another toxicity study on *A. galanga* found no significant mortality or weight gain in rats. However, the *A. galanga* treated animals showed a significant rise in red blood cell levels, weight gain of sexual organs and increased sperm motility and sperm counts. No spermatotoxic effects were noted. [27]

Cytotoxic diterpenes have been found in the seeds of *A. galanga*.[10]

SUMMARY: The rhizomes of *Alpinia officinarum* have had long use as aromatic, stimulant, carminative and condiment agents. Numerous recent studies reveal the presence of many pharmacologically active compounds in various species of the genus. Among the newer activities revealed for the various *Alpinia* species are anthelmintic effects, antifungal properties, anti-ulcer effects in seeds, a cardiotonic property, diuretic and hypotensive effects, inhibition of gastric lesions, antiplatelet action, antitumor principles and inhibition against prostaglandin synthetase. Toxicity is generally low in the *Alpinia* species. Because most of these investigations deal with animal studies, much more is needed to verify these effects and provide proof of true clinical usefulness.

PATIENT INFORMATION — Alpinia

Uses: Beyond common use as a flavoring, aromatic stimulant, carminative, and traditional use to treat children's respiratory complaints, Alpinia species show promise as antifungals, hypotensives, enhancers of sperm count and motility, etc. Antitumor and anti-dementia effects have been observed in rodents.

Side Effects: Toxicity is low; injections can produce psychomotor excitation and the like.

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- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALPINIA

ALTHEA

DATE OF ISSUE: FEB 2000

REPLACES MONOGRAPH DATED: DEC 1991

SCIENTIFIC NAME(S): *Althaea officinalis* L. Family: Malvaceae

COMMON NAME(S): Altheae radix, althea, marshmallow

BOTANY: Althea is a perennial that grows to 5 feet in salt marshes and moist regions throughout Europe, western and northern Asia, and the eastern US. Its 3-lobed leaves are velvety, and the plant resembles hollyhock (*Althaea rosea*). The plant blooms from July to September. The family Malvaceae is known as the mallow family, and confusion may surround the common nomenclature and identification of the plants in this group. The root is collected in the fall, peeled of its brown corky layer, dried, and used in commerce. The leaves share many of the properties of the bark and have also been used in traditional medicine. [1,2]

HISTORY: Althea root has been recognized as a source of useful mucilage, which has been used for more than 2 millennia to treat topical wounds and as a remedy for sore throats, coughs, and stomach ailments. The mucilage is incorporated into ointments to soothe chapped skin and is added to foods in small quantities (˜ 20 ppm) to provide bulk and texture.[1] One report discusses Althea-type plants in a Neanderthal gravesite in Iraq. [3]

CHEMISTRY: The root contains 25% to 35% of mucilage,[1,4] but the content of the individual, purified mucilaginous polysaccharides is much lower. The mucilage content varies considerably with the season, being highest in the winter. A purified mucilage has been shown to be composed of L-rhamnose:D-galactose:D-galacturonic acid:D-glucuronic acid in a molar ratio of 3:2:3:3. [1] Asparagine (2%), sugars, pectin, and a tannin have also been identified in the root.[2,4] Fatty oil of althea has been addressed. [5] Flavonoid compounds of the leaves, flowers, and roots have also been described, including glucosidoesters and monoglucosides.[6,7]

PHARMACOLOGY: The mucilaginous properties of the althea root yield a soothing effect on mucous membranes. Althea reduces the transport velocity of isolated ciliated epithelium cells of the frog esophagus in vitro and may be useful in the management of coughs and colds because of its ability to protect mucous layers in the hypopharynx along with its spasmolytic, antisecretory, and bactericidal activity. [8] Althea extract and polysaccharide were tested for antitussive activity in cats. Although the polysaccharide component was more effective, both possessed cough-suppressing capabilities. [9]

Combinations of althea extracts with steroids have been used in the management of dermatologic conditions, [10,11] and the plant appears to possess anti-inflammatory activity that potentiates the effect of topical steroids. [12]

TOXICOLOGY: Althea extracts have not been generally associated with toxicity.

SUMMARY: Althea root and extracts have demulcent properties that make them useful in the management of sore throats and coughs along with topical dermal irritations. The plant has a long history of use and is not associated with any important toxicity.

PATIENT INFORMATION — Althea

Uses: Althea mucilage has been used to soothe dermal irritations, sore throats, and coughs. It appears to have bactericidal and anti-inflammatory properties.

Side Effects: Long used as a food additive, althea has no observed toxicity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ALTHEA

AMBRETTE

DATE OF ISSUE: MAY 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Abelmoschus moschatus* Medic. Family: Malvaceae

COMMON NAME(S): Ambrette, musk okra, muskmallow

BOTANY: This plant is cultivated for its seeds, which have a characteristic musk-like odor. The seeds are the source of ambrette, an aromatic oil used in perfumery. The plant grows to about 3 feet with showy yellow flowers with crimson centers. The plant is indigenous to India and is cultivated throughout the tropics. [1]

HISTORY: Several parts of the plant have been used throughout history, most notably the seed oil, which is valued for its fragrant smell. The oil is used in cosmetics and has been used to flavor alcoholic beverages, especially bitters, and coffee. [2] The tender leaves and shoots are eaten as vegetables and the plant is often grown as an ornamental.

Philippine native have used decoctions of the plant to treat stomach cancer, and extracts of the plant have bene used to treat such diverse ailments as hysteria, gonorrhea and respiratory disorders.[2]

CHEMISTRY: Distillation of the plant yields farnesol and furfural. The volatile oil is high in fatty acids, including palmitic and myristic acids. The ketone ambrettolide (a lactone of ambrettolic acid) is responsible for the characteristic muck-like odor. A variety of other related compounds have also been identified in quantities of less than 1% of the oil.[1]

The bark yields a fiber that is used to produce tough cloths. [2]

PHARMACOLOGY: Little is known about the pharmacologic activity of this plant. The related species *A. manihot* has been shown to limit the development of renal injury in rabbits with immune complex-induced glomerulonephritis, and *A. ficulneus* may contain substances that inhibit the development of the fetal sheep brain and that may impair the health of the ewe.[3]

TOXICOLOGY: Although the seeds were once considered to be stimulants with antispasmodic activity, the plant has been classified as an "Herb of Undefined Safety" by the FDA.[2] However, the extracts are classified as GRAS (Generally Recognized as Safe) for use in baked goods, candies and alcoholic beverages. Ambrettolide is reported to be nontoxic.[1]

Ambrette and related "nitro musks" are highly lipophilic and have been shown to persist in human mother's milk, presumably following absorption through the skin from dermally-applied cosmetics.[4]

Musk ambrette and musk ketone, both found in cosmetics and aftershaves, have been shown to cause photosensitivity and dermatitis in sensitive individuals. [5,6]

SUMMARY: Ambrette is commonly used as a fragrance in perfumes and cosmetics. The safety of ingesting the oil and other extracts of the seeds has been questioned and extracts and components of the plant are known to cause dermal irritation. In small quantities, however, ambrette is safe for internal consumption as a flavor for foods and drinks.

PATIENT INFORMATION — Ambrette

Uses: Ambrette has been used as a stimulant and as treatment for a variety of ills, from stomach cancer to hysteria. It is commonly used to scent cosmetics and to flavor foods and drinks.

Side Effects: Ambrette has been eaten as a vegetable. With the possible exception of seed extracts, ingestion of small amounts is considered safe. Ingestion or application of ambrette derivatives produces photosensitivity and dermatitis in some individuals.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AMBRETTE

AMMI

DATE OF ISSUE: FEB 2000

REPLACES MONOGRAPH DATED: JUN 1991

SCIENTIFIC NAME(S): *Ammi majus* L. and *A. visnaga* Lam. Family: Umbelliferae

COMMON NAME(S): Ammi, visnaga, bishop's weed

BOTANY: These annual plants grow to ˜ 120 cm in height, primarily in Egypt, other regions of the Middle East, and the Mediterranean. *A. visnaga* has been naturalized to parts of the southeastern US. It has a slightly aromatic odor and a very bitter taste. The drug product of ammi consists of the dried ripe fruits, typically of *A. visnaga*.

HISTORY: The plant has been cultivated for hundreds of years and was known by the Assyrians. *A. majus* was cultivated for the cut-flower trade, and both species have been used medicinally. These plants have been used in traditional medicine for millennia, particularly for the management of angina and respiratory diseases. Portions of the plant are made into toothpicks.[1] The fruits have been used in Egyptian folk medicine as diuretics and for the treatment of kidney and bladder stones.[2] Ammi has also been used for the traditional management of diabetes in Israel.[3]

CHEMISTRY: *A. visnaga* contains coumarins and furocoumarins (psoralens), the most important of which are khellin and visnagin. Khellin is present in fruits in a concentration of ˜ 1% and visnagin in a concentration of ˜ 0.3%.[4] Biosynthesis of khellin, visnagin, furocoumarin, and visnadin have been investigated.[5] Two furocoumarins, xanthotoxin (methoxsalen) and ammidin (imperatorin), from ammi fruits have been discovered, as well.[6] Solubility and dissolution studies of khellin have also been described.[7]

Numerous reports regarding ammi constituents are available evaluating their concentrations at various stages of maturity,[2,8] their presence in certain plant parts,[9] and interactions with different plant extracts.[10]

Various methods for determination of ammi components have been performed including the following: Micro method (khellin and visnagin),[11] TLC separation (khellin and visnagin),[12] spectrometric determination (khellin and bergapten),[13] HPLC (khellin and visnagin),[4,14] and a polarographic method (khellinum in fruits).[15] Recent improved analyses to determine ammi components have also been performed.[16,17]

Dihydroseselins have been determined from ammi fruits and extracts.[18] Genetically transformed ammi cultures have been evaluated.[19] In addition, marmesin, ammoidin, and ammidin have been characterized.[20] The fruit contains a small amount (< 0.03%) of a volatile oil.

PHARMACOLOGY: Khellin is commercially available in several multi-ingredient European proprietary preparations for oral and parenteral administration as a vasodilator. It is used in the management of bronchial asthma and angina pectoris.[6] The structure of cromolyn sodium, used in the management of allergic respiratory illness, was based on components derived from *A. visnaga*.[21] Lipophilic extracts from the plant, including the active components visnadin, khellin, and visnagin exhibited calcium channel blocking actions, with visnadin being the most active.[22] Acting at multiple sites, visnagin inhibited induced contractile responses in rat vascular smooth muscle.[23] Similarly, visnadine demonstrated peripheral and coronary vasodilatory activities in isolated rat vascular smooth muscle.[24]

Ammi extract showed marked antimicrobial activity against gram-positive bacteria and *Candida* species.[25] Constituent khellin from ammi fruit parts inhibited the mutagenicity of certain promutagens in *Salmonella typhimurium*.[26]

An ethnobotanical survey including 130 respondants reported ammi to be one of 16 species of Israeli medicinal plants used for diabetes.[3] However, literature searches found no clinical trials to support this hypoglycemic action.

Extracts of *A. majus* seeds fed to rats with experimentally-induced kidney stones showed no beneficial effect in terms of stone passage or size reduction.[27]

A combination product containing ammi demonstrated spasmolytic activity on guinea pig ileum in one report.[28] Extracts of the plants have been used to treat vitiligo and psoriasis.[2] When given orally in a dose of 50 mg 4 times daily, khellin increases HDL-cholesterol levels without affecting total cholesterol or triglyceride concentrations.[7]

TOXICOLOGY: *A. majus* has been associated with the development of severe ophthalmologic changes, particularly pigmentary retinopathy in photosensitized fowl.[29,30] Therefore, patients receiving *ammi* or its extracts should be monitored for ophthalmologic changes.

The furocoumarins (psoralens) may cause photosensitization and dermatitis.[31] One study reports 4 irritant compounds from ammi seeds and evaluates potential for contact dermatitis.[32]

In patients who received khellin to reduce blood lipids, nausea and vomiting were observed frequently. Elevated AST and ALT were also observed during therapy.[33]

SUMMARY: Plants of the genus *Ammi* have been used for thousands of years for the treatment of urologic, dermatologic, and respiratory symptoms. Clinical evidence supports their vasodilatory actions. The plant also possesses antimicrobial activity and inhibits certain mutagens. The use of khellin, a major component of the plant, is limited by toxicity.

PATIENT INFORMATION — Ammi

Uses: Ammi has been used for the treatment of urologic, dermatologic, and respiratory symptoms. The plant also possesses antimicrobial activity and inhibits certain mutagens.

Side Effects: Monitor for ophthalmic changes. The use of khellin is limited by toxicity (eg, elevated liver enzymes, phototoxicity, dermatitis).

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AMMI

ANDRACHNE

DATE OF ISSUE: SEP 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Andrachne cordifolia* Muell. and related species viz. *A. aspera* Spreng. and *A. phyllanthoides* (Nutt.) Muell. Arg. Family: Euphorbiaceae

BOTANY: The Andrachne genus has about 20 tropical American species and a few species in North Africa, Europe and elsewhere. [1] These are generally seen as shrubs and undershrubs, possessing many ascending leafy branches, in tropical and warm regions. The leaves are oval or obovate, while the flowers are monoecious, pedicellate and usually solitary in the axils. The fruit is dry, splitting into three 2-valved carpels. *A. phyllanthoides* is found in the dry hills and rocky barrens from Montana to Texas in May through October.[2] *A. aspera* is widely distributed throughout the Middle East.

CHEMISTRY: Two bisbenzylisoquinoline alkaloids, cocsuline and pendulin, have been isolated from the roots of *A. cordifolia*.[3] Previously, the two alkaloids were reported only from the Menispermaceae family.

PHARMACOLOGY: The plants in the genus are marginally used as medicinal plants in some countries. *A. aspera roots* are used for treating eye inflammation in Yemen, where pieces of the crushed roots are placed on the eyelids.[4] Some species also have pest-control properties.

TOXICOLOGY: No toxicological data have been recorded for this genus.

SUMMARY: Andrachne species have marginal folkloric use for treating eye inflammation. Some are used for controlling pests.

PATIENT INFORMATION— Andrachne

Uses: One species has been used to treat eye inflammation in Yemen. Others act as pest controls.

Side Effects: No data available.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ANDRACHNE

ANDROGRAPHIS

DATE OF ISSUE: JUL 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Andrographis paniculata (Burm.f.)*Nees Acanthaceae (acanthus family)

COMMON NAME(S): Kalmegh (Hindi), Chuanxinlian (Chinese), Kalupnath, Kiriat, Mahatita ("King of Bitters"), Alui, Bhunimba, Yavatikta (Sanskrit), Sambiloto (Malay)

BOTANY: *A. paniculata* is an erect annual herb native to India, China, and Southeast Asia. The square stem has wings on the angles of new growth and is enlarged at the nodes, while the small flowers are borne on a spreading panicle. It is widely cultivated in Asia. The above-ground parts are collected in the fall. The genetic variability of the species has been examined.[1]

HISTORY: The herb has been used primarily for liver complaints and to reduce fevers in the traditional medicine of India and China, as well as for its bitter tonic properties. A large variety of Indian herbal patent medicines are available in which *A. paniculata* is a prominent ingredient.

CHEMISTRY: The diterpene lactone andrographolide was first isolated as a major constituent[2] and later characterized as a lactone.[3,4] Its full structure was determined by Cava's group in the 1960s,[5,6] while X-ray crystallography later confirmed the structure.[7] A number of related minor diterpenes and their glycosides have since been identified.[8,9,10,11,12] Methods of analysis including high pressure liquid chromatography (HPLC),[13] and nuclear magnetic resonance (NMR)[14] have been published. A method for rapid isolation of andrographolide is also available.[15] When callus cultures of the plant were investigated, it was found that andrographolide and the other diterpenes were not produced. Instead, the sesquiterpenes paniculides A-C were found.[16] Other constituents of the plant include various flavones.[17]

PHARMACOLOGY

Liver: The aqueous extract of *A. paniculata*protected mice from liver damage induced by hexachlorocyclohexane,[18] while andrographolide protected rat hepatocytes from damage by acetaminophen.[19] Several isolated *Andrographis* diterpenes protected mice from liver damage by carbon tetrachloride or tert-butylhydroperoxide.[20] Both the extract and andrographolide induced hepatic drug metabolizing enzymes in rats, although the extract was more effective than the isolated compound.[21] An increase in bile flow was noted with administration of andrographolide to rats and guinea pigs, while it blocked the decrease in bile flow induced by acetaminophen.[22]

Immunostimulant and anti-infective: Both antigen-specific and nonspecific immune responses in mice were stimulated by andrographolide and an ethanolic extract, although the extract was more potent than andrographolide, suggesting that other constituents were also immunostimulants.[23] Inhibition of passive cutaneous anaphylaxis and mast cell stabilization was observed in studies of the purified diterpenes in rats.[24] A small clinical study found the extract to shorten the duration of common colds and to reduce symptoms.[25] Extracts of *Andrographis*have shown modest activity in vitro against HIV;[26,27,28] however, a phase ? study of andrographolide showed no effect on viral replication, while adverse effects required interruption of the trial after 6 weeks.[29] Succinoylated derivatives of andrographolide have been studied for their protease inhibitory properties, which were suggested to be involved in the anti-HIV activity in vitro.[30] Activity in antimalarial screens has also been noted for *Andrographis* extracts.[31,32]

Other: The extract of *A. paniculata* has been shown to block *E. coli* enterotoxin-induced secretion in rabbit and guinea pig models of diarrhea.[33] Andrographolide and 3 other related diterpenes were responsible for this action.[34] An ethanol extract of *Andrographis*reversed elevation in blood glucose caused by streptozotocin in rats.[35] Two purified *Andrographis*diterpenes stimulated nitric oxide release from cultured human endothelial cells, an effect linked to their hypotensive effect in rats.[36] Several fractions of *Andrographis* were shown to reduce mean arterial blood pressure in rats, although andrographolide was not active in this model.[37]

A water soluble extract of the plant was reported to delay death from cobra venom in mice, in line with its folk use for snakebite in India.[38] Andrographolide has demonstrated anti-inflammatory effects in several cellular systems, including prevention of phorbol ester-induced reactive oxygen species and *N*-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced adhesion in rat neutrophils[39] and inhibition of TNF-induced upregulation of intercellular adhesion molecule-1 (ICAM-1) expression and monocyte adhesion.[40] Additionally, *Andrographis* extract blocked rat vas deferens voltage-gated calcium channels[41] and induced cell differentiation in mouse myeloid leukemia cells, as did several diterpenes from the extract.[42] The diversity of pharmacologic activities observed for extracts of *Andrographis* and its diterpenes begs the question of pharmacologic specificity, which more studies will clarify.

TOXICOLOGY: *Andrographis* extracts are not acutely toxic, but the male reproductive toxicology of *Andrographis* has been studied. Reported infertility in rats led to a subchronic 60-day study in male rats that showed no changes in testicular weight, histology, or testosterone levels.[43] However, detailed studies with purified andrographolide in rats over 48 days have shown decreases in sperm counts and motility, linked to disruption of spermatogenesis.[44]

SUMMARY: *Andrographis* is official in both the Indian and Chinese Pharmacopeias. *A. paniculata*is a bitter-tasting medicinal plant widely used in India and China for a variety of purposes (eg, antipyretic, anti-inflammatory, immunostimulant). It has been touted as an "Indian echinacea" in herbal supplement marketing. A few human clinical studies tentatively support its use in colds and fevers. Trials in AIDS have not been promising; however more research is required to substantiate these initial findings. Testicular toxicology questions remain to be answered.

PATIENT INFORMATION— Andrographis

Uses: *Andrographis* has been used for liver complaints and fevers and as an anti-inflammatory and immunostimulant. In clinical trials, *Andrographis* extract shortened duration and reduced symptoms of colds.

Side Effects: Male reproductive side effects have been studied. In rats, *Andrographis* decreased sperm count and motility.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ANDROGRAPHIS

ANGELICA

DATE OF ISSUE: DEC 2000

REPLACES MONOGRAPH DATED: NOV 1995

SCIENTIFIC NAME(S): *Angelica archangelica* L., synonymous with *Archangelica officinalis* Hoffm. Family: Apiaceae (carrots)

COMMON NAME(S): European angelica, Echt engelwurz (German)

BOTANY: Angelica is a widely cultivated, aromatic biennial, northern European herb with fleshy, spindle-shaped roots, an erect stalk, and many greenish-yellow flowers arranged in an umbel. The seeds are oblong and off-white. It is similar to and sometimes confused with the extremely toxic water hemlock, *Cicuta maculata*.

There are several recognized varieties of *A. archangelica*, wild and cultivated. In the US, *A. atropurpurea* L. is often cultivated in place of the European species.

HISTORY: Angelica has been cultivated as a medicinal and flavoring plant in Scandinavian countries since the 12th century and in England since the 16th century. The roots and seeds are used to distill about 1% of a volatile oil used in perfumery and as a flavoring for gin and other alcoholic beverages. The candied leaves and stems are used to decorate cakes. The oil has been used medicinally to stimulate gastric secretion, treat flatulence, and topically treat rheumatic and skin disorders.

CHEMISTRY: The volatile oil contains many monoterpenes; ß-phellandrene is the principal component of var. *angelica*, while sabinene is the most abundant monoterpene of var. *sativa*.[1] Sesquiterpenes are also numerous in the oil; a-copaene and other tricyclic sesquiterpenes are characteristic constituents. [2] Supercritical fluid extraction has been studied as an alternative method of extracting angelica volatiles. [3] The shelf life of the root is limited because of the loss of the volatile oil while in storage.

The small organic acid, angelic acid, was the first compound purified from the root in 1842. [4] 15-pentadecanolide (*Exaltolide*) is a fatty acid lactone constituent of the root with a musk-like odor, used as a fixative in perfumes.[5]

As with most of the many species of angelica, *A. archangelica* contains a wide variety of coumarins and their glycosides. The angular furanocoumarins, archangelicin [6] and angelicin,[7] and congeners[8] are present in the roots, and many glycosides and esters of linear furanocoumarins have also been reported.

A trisaccharide, umbelliferose, was originally isolated from angelica roots. [9]

PHARMACOLOGY: Angelic acid was formerly used as a sedative. The angular furanocoumarin angelicin has also been reported to have sedative properties, although recent experimental evidence of this is limited. The carminative action of the volatile oil is because of an unremarkable monoterpene content. Angelica root oil was preferentially relaxant on tracheal smooth muscle preparations compared to ileal muscle. [10] The oil had no effect on skeletal muscle in a second study.[11] The calcium-blocking activity of angelica root has been examined relative to solvent used in extraction, and furanocoumarins were identified as the likely active species. [12] The root oil has been found to have antifungal and antibacterial activity. [13]

INTERACTIONS: Theoretically, there is a possible increased risk of bleeding when using angelica root concurrently with warfarin. The additive or synergistic effects of courmarin or coumarin derivatives possibly may be present in angelica root. [14,15] Because warfarin has a narrow therapeutic index, it would be prudent to avoid concurrent use.

TOXICOLOGY: The linear furanocoumarins are well-known dermal photosensitizers, while the angular furanocoumarins are less toxic. [16] The presence of linear furanocoumarins in the root indicates that the plant parts should be used with caution if exposure to sunlight is expected. The coumarins are not important constituents of the oil, which therefore gives the oil a greater margin of safety in that respect. However, poisoning has been recorded with high doses of angelica oils.

SUMMARY: Angelica and its oils have been used as digestive aids for many years in Europe. At high doses, the oils can be toxic, and furanocoumarins in the plant can cause photodermatitis.

Angelica root is official in the German and Austrian pharmacopoeias and is listed as approved in the German Commission E monographs for GI disorders, although the leaf and seed are unapproved. It was official in the *United States Pharmacopeia* and the *National Formulary* from 1820 to 1936. It is monographed in the *British Herbal Pharmacopeia*, (vol. 2), and in the *WHO Selected Medicinal Plants* (vol. 2). An *American Herbal Pharmacopoeia* monograph is in process. Angelica root and seed oil is listed as Generally Recognized as Safe (GRAS) for food use in the United States. [17]

PATIENT INFORMATION — Angelica

Uses: Often used as a flavoring or scent, angelica has been used medicinally to stimulate gastric secretion, treat flatulence, and topically treat rheumatic and skin disorders; however, there is little documentation to support these uses.

Interactions: Avoid using angelica root concurrently with warfarin.

Side Effects: Furanocoumarins in the plant may cause photodermatitis. Poisoning has been reported with high doses of angelica oils.

Dosing: Angelica root typically is given at doses of 3 to 6 g/day of the crude root. [18]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ANGELICA

ANISE

DATE OF ISSUE: JAN 1998

REPLACES MONOGRAPH DATED: OCT 1990

SCIENTIFIC NAME(S): *Pimpinella anisum* L. Family: Umbelliferae (Apiaceae). In some texts, anise is referred to as *Anisum vulgare* Gartner or *A. officinarum* Moench. Do not confuse with the "Chinese star anise" (*Illicium verum* Hook. filius. Family: Magnoliaceae).

COMMON NAME(S): Anise, aniseed, sweet cumin

BOTANY: Anise is an annual herb that grows 1 to 2 feet and is cultivated widely throughout the world. [1] The flowers are yellow, compound umbels. Its leaves are feather-shaped. The 2 mm long, greenish-brown, ridged seeds are used for the food or the drug. They are harvested when ripe in autumn. [2] Aniseed has an anethole-like odor and a sweet, aromatic taste,[3] described as "licorice-like," which has led to traditional use of anise oils in licorice candy. [1]

HISTORY: Anise has a history of use as a spice and a fragrance. It has been cultivated in Egypt for at least 4000 years. Recordings of its diuretic use and treatment of digestive problems and toothache are seen in medical texts from this era. In ancient Greek history, writings explain how anise helps breathing, relieves pain, provokes urine and eases thirst.[2] The oil has been used commercially since the 1800s. The fragrance is used in food, soap, creams and perfumes. Anise is often added to licorice candy or used as a "licorice" flavor substitute; it is a fragrant component of anisette.

CHEMISTRY: Anise oil (1% to 4%) is obtained by steam distillation of the dried fruits of the herb. The highest quality oils result from anise seeds of ripe umbels in the central location of the plant. [4] A major component of the oil is trans-anethole (75% to 90%), responsible for the characteristic taste and smell, as well as for its medicinal properties.[3,5,6] The cis-isomer is 15 to 38 times more toxic than the trans-isomer.[7] Spectrophotometric determination of anethole in anise oil has been performed.[8]

The volatile oil also has related compounds that include estragole (methyl chavicol, 1% to 2%), anise ketone (p-methoxyphenylacetone) and betacaryophyllene. In smaller amounts are anisaldehyde, anisic acid, limonene, alpha-pinene, acetaldehyde, p-cresol, cresol and myristicin (the psychomimetic compound previously isolated from nutmeg).[3,9,10,11] Oil of *Feronia limonia* has some similarity to anise oil and may be used as a substitute.[12]

Other constituents include coumarins such as umbelliferone, umbelliprenine, bergapten and scopoletin. Lipids (16%) include fatty acids, beta-amyrin, stigmasterol and its salts.[1,11] Flavonoids in aniseed include flavonol, flavone, glycosides, rutin, isoorientin and isovitexin, [11] protein (18%) and carbohydrate (50%). Terpene hydrocarbons in the plant have also been described.[13]

PHARMACOLOGY: Anise is widely used as a flavoring in all food categories including alcohols, liqueurs, dairy products, gelatins, puddings, meats and candies. [1] It is sold as a spice, and the seeds are used as a breath freshener. [7] The essential oil is used medicinally as well as in perfume, soaps and sachets. [1,5] The oil, when mixed with sassafras oil, is used against insects. [5] Applied externally, the oil has been used for lice and scabies. [2] As a skin penetration enhancer, anise oil has little activity compared with eucalyptus oil and other,. [14] but topical application of the constituent bergapten, in combination with ultraviolet light has been used in psoriasis treatment.[11]

Pharmacological effects of anise are mainly caused by anethole, which has structural similarities to catecholamines (eg, adrenaline, noradrenaline, dopamine). [11] Sympathomimetic-type effects have been attributed to anethole in at least 1 report.[15]

Anise is well known as a carminative and an expectorant. Its ability to decrease bloating and settle the digestive tract is still used today, especially in pediatrics. In higher doses, anise is used as an antispasmodic and an antiseptic for cough, asthma and bronchitis. [2,3,5,11]

Anise has also been evaluated for its antimicrobial action against gram-negative and gram-positive organisms. [16] Constituent anethole also inhibits growth of mycotoxin producing *Aspergillus*in culture.[1] Anise is used in dentifrices as an antiseptic and in lozenges and cough preparations for its weak antibacterial effects. [1,7] A German report testing aromatic waters (including anise) on the growth and survival of *Pseudomonas aeruginosa* has been published.[17] Anise has been tested for odor preference in rats[18] and dietary preference in cows.[19] Anise has promoted iron absorption in rats, suggesting possible use as a preventative agent in iron deficiency anemia.[20]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Anise oil has GRAS status and is approved for food use. The acute oral LD-50 of the oil in rats is 2.25 g/kg. No percutaneous absorption of the oil occurred through mouse skin within 2 hours.[21] The oral LD-50 of anethole is 2090 mg/kg in rats; rats fed a diet containing 0.25% anethole for 1 year showed no ill effects, while those receiving 1% anethole for 15 weeks had microscopic changes in hepatocytes. [7]

The German commission E monograph lists side effects of anise as "occasional allergic reactions of the skin, respiratory tract and gastrointestinal tract." [3] When applied to human skin in a 2% concentration in petrolatum base, anise oil produced no topical reactions. The oil is not considered to be a primary irritant. However, anethole has been associated with sensitization and skin irritation and may cause erythema, scaling and vesiculation. [10] Anise oil in toothpaste has been reported to cause contact sensitivity, cheilitis and stomatitis.[7] The constituent bergapten may cause photosensitivity.[11] As mentioned, the cis-isomer of anethole is 15 to 38 times more toxic to animals than the trans-isomer, their relative content being dependent on plant species. [1,7] Ingestion of the oil in doses as small as 1 ml may result in pulmonary edema, vomiting and seizures.[22] Large doses may interfere with anticoagulant and MAOI therapy. Anethole's (and its dimers') estrogenic activity may alter hormone therapy (eg, contraceptive pills). Aniseed is a reputed abortifacient. Excessive use is not recommended in pregnancy. [2,11]

The mycoflora of anise seed has been evaluated, making it possible to isolate 15 fungal genera, 78 species and six varieties, including *Aspergillus*, *Penicillium* and *Rhizopus*.[23] Naturally occurring mycotoxins are also present in TLC analysis of anise spice extract. [24] Gamma radiation has inhibited mold growth on anise in humid conditions.[25]

SUMMARY: Anise oil is a common fragrance, flavorant and spice. It has a history of uses in traditional medicine. It has carminative, antimicrobial and expectorant effects and may also be useful for psoriasis and iron deficiency anemia. Anise may cause occasional skin, respiratory and GI allergic reactions in sensitive individuals.

PATIENT INFORMATION — Anise

Uses: Anise has been used as a flavoring in alcohols, liqueurs, dairy products, gelatins, puddings, meats and candies and as a scent in perfumes, soaps and sachets. The oil has been used for lice, scabies and psoriasis. Anise is frequently used as a carminative and expectorant. Anise is also used to decrease bloating and settle the digestive tract in children. In high doses, it is used as an antispasmodic and an antiseptic and for the treatment of cough, asthma and bronchitis.

Interactions: Anise may interfere with anticoagulant, MAOI therapy and hormone therapy.

Side Effects: Anise may cause allergic reactions of the skin, respiratory and GI tract. Ingestion of the oil may result in pulmonary edema, vomiting and seizures. It is not recommended for use in pregnancy.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ANISE

APPLE

DATE OF ISSUE: JAN 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Malus sylvestris* Mill. Family: Rosaceae

COMMON NAME(S): Apple

BOTANY: The apple is a deciduous tree with simple clusters of flowers. The fruit is termed a "pome." Apple trees are widely cultivated throughout the temperate climates of the world and the fruit is broadly available in commercial markets. [1] More than 1000 cultivars of apple have been identified. [2]

HISTORY: The apple has long been recognized as a valuable food. Its uses in traditional medicine have been varied, including the treatment of cancer, diabetes, dysentery, fever, heart ailmetns, scurvy and warts. [3] Apples are also said to be effective in cleaning the teeth. The fruit juice is drunk fresh, fermented as cider or as apple brandy. The wood of the apple tree is valued as a firewood.

CHEMISTRY: Apple leaves, bark and root contain an antibacterial substance (phloretin), which is active in vitro in low concentrations. [3] Hydrogen cyanide (HCN), present in the form of a cyanogenic glycoside (amygdalin), is found in the seeds. [1,3] In addition, the seeds contain a yellow semi-drying oil (Glucoside phlorizin with the odor of bitter almonds.

The fruit contains up to 17% pectin and pectic acids. A variety of other components, many of them with aromatic qualities, are found in apples, including tannins, quercetin, alpha-farnesene, shikimic acid and chlorogenic acid. [3]

PHARMACOLOGY: The apple is often eaten to alleviate contipation or to control diarrhea. Both therapeutic effects appear to be related to the fruit's pectin content. Pectin absorbs water in the gastrointestinal tract and swells to a gummy mass. As such, it can provide bulk and moisture to hardened stools, or aid in producing formed stools by adding bulk in the presence of diarrhea.

The antibacterial phloretin is active agains some gram-positive and gram-negative pathogens. [4] Extracts of the related *M. sativa* have been shown to be active against *Vibrio cholerae*. [5]

TOXICOLOGY: Because of their HCN content, apple seeds should not be ingested in large quantities. (A small number of seeds, however, may be ingested without symptoms). [1] Large amounts of seeds have the potential for toxicity. One recurring report cites the case of a man dying of cyanide poisoning after ingesting a cupful of apple seeds. [3] Because cyanogenic glycoside must be hydrolyzed in the stomach in order to release cyanide, several hours may elapse before symptoms of poisoning occur. [1]

SUMMARY: The apple is a widely cultivated fruit that has been used as a food for thousands of years. It has also been used in traditional medicine for a variety of applications; the most consistent pharmacologic effect appears to be related to the fruit's pectin content, which helps regulate bowel consistency.

PATIENT INFORMATION — Apple

Uses: Traditional uses include treatment for cancer, diabetes, fever, heart ailments, scurvy, and warts. Leaves, bark, and root contain antibacterials active in low concentrations. The large pectin content makes the fruit valuable for both constipation and diarrhea.

Side Effects: The seeds, which contain hydrogen cyanide, should not be consumed in large quantities.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    APPLE

APRICOT

DATE OF ISSUE: AUG 1997

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Prunus armeniaca* L. (Rosaceae)

COMMON NAME(S): Apricot, Chinese almond

BOTANY: Apricots grow on trees up to 30 feet in height. The plant's leaves are oval and finely serrated. The five-petaled, white flowers grow together in clusters. Fruits vary in color from yellows and oranges to deep purples. They ripen in late summer.

The apricot is native to China and Japan but is also cultivated in warmer temperate areas of the world, mainly the regions including Turkey through Iran, Southern Europe, South Africa, Australia and California. There are many varieties and species of apricot, differing in flavor, color and size. [1,2,3,5]

HISTORY: In India and China, the apricot has been used for over 2000 years. During the 2nd century AD, a physician, Dong Feng, is said to have received his payment in apricot trees. There are also biblical references to the plant. [1,2]

The Greeks wrongly assumed the apricot to have originated in Armenia, hence its botanical name " *Prunus armeniaca*." The Romans termed the fruit "praecocium" meaning "precocious," referring to the fruit's early ripening. From this, the name "apricot" evolved. [5]

CHEMISTRY: Acids present in apricot fruits include malic, citric, tartaric, quinic, succinic, acetic, caffeic, p-coumaric and ferulic. [1,3]

The cyanogenic glycoside amygdalin also present in the plant has been determined from seeds, using gas chromatography. [6] Cyanide content in kernels varies from 2 to 200 mg/100 g.[3] Kernels contain up to 8% amygdalin, which yields laetrile and hydrocyanic acid. [2]

Sugars present in apricot include xylose, glucose, fructose and sorbitol. [1] Araginose and galactose have been detected by thin layer chromatography (TLC). [6] Vitamins include K, C, ß-carotene, thiamine, niacin and iron. [1]

Other constituents in apricot include tannins (bark), volatile essences (myrcene, limonene, p-cymene, geranial and others), cholesterol, flavonols and pectin (fruits).[1,2,3] The apricot gum has been studied in tablet and emulsion preparations. [7] Tablets prepared with apricot gum are comparable with those made with acacia gum.[8]

PHARMACOLOGY: Apricots are usually eaten as a fruit, either fresh or dried, made into jams and jellies or alcoholic beverages. The seeds are used like almonds by Chinese and Afghan cultures. The oil (apricot kernel oil) is also used. Its use in food, flavorings, confection, juices, jams, etc. is common. Some cultures use certain varieties of apricot kernels as almonds. [1,3]

In very small amounts, the toxic prussic acid (hydrogen cyanide) present in apricot kernels is prescribed in Chinese medicine for asthma treatment, cough and constipation.[2] Decoction of the plant's bark serves as an astringent to soothe irritated skin. [2] The oil is used in cosmetics or as a pharmaceutical vehicle. [1,2] Other folk medicine uses of apricot include treatment of hemorrhage, infertility, eye inflammation and spasm. [1] Apricot kernel paste may help eliminate vaginal infections. [2]

Laetrile, a semi-synthetic derivative of the naturally occuring "amygdalin," has been used (during late '70s, early '80s) in a highly controversial treatment for cancer. [2,3] A theory claimed that laetrile, when metabolized by the enzyme beta-glucosidase, released toxic cyanide. The enzyme was said to be most prevalent in tumor tissue (as opposed to normal tissue). As a result, this reaction was believed to destroy mainly cancer cells. It was later proven that both cancerous and normal cells contained only trace amounts of this enzyme. Although the treatment may have had slight activity in some cases, it was not as valuable as once thought. [4] A report in 1980 concluded laetrile to be ineffective in cancer treatment. Other proposed theories of laetrile in cancer treatment have not been substantiated by scientific evidence.[1,2,3]

TOXICOLOGY: Excess ingestion of apricot fruit may cause bone and muscle harm, blindness, hair loss and reduction in mental capacity. [1] Contact dermatitis has been reported from apricot kernels. Kernel ingestion may be teratogenic as well. [3]

Apricot kernel ingestion is a common source of cyanide poisoning, with over 20 deaths reported. [3] Deaths are reported from as little as ingesting two kernels. [1] Extract of amygdalin and water extract of apricot kernel produced sedation, convulsion, hyperventilation and death in mice. [8] Amygdalin content in apricot pits varies and can be up to 8%. Wild varieties may contain 20 times the amount of cultivated apricot varieties. [1] Hydrolysis of amygdalin yielding the toxic hydrogen cyanide (HCN) is more rapid in alkaline pH (than acidic, in the GI tract), which can delay symptoms of poisoning. Symptoms of cyanide toxicity include: Dizziness, headache, nausea/vomiting; and quickly progress to palpitations, hypotension, convulsion, paralysis, coma and death, from 1 to 15 minutes after ingestion. Antidotes to cyanide poisoning include nitrite, thiosulfate, hydroxocobalamin and aminophenol. [3]

SUMMARY: The apricot, native to China and Japan, has become a popular fruit. Apricots contain acids, sugars, tannins and the cyanogenic glycoside amygdalin. Prussic acid (hydrogen cyanide), present in the kernels, has been used in Chinese medicine. Apricot has also been used for asthma, inflammation and infection. In the late 1970s, laetrile (a synthetic derivative of amygdalin) had been used for cancer treatment but was later found to be ineffective. Excess ingestion of apricot kernels causes cyanide poisoning in both animals and humans. The apricot kernel oil is used in cosmetics.

PATIENT INFORMATION— Apricot

Uses: Apricots are usually eaten as fruit. Apricot kernel oil is used in cosmetics. In Chinese medicine, it has been used for asthma, cough and constipation.

Side Effects: Excess ingestion of apricot fruit may cause bone and muscle damage, blindness, hair loss and reduction in mental capacity. Ingestion of apricot kernels causes cyanide poisoning.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    APRICOT

ARNICA

DATE OF ISSUE: OCT 1998

REPLACES MONOGRAPH DATED: FEB 1991

SCIENTIFIC NAME(S): *Arnica montana* L. In addition, other related species have been used medicinally including *A. sororia* Greene, *A. fulgens* Pursh., *A. cordifolia* Hook., *A. chamissonis* Less. subsp. *foliosa* (Nutt.) Family: Compositae or Asteraceae

COMMON NAME(S): Leopard's bane, mountain tobacco, mountain snuff, wolf's bane

BOTANY: Arnica is a perennial that grows from 1 to 2 feet.[1,2] Its oval, opposite leaves form a basal rosette close to the soil surface. It has bright yellow, daisy-like flowers.[1,2,3] The dried flower heads are the primary parts used from the plant. The rhizome is also used.[2,4] Arnica is native to the mountainous regions of Europe to southern Russia.[3,4] The unrelated plant, monkshood (*Aconitum* spp) is sometimes referred to as wolf's bane.

HISTORY: Internal and external preparations made from the flowering heads of arnica have been used medicinally for hundreds of years. Alcoholic tinctures were used by early settlers to treat sore throats, as a febrifuge, and to improve circulation. Homeopathic uses included the treatment of surgical or accidental trauma, as an analgesic, and in the treatment of postoperative thrombophlebitis and pulmonary emboli.[5] It has been used externally for acne, bruises, sprains and muscle aches, and as a general topical counterirritant.[6] Arnica has been used extensively in European folk medicine. German philosopher Johann Wolfgang von Goethe (1749 to 1832) was said to have drunk arnica tea to "ease" his angina.[2] Arnica's bactericidal properties were employed for abrasions and gunshot wounds.[7]

CHEMISTRY: A number of flavonoid glycosides have been identified in arnica.[8] Flavonoids (0.4% to 0.6%)[3] include betuletol, eupafolin, flavonol glucuronides hispidulin, isorhamnetin, luteolin, patuletin, spinacetin, tricin, 3,5,7,-trihydroxy-6,3',4'-trimethoxyflavone, kaempferol, quercetin,[9] and kaempferol and quercetin derivative,[10] jaceosidin, and pectolin-arigenin.[4] Isomeric alcohols include arnidiol and foradiol.[7,8]

Terpenoids in arnica include arnifolin, arnicolide,[2] sesquiterpenes (helenalin[9] and helenalin derivatives,[11] dihydrohelenalin, etc). Pseudoguaianolide helenalinmethacrylate, a helenalin ester, has been isolated from the flowers.[12]

Amines present in the plant are betaine, choline, and trimethylamine. Coumarins include scopoletin and umbelliferone.[9]

Carbohydrates such as mucilage and polysaccharides (ie, inulin) are found in arnica.[2] Two homogeneous polysaccharides, for example, include an acidic arabino-3,6-galactan-protein, and a neutral fucogalactoxyloglucan.[13] Further polysaccharide isolation has been performed on a group of water-soluble acidic heteroglycaines.[14]

Volatile oils (0.3% to 1%) may be obtained from rhizomes and roots or from flower parts (used in perfumery).[7] Constituents in the oil include thymol, its derivatives,[2] and fatty acids (palmitic, linoleic, myristic, and linolenic).[4] The fatty acid content in arnica leaf essential oil has been evaluated, as well.[15]

Other components found in arnica include bitter compound arnicin, caffeic acid,[7,9] carotenoids (alpha- and beta-carotene, cryptoxanthin, lutein),[4,9,16] phytosterols, resin, tannins,[2,4] and anthoxanthine.[7]

PHARMACOLOGY: Not only is arnica employed in hair tonics, antidandruff preparations, perfumery, and cosmetics, it is used in herbal and homeopathic medicines as, well.[4,7] The plant possesses a slight anti-inflammatory and mild analgesic effect, most likely due to the sesquiterpene lactones. Helenalin and dihydrohelenalin exert mild anti-inflammatory and antibacterial activity.[6,9] They expressed anti-inflammatory activity in mice and rats,[4] and in humans, as well. Arnica improved feelings of stiffness associated with hard physical exertion (vs placebo) when tested in 36 marathon participants in a double-blinded, randomized trial.[17] However, in another report, contradictory results were seen.

Patients who had impacted wisdom teeth removed received either metronidazole, arnica, or placebo. Metronidazole was more effective than arnica in controlling postoperative pain, inflammation, and healing. Patients receiving arnica had greater pain and inflammation than those receiving placebo.[18]

Arnica contains a group of polysaccharides with 65% to 100% galacturonic acid that can inhibit the complement system, thereby modifying the immune system reponse.[19] This polysaccharide displays marked phagocytosis enhancement in vivo.[13] Yet another compound stimulates macrophages to excrete tumor necrosis factor.[20] Arnica, as well as other plant polysaccharides, possesses significant immunostimulatory activity.[14,21] Phenolic compounds of arnica improved toxic liver injury in rats.[22]

Extracts of arnica blossoms have been used in traditional medicine to improve blood flow. The sesquiterpene lactones helenalin and 11-alpha, 13-dihydrohelenalin have been shown to inhibit platelet aggregation by interacting with platelet sulfhydryl groups, suggesting therapeutic potential for these compounds.[23] Arnica increases the rate of reabsorption of internal bleeding.[2] However, in one report, it was not shown that arnica had any significant impact on certain blood coagulation parameters in a randomized, controlled trial.[24]

A report on arnica's use in facial injury is available.[25]

Arnica has been used traditionally as a topical agent to improve wound healing. It has been used externally (eg, ointment, compress) for acne, boils, bruises, rashes, sprains, pains, and other wounds.[3,7] Constituent helenalin and related esters have strong antimicrobial activity.[3] It has bactericidal (against salmonella, for example)[9] and fungicidal activity, as well.[4,7] The plant also possesses counterirritant properties[9] due to constituents arnidiol and foradiol, two isomeric alcohols.[26]

Arnica has been used for heart problems[2,3,7] (as it contains a cardiotonic substance[9]), to improve circulation,[3] to reduce cholesterol,[3,7] and to stimulate the CNS.[7]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: The internal use of arnica and its extracts cannot be recommended. The plant is considered poisonous, and oral use should be avoided (or very strictly controlled).[2,3,9] Arnica irritates mucous membranes, causes stomach pain, diarrhea, and vomiting.[4,9] Gastroenteritis has occurred with high oral dosages; dyspnea and cardiac arrest may occur and result in death.[3] The flowers and roots of the plant have caused vomiting, drowsiness, and coma when eaten by children. Gastric lavage or emesis followed by supportive treatment is recommended.[27] A 1 oz tincture reportedly produced serious, but not fatal effects.[4]

The helenolide constituents of arnica are cardiotoxic, proven in animal experimentation.[3,9]

The plant's sesquiterpene lactones are responsible for its oxytocic activity. In folk medicine, arnica was used as an abortifacient because of these actions.[3]

Numerous cases of contact dermatitis related to arnica have been reported. Chemical and animal experimentation have proven the high sensitizing capacity of the

plant. Sesquiterpene lactones helenalin, helenalin acetate, and methacrylate are the primary "culprits" in this type of allergy. [28] Another report is available identifying the allergans in arnica.[29] Three cases of patients with occupational contact dermatitis to arnica have been reported. [30] A case report of a 65-year-old male (a garden hobbyist) suffered from chronic eczema on his face and hands related to arnica's sesquiterpene lactones. [31] Cases such as these and others confirm arnica's prevalence in this allergy class.

SUMMARY: Although arnica and its extracts have a long history of use, few studies suggest its extracts are clinically useful. Its use as a topical counterirritant and wound-healing stimulant continues. Internal consumption of arnica is not recommended, because it is considered poisonous. Numerous cases of contact dermatitis have been reported from the plant.

PATIENT INFORMATION— Arnica

Uses: Arnica and its extracts have been widely used in folk medicine. It is used externally as a treatment for acne, boils, bruises, rashes, sprains, pains, and other wounds. It has also been used for heart and circulation problems, to reduce cholesterol, and to stimulate the CNS.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: The plant is poisonous and ingestion can cause stomach pain, diarrhea and vomiting, dyspnea, cardiac arrest, and death. Contact dermatitis also has occurred.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ARNICA

ARTICHOKE

DATE OF ISSUE: DEC 2000

REPLACES MONOGRAPH DATED: JUNE 1999

SCIENTIFIC NAME(S): *Cynara scolymus* L., *C. cardunculus*, Family: Compositae or Asteraceae

COMMON NAME(S): Globe artichoke, garden artichoke, alcachofra (Brazil)

BOTANY: The artichoke is a member of the milk thistle family. It is a perennial herb, widely cultivated in the Mediterranean regions and adjoining parts of central Europe. This well-known plant grows to a height of approximately 2 meters. It has a strong, erect stem and its large leaves are lobed and gray-green. The edible flower bud is purple-green in color, and has scales or bracts that enclose it. They bloom from July to August. [1,2,3,4]

HISTORY: The artichoke has been cultivated for thousands of years.[1] In the first century AD, Dioscorides recommended applying mashed roots on the body to sweeten offensive odors.[2]

The artichoke was used as food and medicine by ancient Egyptians, Greeks, and Romans. The artichoke appeared in Europe in the 15th century. [4] The botanical name is derived in part from the tradition of fertilizing the plant with ashes, and partly from the Greek *skolymos*, meaning "thistle" from the spines found on the bracts (they are not leaves) that enclose the flower heads forming the edible portion of the plant. [5] The French have used artichoke juice as a liver tonic. The herb's abilities to break down fat and improve bile flow have been recognized. [6] Artichoke has been used traditionally to treat a variety of conditions including hepatic diseases, jaundice, dyspepsia, and chronic albuminuria. It has also been used as a diuretic and to manage postoperative anemia. [2] The flower head is cooked and eaten as a delicacy. The flower contains a sweetener that enhances flavor perception, while the leaves contain bitter principles that are used in the preparation of aperitif liqueurs.[7]

CHEMISTRY: Nutritionally, one large (100 g) artichoke contains 38 calories, 1 g fat, 5.8 g carbohydrates, and 3.4 g protein. [1] This protein contained phenylalanine, tyrosine, histidine, alanine, glycine, and others in one report. [8] In another report, aspartic and glutamic acids were abundant amino acids present, along with sugars. [9] Galactose is present in < 0.1 mg/100 g of artichoke in a report discussing diet in galactosemic patients. [10] Artichoke also contains fiber,[1,11] calcium, phosphorus, potassium, folic acid, vitamin C, niacin, thiamine, trace minerals,[1,4] and carotenoids.[12]

Acids present in artichoke consist primarily of acid alcohols, including glyceric, malic, citric, glycolic, lactic, and succinic acids. [13] Much of the pharmacologic activity of the leaves has been attributed to the presence of caffeoylquinic acid derivatives, mono- and di-caffeoylquinic acids, including chlorogenic, neochlorogenic, and cryptochlorogenic acids, luteolin, and cynarin. [14,15,16] HPLC determination of these derivatives has been performed. [17] The relative proportion of these compounds varies with the strain, age, and generation of the plant. [18,19] For example, germinating seeds of the artichoke have higher cynarin content than the leaves. [20] Caffeic acid specifically and these derivatives have been widely studied and percentages can vary depending on certain factors. [3,14,21,22] Hydroxymethylacrylic acid also has been isolated from artichoke.[23]

Bitter sesquiterpene principles such as geosheimin, cynaratriol, and cynaropicrin have been found from Cynara species. [24] Cynaropicrin content exists in highest content in young leaves, but not in root mature fruits and flowers. [14] Dehydrocynaropicrin, grossheimin,[3] grosulfeimin and related guaianolides,[25,26] and cynarolide[27] have been isolated from the plant. Flavonoids (0.1% to 1%), including flavone glycosides and rutin, are present in artichoke. [3,14,28] Flavonoid glycosides apigenin, luteolin, cynaroside, scolimoside, cosmoside, quercetin, isorhamnetin, maritimein, and others also have been reported. [29,30] Analysis of phenolic compounds in fresh vs cooked/canned artichoke has been performed.[31]

Volatile oils have been found in artichoke, including beta-selinene and caryophyllene as major sesquiterpenes, eugenol, phenylacetaldehyde, and decanal. [14] Analysis of volatile oil in artichoke from another report finds 32 compounds. [32] Fatty acid composition of oil has been investigated. [33] Artichoke is an ideal source for essential polyunsaturated fatty acids, containing stearic, palmitic, oleic, and linoleic (50%) acids. [34] Color and anthocyanic pigments in artichoke have been evaluated. [35]

Numerous enzymes, including oxidases, peroxidases, cynarase, and ascorbinase are present in artichoke. [7,14] Ribulose-1,5-diphosphate carboxylase has been investigated.[36,37] Artichoke polyphenol oxidase has also been found in the plant. [38,39] Milk-clotting proteinases, possibly aspartic proteinases, exist in artichoke as well.[40]

Other constituents in artichoke include phytosterols (taraxasterol), tannins, sugars, starch, and inulin. [14] At low temperatures, artichoke contains more inulin and less starch; at high temperatures, the opposite is observed.[41] L-asparagine was found in artichoke fluid. [42]

Overviews of artichoke constituents/preparations are available; however, they are written in German or Russian. They discuss chemical composition in review of major materials[43] and evaluate artichoke preparations, including freshly squeezed juice and dried preparations. [44,45,46] A report in English evaluated by HPLC, the active ingredients in artichoke and variations in compounds according to different parameters. [47]

PHARMACOLOGY: Artichoke possesses many properties, including antioxidant effects, hepatoprotective ability, GI soothing qualities, and cholesterol-lowering effects.

Antioxidant activity: The flavonoid constituents in artichoke (eg, luteolin) demonstrate antioxidant activity. [48] Flavonoids/Polyphenol fractions possess chemopreventive effects as well, as seen with mouse skin cancers.[49,50] Similarly, triterpene taraxasterol from artichoke was found to also markedly inhibit induced skin tumors in mice.[51] Flavonoid silymarin from the plant had similar actions. [52]

Antioxidant effects of artichoke in the liver have been numerously reported. Certain extracts have been demonstrated to be effective in regeneration of rat liver. [53,54] Later reports confirm artichoke extracts as having antioxidative and protective potential in rat hepatocytes. Constituents cynarin and caffeic acid specifically have been shown to be responsible for these effects.[55,56,57]

GI effects: GI effects of artichoke include beneficial actions in digestive and dyspeptic ailments, loss of appetite, and gallbladder problems. [2,3,15] Artichoke flavonoids and caffeoylquinic acids are responsible for these actions, including hepatobiliary dysfunction and digestive complaints. [58] Naturally occurring fructose-containing oligosaccharides in artichoke act as prebiotics in the gut. [59]

Cholesterol-lowering effects: Artichoke has been found to possess cholesterol-lowering effects. Leaf extracts were found to inhibit cholesterol biosynthesis. Constituents cynaroside and its aglycone luteolin were mainly responsible for this effect, while chlorogenic, caffeic dicaffeoylquinic acids, and cynarin demonstrated little or no inhibitory effects.[60,61] Another report also concluded the ineffectiveness of cynarin, demonstrating no hypolipidemic actions in 17 patients with familial type II hyperlipoproteinemia.[62] A prospective study investigating 143 patients with total cholesterol > 280 mg/dl reported that patients given 1800 mg dry extract/day vs placebo over a 6-week period experienced statistically significant changes in total and LDL cholesterol. Total cholesterol was decreased 18.5% vs 8.6% and LDL

cholesterol was reduced 22.9% vs 6.3% in patients using the dry artichoke extract vs placebo, respectively. Thus, dry artichoke extract was recommended to treat hyperlipoproteinemia, preventing atherosclerosis and coronary heart disease. [63]

Other uses: A review on artichoke leaf extract is available, discussing digestive, antioxidative, hepatoprotective, lipid-lowering, and other effects. [64]

Other reported effects of artichoke include analgesic/anti-inflammatory [65] and hypoglycemic.[25] The artichoke is a good source of nutrition, including protein and fiber.[1,8,9,11] Artichoke extracts also may exert mild diuretic activity. Cynarase has been used commercially to curdle milk during cheese-making processes, clotting milk at a dilution of 1 part in 150,000.[7]

Artichoke seed oil was suggested to be of use as a component in making soaps, shampoos, resins, and polishes. [66]

TOXICOLOGY: In a 143-patient study, no adverse events were reported from artichoke administration, indicating excellent tolerability of dry extract. [63] Frequent contact with artichoke and other compositae family plants; however, has caused allergic reactions in sensitive individuals. Reports of contact dermatitis [67] and urticaria syndrome from occupational contact with artichoke have been documented, identifying the responsible components as cynaropicrin and other sesquiterpene lactones.[67,68,69] One study in guinea pigs demonstrated no skin or eye irritation with one artichoke preparation. [70] Another article by the same authors found no injury or stimulating effects in gonad morphology caused by artichoke when administered to male rats. [71]

According to the German Commission E Monographs, contraindications to the use of artichoke include allergy to compositae family plants and any bile duct obstruction. Presence of gallstones warrants a physician's consultation. [15] Lack of toxicity data suggests limiting use of artichoke during pregnancy and lactation. [14]

SUMMARY: The artichoke is a well-known edible plant that has been used traditionally in herbal medicine. Its actions include antioxidant, hepatoprotective, GI, and cholesterol-lowering effects. The main adverse reaction is dermatitis in allergic people. Lack of toxicity data suggests limited use during pregnancy and lactation.

PATIENT INFORMATION— Artichoke

Uses: Artichoke has been used for its antioxidant and GI soothing effects. It also may have cytoprotective actions in the liver and hypocholesterolemic effects.

Side Effects: Artichoke can cause allergic reactions, most commonly dermatitis.

Dosing: Artichoke leaf extract at 1.5 g/day was found to lower serum cholesterol and triglycerides in a post-marketing survey study. [72]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ARTICHOKE

ASPARAGUS

DATE OF ISSUE: JUL 1995

REPLACES MONOGRAPH DATED: OCT 1988

SCIENTIFIC NAME(S): *Asparagus officinale* L. Family: Liliaceae

COMMON NAME(S): Garden asparagus

BOTANY: Asparagus is a dioecious perennial herb with scale-like leaves and an erect, much-branched stem that grows to a height of up to 3 meters. Asparagus is native to Europe and Asia and is widely cultivated. The part used as a vegetable consists of the aerial stems, or spears, arising from rhizomes. The fleshy roots and, to a lesser degree, the seeds have been used for medicinal purposes.

HISTORY: Asparagus spears are widely used as a vegetable and are frequently blanched before use. Extracts of the seeds and roots have been used in alcoholic beverages, with the maximum levels averaging 16 ppm. The seeds have been used in coffee substitutes, diuretic preparations, laxatives, remedies for neuritis and rheumatism, to relieve toothache, to stimulate hair growth and as cancer treatments. Chinese medicine has used them to treat parasitic diseases. Extracts are said to have served as contraceptives. Home remedies have employed the topical application of preparations containing the shoots and extracts to cleanse the face and dry acneiform lesions.

CHEMISTRY: Asparagus roots contain inulin and at least eight fructo-oligosaccharides. Two glycoside bitter principles, officinalisins I and II, were isolated from dried roots in yields of 0.12% and 0.075%, respectively. Other root components are beta-sitosterol, steroidal glycosides (asparagosides A to I, in order of increasing polarity) and asparagusic acid. The shoots have several sulfur-containing acids (asparagusic, dihydroasparagusic and S-acetyldihydroasparagusic); alpha-amino-dimethyl-gamma-butyrothetin, a glycoside bitter principle different from those in roots; flavonoids (rutin, quercetin and kaempferol); as well as asparagine, arginine, tyrosine, sarsasapogenin, beta-sitosterol, succinic acid and sugars. Asparagusic acid, and its derivatives, are plant growth inhibitors; they are also nematocidal (imparting resistance to several important plant parasite nematodes). [1]

Asparagus seeds contain large quantities of sodium hydroxide-soluble polysaccharides consisting of linear chains of beta-glucose and beta-mannose in a 1:1 ratio, 1 to 4 linked to alpha-galactose as a terminal group. [1] Seeds also contain three ribosome-inactivating proteins, in concentrations of 8 to 400 mg/100 g of starting material. These proteins, with molecular weights of about 30,000, have alkaline isoelectric points and inhibit protein synthesis by rabbit reticulocyte lysate. [2] Asparagus stalks contain folate and the folate conjugases asparagusate dehydrogenase I and II, as well as lipoyl dehydrogenase. Folate levels can be accurately measured only after inactivation of the conjugases. [3] Stalks may also contain residues of permethrin, an insecticide often applied to protect asparagus during growth. These residues peak about 3 days after insecticide treatment and then decline by about 85% by the seventh day. [4] Other herbicides applied during the growth of asparagus have been detected in commercial stock. [5]

PHARMACOLOGY: Asparagus roots have been used in diuretic preparations, but no data are available to substantiate this pharmacologic effect.

Ingestion of asparagus spears produces a characteristic pungent odor in the urine of some individuals within a few hours. [6] According to one report, the odor is produced by a combination of six sulfur-containing alkyl compounds: methanethiol, dimethyl sulfide, dimethyl disulfide, bis- (methylthio)methane, dimethyl sulfoxide and dimethyl sulfone. Possible precursors of these compounds are S-methylmethionine and asparagusic acid. [7] Other researchers attribute the urine odor to S-methylthioacrylate and S-methyl 3-(methylthio)thiopropionate. [8]

In one study, 43% of 800 volunteers had urine odor following asparagus ingestion. Production of the odor appears to be an autosomal dominant genetic trait that is evident throughout life. [9] A study of 307 volunteers found that 10% had the ability to smell high dilutions of urine from asparagus-fed individuals, suggesting that the ability to smell asparagus-tainted urine is also a specific trait. [10] A study of 19 volunteers confirmed that only some people have the ability to produce or detect the odor. [11] This may suggest a genetic composition to these traits.

Related species of Asparagus have demonstrated antiviral activity in vitro. [12] Asparagus juice has demonstrated in vitro antimutagenic activity [13] and cytotoxic saponins have been found in the plant. [14]

TOXICOLOGY: There are no reports of serious toxicity from the ingestion of asparagus or its extracts. There is one report of botulism poisoning following the ingestion of improperly home-preserved asparagus. [15]

SUMMARY: Asparagus is cultivated universally and used as a vegetable. The stalks are cooked and eaten, and extracts of the seeds and roots have been used as flavorings. Preparations of asparagus have been used in folk medicine of different nations, although there is little evidence to support any consistent pharmacologic effect. Asparagus is noted for its ability to produce a pungent odor in the urine of many persons consuming it.

PATIENT INFORMATION — Asparagus

Uses: The stalks are commonly eaten. Roots, seeds and extracts of these have been used as a treatment for varous ills and as a diuretic.

Side Effects: None known except for pungent odor in urine of almost half those who eat it.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ASPARAGUS

ASPIDIUM

DATE OF ISSUE: FEB 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Dryopteris filix-mas* (L.) Schott Family: Polypodiaceae

COMMON NAME(S): Aspidium, male fern, bear's paw, knotty brake, shield fern

BOTANY: *D. filix-mas* is a hardy ornamental fern.[1] It grows in dry terrain in rich woods and on rocky slopes. It is found throughout many areas of the United States.

HISTORY: The fern has been used in traditional medicine for the treatment of worm infections. The early physician Theophrastus recognized the value of the fern for treating tinea (ringworm) infections.[1] In Chinese medicine, extracts are used to treat recurrent bloody nose, heavy menstrual bleeding and wounds. The components of the plant have been used as veterinary vermifuges.

CHEMISTRY: The fern contains about 6% of an oleoresin. In addition, the plant is the source of albaspidin, filicic (filixic) acid, filicin, margaspidin, filmarone and more than two dozen additional chemically unique compounds.[1]

PHARMACOLOGY: Filicin and filmarone are active vermifuges and are particularly toxic to tapeworms. [1,2] Following ingestion of the drugs, tinea are expelled within hours; however, a purgative is typically ingested concomitantly with the vermifuge to aid expulsion. [3]

The oleoresin paralyzes intestinal voluntary muscle and the analogous muscles of the tapeworm, which is then readily eliminated by the action of the purgative. [1]

TOXICOLOGY: Large doses of the extracts are potentially toxic resulting in muscular weakness, coma and temporary or permanent blindness. [1] Even therapeutic doses are associated with adverse events.[2] Symptoms include headache, dyspnea, nausea, diarrhea, vertigo, tremors, convulsions and cardiac and respiratory failure.[1,2]

SUMMARY: Aspidium is no longer commonly used in the United States, although it had been listed in the US Pharmacopeia as late as 1965. [4] Some herbal enthusiasts may continue to find access to the extracts. While the evidence from traditional uses strongly indicates that extracts are potent vermifuges, their potential toxicity precludes any recommendation of their use.

PATIENT INFORMATION— Aspidium

Uses: A traditional vermifuge

Side Effects: Aspidium can produce adverse reactions, from headache to cardiac and respiratory failure.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ASPIDIUM

ASTRAGALUS

DATE OF ISSUE: MAY 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Astragalus membranaceus* Bunge, and *Astragalus membranaceus* var. mongholicus (Bunge) P.K. Hsiao, Family: Fabaceae (Beans)

COMMON NAME(S): Huang chi, huang qi, astragalus

BOTANY: The genus *Astragalus* is an enormous group of more than 2000 species distributed worldwide, commonly known as milk vetches. The Chinese species *A. membranaceus* and the related *A. mongholicus* are now thought to be varieties of the same species.[1] Both are perennial herbs native to the northern provinces of China and are cultivated in China, Korea, and Japan. The dried root is used medicinally. Astragalus roots are sold as 15- to 20-cm long pieces, which have a tough, fibrous skin with a lighter interior. Some products are produced by frying the roots with honey, although the untreated root itself also has a sweetish, licorice-like taste.

HISTORY: Astragalus root is a very old and well-known drug in traditional Chinese medicine, and is currently official in the Chinese Pharmacopeia. It is used in China principally as a tonic and for treatment of diabetes and nephritis. It is an important component of Fu-Zheng therapy in China, where the goal is to restore immune system function. There is extensive Chinese language literature on the drug.

CHEMISTRY: A PCR method for measuring astragalus content in a polyherbal preparation has been published. Markers for each component were developed using decamer oligonucleotide primers.[2] Hairy root culture of Astragalus have been established and found to produce cycloartane saponins. [3,4,5]

Astragalus root contains a series of cycloartane triterpene glycosides denoted astragalosides ? to V??, that are based on the genin cycloastragenol and contain from 1 to 3 sugars attached at the 3-, 6-, and 25-positions. [6,7,8,9] In the predominant astraglosides ? to ??? the 3-glucose is acetylated. Several saponins based on the oleanene skeleton have also been reported.[10] The aboveground parts of astragalus contain similar but distinct saponins in the cycloartane series. [11,12] and many other species of astragalus contain cycloartane saponins. [13]

A variety of polysaccharides have been reported from astragalus root. Astragalan ? is a neutral 36 kD heterosaccharide containing glucose, galactose, and arabinose, while astragalans ?? and ??? are 12 kD and 34 kD glucans, respectively. [1,14] Huang, et al., isolated 3 similar polysaccharides and an acidic polysaccharide, AG-2, as well.[1] Tomoda reported a complex 60 kD acidic polysaccharide, AMem-P with a high hexuroic acid content from *A. membranaceus*[15] and a similar but distinct 76 kD acidic polysaccharide, AMon-S from *A. mongholicus*.[16] Bombardelli and Pozzi patented polysaccharides known as astroglucans A-C from *A. membranaceus*.[17]

Isoflavan glycosides based on mucronulatol and isomucronulatol have been found in the roots of *A. membranaceus*.[9,18] Several products appear to use these compounds for standardization despite the lack of reported biological activity. In addition, the free isoflavones afrormosin, calycosin, formononetin, and odoratin have been isolated from the roots.[19,20]

A unique biphenyl was isolated from *A. membranaceus* var. mongholicus as an antihepatotoxic agent.[18]

PHARMACOLOGY: The most common use of astragalus root in herbal medicine in the US is as an immunostimulant to counteract the immune suppression associated with cancer chemotherapy. This use is based on several observations. The cycloartane saponins are capable of stimulating the growth of isolated human lymphocytes.[13] The polysaccharides astragalans ? and ?? were found to potentiate immunological responses in mice following IP administration, though not after oral administration.[14] The glycans AMem-P and AMon-S increased phagocytic indices on IP injection into mice. [15,16]

Aqueous extract of astragalus root stimulated phagocytosis of murine macrophages, and augmented proliferation of human monocytes in response to phytohemagglutinin, concanavalin A, and pokeweed mitogen. [21,22] In cells from cancer patients, which were comparatively resistant to such stimulation, astragalus extract also stimulated mononuclear cells. Using a graft-vs-host model, astragalus extract restored the GVH reaction in vivo for healthy and immune-suppressed patients.[23]

These in vitro and in vivo effects justify further human trials of the immunostimulant activity of astragalus root extracts in patients whose immune system has been suppressed by cancer chemotherapeutic drug regimens.

A second use of astragalus root in the US is for HIV infection. Such use must depend on a host-mediated response because the aqueous extract of astragalus had no direct effect on viral infectivity, [24] and little effect on viral reverse transcriptase. [25] A pilot trial of a Chinese herbal formula containing astragalus root was found to improve subjective measures and symptomatology; however, the number of subjects was too small to detect statistically meaningful effects.[26]

A series of reports from China claim that treatment with herbal mixtures including astragalus can induce seronegative conversion in a small fraction of HIV patients.[27,28] These reports need to be verified.

In view of revised opinions on the population dynamics of the HIV virus in infected humans, an attempt to stimulate T-cell proliferation may not be a realistic therapeutic objective because the turnover rate is already quite rapid. Nevertheless, improvement in subjective symptoms in the above study [26] cannot be ignored, and a larger clinical trial might confirm these effects as significant.

Astragalus is often recommended for the prevention of the common cold; however, there are no published clinical trials that support this use.

The bipyhenyl compound 4,4´,5,5´,6,6´-hexahydroxy- 2,2´-biphenyldicarboxylic acid 5,6:5´,6´-bis (methylene), 4,4´-dimethyl ether, dimethyl ester was isolated as the antihepatotoxic principle of astragalus root.[18] The isoflavones afrormosin, calycosin, and odoratin had antioxidant activity similar to butyl hydroxytoluene or alpha-tocopherol in several experimental models of air oxidation of lipids. [19,20]

Astragalus root saponins also have been found to have diuretic activity which was presumed to be caused by local irritation of the kidney epithelia. [29] Astragalus saponins showed anti-inflammatory and hypotensive effects in rats.[1]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: An astragalus hot water extract that had been boiled for 90 minutes was mutagenic in the Ames test in *S. typhimurium* TA98 when activated by S9 rat liver fractions. The activity was dose-dependent. In addition, the mutagenic activity was not removed by XAD-2 resin treatment. The same preparations given by IP injection at 1 to 10 g/kg produced chromosomal abberations in the bone marrow of mice, and increased the incidence of micronucleated cells in bone marrow. No attempt was made to isolate the mutagenic compounds responsible for these effects.[30]

The pharmacology and toxicology of the genus *Astragalus* have been reviewed.[31]

SUMMARY: Astragalus root is a well-known Chinese traditional medicine that may have use in the restoration of immune function after cancer chemotherapy. The active principles are primarily cycloartane saponins and polysaccharides. The root appears to be safe; however, an observation of mutagenicity in the Ames test must

be explored. Astragalus root is monographed by the World Health Organization, vol. 1. [32] An American Herbal Pharmacopeia monograph is nearing completion.

PATIENT INFORMATION— Astragalus

Uses: Astragalus root may have use in the restoration of immune function after cancer chemotherapy and for the treatment of HIV infection.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: There is no known toxicity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    ASTRAGALUS

AUTUMN CROCUS

DATE OF ISSUE: AUG 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Colchicum autumnale* L. Other species used medicinally have included *C. speciosum* Steven and *C. vernum* (L.) Ker-Gawl. Family: Liliaceae

COMMON NAME(S): Crocus, autumn crocus, fall crocus, meadow saffron, mysteria, vellorita, wonder bulb

BOTANY: These plants are members of the lily family and are often cultivated for their long, ornamental flowers. This perennial herb grows to about 1 foot in height and has a fleshy conical root (corm). The corm has a bitter, acrid taste and radish-like odor. [1] Low-lying leaves are found around the base of the plant, emanating from the bulb. The plant is native to grassy meadows and woods and riverbanks in Ireland, England and portions of Europe, and has been cultivated throughout much of the world.

HISTORY: The plant and its extracts have been used for centuries in the treatment of gout, rheumatism, dropsy, prostate enlargement and gonorrhea. [1] Extracts have been used to treat cancers. Today the plant serves as the primary source of colchicine, which is used therapeutically to treat gout and experimentally in cellular chromosomal studies. In addition to its FDA approved use (gout), colchicine has been used in the following conditions: Treatment of neurologic disability due to chronic progressive multiple sclerosis, familial Mediterranean fever, hepatic cirrhosis, primary biliary cirrhosis, adjunctive treatment of primary amyloidosis, Behcet's disease, pseudogout, skin manifestations of scleroderma, psoriasis, palmo-plantar pustulosis and dermatitis herpetiformis. [2]

CHEMISTRY: Colchicine is the main active principle and is present in a concentration of about 0.6% in the corm; concentrations can exceed 1% in the seeds. [1] A variety of other related alkaloids have been isolated from the plant including colchicerine and colchamine. Colchicine is not destroyed by heat or boiling and is highly soluble in water.[1]

PHARMACOLOGY: Colchicine inhibits normal cell division, specifically by interfering with microtubule growth and mitosis during cell division. It also may interfere with the normal function of cAMP or the cellular membrane.[2]

Because colchicine arrests mitosis during metaphase, it was hoped that it might be useful as an anticancer agent. Although it demonstrates antineoplastic activity in vitro and in some in vivo models, the toxicity of the drug has limited use in humans. [1]

Colchicine is now being investigated for its effectiveness in limiting the progression of chronic hepatitis and cirrhosis; it appears to decrease inflammation, inhibit collagen synthesis and increase collagen degradation, thereby slowing disease progression and fibrosis and perhaps extending survival time. [3,4,5,6,7]

TOXICOLOGY: The entire plant is toxic, due primarily to the colchicine content. Gastrointestinal disturbances are common following acute therapeutic use of colchicine.

After ingestion of the plant, immediate burning of the mouth and throat is followed by intense thirst, nausea and vomiting. Abdominal pain and persistent diarrhea develop. Fluid loss may lead to hypovolemic shock. Renal impairment with oliguria has been reported. [8] The intoxication follows a long course due to the slow elimination of colchicine from the body. Fluid replacement and supportive therapy is recommended. [8] No specific antidote is available for colchicine poisoning. Emesis followed by gastric lavage has been of value along with supportive therapy for shock. [9]

Veterinary poisonings have been associated with the autumn crocus, and these are often observed in grazing animals. Children, as well as calves, have been reported to have been intoxicated by drinking milk from cows that have ingested the plant. Human intoxications have occurred after corms were mistaken for onions and others have suffered overdosages from seed- or corm-derived natural medicinals. [1]

The volatiles emitted during the commercial slicing of the fresh corm can irritate the nostrils and throat and fingertips holding the corm may become numb. [1] Toxicity has been observed when colchicine accidentally was taken by nasal insufflation in place of methamphetamine. [9]

Prolonged therapeutic use of colchicine may cause agranulocytosis, aplastic anemia and peripheral neuritis. The lowest reported human lethal dose is 186 g in 4 days.[9] Although ingestion of 7 mg of colchicine has been reported to be lethal to man, the more typical lethal dose is 65 mg. [1]

SUMMARY: The autumn crocus is a pretty ornamental that has a long history of medicinal use. The main component, colchicine, is highly effective in the management of gout and related inflammatory disorders, but also is extremely toxic. Colchicine is now being investigated for the management of chronic inflammatory hepatic diseases.

PATIENT INFORMATION — Autumn Crocus

Uses: The plant and its extracts are used to treat gout and related inflammatory disorders. Autumn crocus may ameliorate hepatitis, cirrhosis and various other ills.

Side Effects: All parts are highly toxic. It can produce intoxication, severe gastric distress, shock, etc., and inhibit normal cell growth.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AUTUMN CROCUS

AVOCADO

DATE OF ISSUE: NOV 2001

REPLACES MONOGRAPH DATED: APR 1993

SCIENTIFIC NAME(S): *Persea americana* Mill. Synonymous with *P. gratissima* Gaertn. Also referred to as *Laurus persea* L. Family: Lauraceae

COMMON NAME(S): Avocado, alligator pear, ahuacate, avocato

BOTANY: The avocado grows as a large tree to heights of 15 to 18 meters. It bears a large fleshy fruit that is oval or spherical in shape; the skin of the fruit can be thick and woody. Although the plant is native to tropical America (Mexico and Central America), numerous varieties are now widely distributed throughout the world. [1]

HISTORY: The avocado has been the subject of intense and varied use during the past, not only for food but also for medicinal purposes. The pulp has been used as a pomade to stimulate hair growth and to hasten the healing of wounds. The fruit also has been purported as an aphrodisiac and emmenagogue. American Indians have used the seeds to treat dysentery and diarrhea. Today, the fruit is eaten widely throughout the world, and the oil is a component of numerous cosmetic formulations.

CHEMISTRY: The pulp of the avocado fruit is rich in a fatty oil, and this can account for up to 40% of its composition. In addition to sugars and carbohydrates, 2 bitter substances have been identified. [1]

Avocado oil is derived from the fruit pulp and is composed primarily of glycerides of oleic acid and ˜ 10% unsaponifiable compounds, such as sterols and volatile acids. Oleic acid is a beneficial monounsaturated fatty acid and its concentration ranges from 61% to 95% in an avocado. [2] The vitamin D content of the oil exceeds that of butter or eggs. [1]

The large seed contains a wide variety of compounds, including fatty acids, alcohols, and a number of unsaturated compounds with exceedingly bitter tastes.

The leaves of the Mexican avocado have been reported to contain ˜ 3% of an essential oil composed primarily of estragole and anethole.

PHARMACOLOGY: Avocado oil has been used extensively for its purported ability to heal and soothe the skin. This use is based on the high hydrocarbon content of the pulp and oil, which is likely to be beneficial to dry skin.

A condensed flavonol isolated from the seed has been reported to have antitumor activity in mice and rats. [1] Several of the unsaturated oxygenated aliphatic compounds in the pulp and seed have been shown to possess strong in vitro activity against gram-positive bacteria, including *Staphylococcus aureus*.

In rats, avocado has been shown to have gastric mucosal protective effects and experimental suppression of hepatic injury. Exact mechanism(s) of these protective measures are under investigation, along with potential human application. [3,4]

Avocados are frequently included in healthy diets, and evidence suggests that they are highly effective in modifying lipid profiles. In a randomized study, women chose a diet high in monounsaturated fatty acids enriched with avocado or a high-complex-carbohydrate diet. After 3 weeks, the avocado diet resulted in a reduction in total cholesterol level from baseline (8.2%); a nonsignificant decrease (4.9%) occurred with the comparison diet. Low density lipoprotein (LDL) cholesterol and apolipoprotein B levels decreased only in the avocado group. The authors concluded that an avocado-supplemented diet rich in monounsaturates can benefit serum lipid levels. [5] An avocado-enriched vegetarian diet was shown to reduce triglycerides and LDL cholesterol; however, a vegetarian diet cannot be recommended unconditionally in dyslipidemic patients. [6] A study in type 2 diabetes mellitus patients demonstrated improved lipid profiles and maintained glycemic control when the complex digestible carbohydrates in the diet were partially replaced with monounsaturated fatty acids, with avocado being one of the main sources. [7]

A combination of avocado/soybean unsaponifiables has been shown in 2 separate randomized trials to reduce nonsteroidal anti-inflammatory usage in patients with symptomatic osteoarthritis of the knee or hip. [8,9,10] Efficacy was greater in patients with hip osteoarthritis. [8,9] In vitro studies of this mixture and an in vivo model for studying cartilage destruction have shown that the mixture of avocado/soybean causes reduction of the spontaneous production of inflammatory mediators (eg, prostaglandin E_2) from chondrocytes. This specific combination of avocado/soybean (1 part avocado and 2 parts soybean), available as a capsule form in France, should be considered a delayed, symptom-modifying drug that has a persistent effect. [11,12,13]

INTERACTIONS: Two case reports suggest that the anticoagulant effects of warfarin may be antagonized by ingestion of avocado. The precise mechanism is unknown. [14]

TOXICOLOGY: The poisoning of grazing animals that have ingested avocado has been reported, and this toxicity also has been observed in species as diverse as fish and birds. [1] Nevertheless, only a small number of reports of toxicity caused by avocado have been published over the past 50 years. A review of avocado toxicity reported that feeding dried avocado seed in a 1:1 ratio with normal food rations killed all mice tested. [15] The amount of avocado ingested ranged from 10 to 14 g. Signs of toxicity became apparent after 2 to 3 days and the animals generally died within the next 24 hours. Gross findings included hemorrhage into the brain, lungs, and liver. In cattle and goats, acute toxicity has been characterized by a cessation of milk flow and nonbacterial mastitis. Fish have been killed as a result of avocado leaves falling into a backyard pond. [15] Although the specific mechanism of toxicity is not clear, leaves fed to goats decreased milk production and increased AST and LDH enzyme levels.

Manifestations of allergy to avocado may be limited to the mouth or throat (oral allergy syndrome: itchy mouth, throat, and swollen tongue) or oral symptoms with generalized symptoms (eg, wheezing, chest tightness, abdominal cramping, diarrhea). [16] Cross-sensitivity has been shown with melons (eg, cantaloupe), peaches, bananas, chestnuts, tomatoes, potatoes, and kiwi fruits. [16,17,18] Cross-sensitivity has also been seen in patients with natural rubber latex (eg, latex gloves) allergy and avocados. [17,18,19] This cross-sensitivity is called the "latex-fruit syndrome." [19] An IgE-mediated inflammatory mechanism has been shown to be similar in producing an allergic reaction to latex, bananas, and avocados. [20,21]

SUMMARY: The fruit of the avocado is widely used as a food and as an ingredient in cosmetics and topical preparations. Ingestion of the fruit has been reported to reduce total cholesterol levels and to improve the overall lipid profile. Avocado in combination with soybeans has shown efficacy in symptom relief in patients with osteoarthritis. No important toxicity has been reported in humans, but toxicities have been observed in animals that have eaten large amounts of the seeds or leaves. Cross-sensitivity has been shown between avocado and latex.

PATIENT INFORMATION — Avocado

Uses: The fruit is commonly eaten and the fruit oil is used for cosmetics. A limited number of studies indicate that avocado reduces cholesterol and improves lipid profile and may reduce symptoms of osteoarthritis. Seed derivatives reportedly have antitumor activity in rodents.

Interactions: Tell your health care provider if you are on warfarin and eat avocados.

Side Effects: Large quantities of seeds or leaves appear to be toxic. Allergy to latex, bananas, melons, and peaches may result in a cross-sensitivity to avocado; if allergic, use products that contain avocado with caution.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "A" MONOGRAPHS
    AVOCADO

"B" MONOGRAPHS

BAICAL SKULLCAP

DATE OF ISSUE: JUL 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Scutellaria baicalensis*Georgi, (*S. macrantha* Fisch.). Family: Labiatae

COMMON NAME(S): Baical skullcap, huang-qin, golden root

BOTANY: Baical skullcap is a herbaceous perennial, growing to 0.3 to 1.2 m in height. It has lancet-shaped leaves and purplish-blue flowers. The plant can be found in Japan, Korea, Mongolia, and Russia. It thrives on sunny, grassy slopes and grows well in dry, sandy soils. The dried root is the part of the plant used in traditional Chinese medicine. Baical skullcap is related to skullcap (*S. laterifolia*), the North American species (see Skullcap monograph).[1]

HISTORY: Baical skullcap is a Chinese medicinal herb used for over 2000 years to treat fevers, hypertension, coughing, and other ailments. It still is used today as a traditional remedy for "hot and damp" conditions such as dysentery and diarrhea. Among other items, baical skullcap was listed as an ingredient in several pharmaceutical preparations in a second century AD tomb in northwestern China.[1]

Baical skullcap is prescribed in China for "hot and thirsty" conditions such as fever, cough, GI, and urinary problems. Clinical trials suggest that these traditional uses are justified. Chinese herbal medicine also uses baical skullcap for inflammation, allergies, dermatitis, hyperlipidemias, and atherosclerosis. [1,2]

CHEMISTRY: Flavonoids present in *S. baicalensis*include baicalin, baicalein, wogonin, and wogonoside.[1,3] RP-HPLC determination of flavonoids from *S. baicalensis* root has been reported.[4] Flavones ? and ??, chrysin, wogonin, apigenin, salvigenin, scutellarein, isoscutellarein, and others were flavonoid constituents also found in *S. baicalensis* leaf parts.[5] Flavones baicalein, oroxylin, and skullcapflavone ?? also were identified. [6] Other reports confirm similar flavonoid content.[7,8] One report describes melatonin in certain plant samples.[9] Other compounds include sterols and benzoic acid.[1] The western species, *S. laterifolia* has limited similarity to baical.

PHARMACOLOGY: The anti-inflammatory effects of bacial skullcap have been well documented. One study reports the methanolic extract of 3 flavonoids, wogonin, baicalein, and baicalin, to have an effect similar to prednisolone. [10] Another study reported the chloroform extract of *S. rivularis* to exhibit greatest inhibitory actions against carrageenan-induced rat paw edema vs indomethacin. Baicalin demonstrated the greatest inhibition activity when compared with baicalein and wogonin.[11] Wogonin, baicalein, and baicalin all have been found to influence some anti-inflammatory pathways via certain proteins, antigens, and enzymes. [12,13,14]

Flavonoids from *S. baicalensis* have been studied for antioxidant effects. Four major flavonoids (baicalein, baicalin, wogonin, and wogonoside) have been studied in various systems, confirming several antioxidant activities.[15]

An extract of the plant demonstrated protective actions against oxidation induced by UV light, suggesting potential use against certain skin diseases. [16] Flavonoid baicalein inhibited lipid peroxidation in rat liver microsomes. [17] Baicalein and baicalin scavenged hydroxyl radical, superoxide anion, and others in a dose-dependent manner.[3] Similarly, baicalein directly scavenged superoxide, hydrogen peroxide, and hydroxyl radicals in cardiomyocytes in another report. [18] Flavonoids wogonin and wogonoside had subtle effects on these radicals but did inhibit nitric oxide production, as did the water extract of the plant in other reports. [3,19,20] Ganhuangenin isolated from *S. baicalensis* had greater antioxidant potency than alpha-tocopherol.[21]

Because of its beneficial effects as an antioxidant, baical skullcap also has been studied in immunology and cancer research. *S. baicalensis* administered to lung cancer patients improved certain immunoglobulins.[22] Another report attributes *Scutellaria* root from a combination Japanese herbal medicine sho-saiko-to as being responsible for improvement in interleukin-12 production in liver cancer patients. IL-12 is an important cytokine that maintains systemic defense and bioregulation. [23] Dry extract of baical skullcap given to 88 lung cancer patients increased hematopoiesis stimulation and improved other anticancer parameters. [24] Flavonoid wogonin also exhibited immunostimulation by activating heat, shock, or stress proteins in another report. [25] Baicalin and baicalein inhibit cell proliferation in certain cell lines, [26] induces quinone reductase,[27] and induces apoptosis in prostate cancer cells.[28] In vitro effects also include antigenotoxic actions of baicalein. [29]

In rats with Pliss lymphosarcoma, a disease associated with disorders in platelet-mediated hemostasis, *S. baicalensis*administration produced a normalizing effect. This activity may be responsible for its antitumor and metastasis-preventing effects.[30] A 14-flavone combination from *S. baicalensis*had marked inhibitory effects on mouse skin tumor promotion in another report.[31] *S. baicalensis* also was found to demonstrate anticancer activity in laboratory mice with head and neck squamous cell carcinoma.[32] *S. baicalensis*, in an herbal preparation with 7 other herbs, has been evaluated for treating prostate cancer. This combination, PC-SPES, stimulates the immune system and possesses antitumor activity. PC-SPES therapy reduced prostate-specific antigen 50% in patients with hormone-resistant prostate cancer. Enzyme prostate acid phosphatase, commonly elevated in prostate cancer, also was decreased by the preparation.[33,34] PC-SPES was recalled in February 2002 because it contained the undeclared prescription drug warfarin.

Several studies evaluating the antimicrobial effects of baical skullcap have been performed. In vitro testing of *S. baicalensis*preparation on selected oral bacteria demonstrated bacteriostatic and bactericidal effects at certain concentrations.[35] Flavone isolate, baicalin, was found to be synergistic with beta-lactam antibiotics against certain resistant strains including beta-lactam and methicilin-resistant *S. aureus*.[36] A *Scutelleria* compound injection vs IV piperacillin was studied in 60 patients with pulmonary infection. Results were comparable in certain parameters, such as effective rates, leucocyte count, and low side effect incidence. However, in the piperacillin group, 4 of the 30 patients had subsequent fungal infection, whereas in the *Scutelleria*group, no fungal infection was found after treatment.[37] High antifungal activity was found against *Candida albicans* caused by *S. baicalensis*in an herbal screening study.[38] Antifungal effect was caused by baicalein in another report in which *S. baicalensis* was found to be active against *Cryptococcus neoformans* and *Pityrosporum*.[39]

Antiviral effects of the plant also have been reported. A flavonoid compound from *S. baicalensis* inhibited T-cell leukemia virus type ? (HTLV-?). Constituent baicalin inhibited reverse transcriptase activity in HTLV-?-infected cells, as well as the activity of purified reverse transcriptase from Moloney murine leukemia virus and Rous-associated virus type 2.[40] Other flavones, such as isoscutellarein from *S. baicalensis*leaves, also show anti-influenza virus activity in vitro.[41] Isoscutellarein-8-methylether from *S. baicalensis*roots had effects against influenza A and B viruses. Inhibition of replication occurs by inhibiting the fusion of viral envelopes with the endosome/lysosome membrane in the early stage of the virus infection cycle. [42]

Baical skullcap is used to help treat circulatory problems such as high blood pressure, arteriosclerosis, varicose veins, and bruising. [1] Flavone baicalein has inhibited thrombin and thrombin-induced calcium and plasminogen activator, suggesting potential benefits in arteriosclerosis and thrombosis. [43] Another report discusses *S. baicalensis* in combination (sanhuang mixture) to inhibit platelet aggregation compared with 50 mg/day aspirin. [44]

Baicalin exhibited hepatoprotective actions in rats as well. [45]

Baical skullcap may have CNS actions, specifically sedative effects.[1] Flavonoids baicalin and baicalein affect glial cells, which play a role in maintaining neural cell function.[45] Flavones baicalein, oroxylin, and skullcapflavone ?? were found to bind with the benzodiazepine site of GABA-A receptors.

Other uses of baical skullcap preparations include treatment of neonatal jaundice, [46] marked antiulcerogenic actions,[47] sores, swelling, boils, and diabetic problems. [1]

TOXICOLOGY: Few side effects of baical skullcap have been reported. No side effects were reported in liver, kidney, or medulla regions in a 60-patient study of IV *Scutellaria* compound.[37] Isolate isoscutellarein from *S. baicalensis* leaves produced negligible toxic effects in mice.[36] A combination product including *S. baicalensis* may have potential to cause cardiovascular and other negative estrogen-like effects. [34]

SUMMARY: Baical skullcap is a Chinese herb used for more than 2000 years. It contains several flavonoids such as baicalin, baicalein, and wogonin, which are responsible for most of the plant's beneficial effects. The dried root is the part of the plant that is used medicinally. Some of these include anti-inflammatory, antioxidant, immunoprotective, anticancer, antimicrobial, and circulatory effects. Few side effects are attributed to the plant.

PATIENT INFORMATION — Baical Skullcap

Uses: Baical skullcap has been used for anti-inflammatory, antioxidant, immunoprotective, anticancer, antimicrobial, and circulatory conditions.

Side Effects: Few side effects have been reported. A combination product including *S. baicalensis* may have potential to cause cardiovascular and other negative estrogen-like effects.[34]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BAICAL SKULLCAP

BARBERRY

DATE OF ISSUE: OCT 2001

REPLACES MONOGRAPH DATED: JUL 1991

SCIENTIFIC NAME(S): *Berberis vulgaris* L. and *B. aquifolium* Pursh. (However, more appropriately designated as *Mahonia aquifolium* Nutt.) Family: Berberidaceae

COMMON NAME(S): Barberry, Oregon grape, Oregon barberry, Oregon grapeholly, trailing mahonia, berberis, jaundice berry, woodsour, sowberry, pepperidge bush, sour-spine[1,2]

BOTANY: The barberry grows wild throughout Europe but has been naturalized to many regions of the eastern US. *M. aquifolium* is an evergreen shrub native to the northwestern US and Canada. Barberry grows to more than 10 feet with branched, spiny, holly-like leaves and is widely grown as an ornamental. Its yellow flowers bloom from May to June and develop into red to blue-black oblong berries. [3]

HISTORY: The plant has a long history of use, dating back to the Middle Ages. Salishan native elders have used *M. aquifolium* to treat acne[4] and native American Indians utilized Mahonia berries to treat scurvy.[5] A decoction of the plant has been used to treat GI ailments and coughs.[3] The alkaloid berberine was included as an astringent in eye drops, but its use has become rare.

The edible fruits have been used to prepare jams, jellies, and juices. The use of the plant in traditional medicine has been limited by the bitter taste of the bark and root. However, > 3 dozen medicinal uses for barberry, including cancer, cholera, and hypertension have been listed. [6,7] Other reported uses of *M. aquifolium* include the treatment of the following conditions: Fever, gout, renal and biliary diseases, rheumatic symptoms, diarrhea, gastric indigestion, and dermatosis. [8,9]

CHEMISTRY: The root and wood are rich in protoberberines (berberine, palmatine, jatorrhizine) and bisbenzylisoquinoline derivatives (oxyacanthine, berbamine) as well as other alkaloids such as bervulcine, magnoflorine, and columbamine. [2,3,8,9] The root may contain as much as 3% alkaloids, which impart a yellow color to the wood. Berberine, berbamine, and oxyacanthine are considered the 3 most important alkaloids. [10] The edible berries are rich in vitamin C, sugars, and pectin.

PHARMACOLOGY: *M. aquifolium* is valued for its antipsoriatic effects and its antibacterial, antifungal, anti-inflammatory, and antioxidant activity. It also has been used for treating acne, eczema, and candida infection.

Products of lipoxygenase metabolism enhance the pathophysiology of psoriasis. Each of the 6 bisbenzylisoquinoline alkaloids (oxyacanthine, armoline, baluchistine, berbamine, obamegine, aquifoline) isolated from *M. aquifolium* exhibited various lipoxygenase inhibitory activity resulting in an anti-inflammatory and antioxidant effect.[11]

Additional studies suggest that the antiproliferative effect is caused by the berberine content of *M. aquifolium*. Berbamine may reduce the synthesis of 5-lipoxygenase and cyclooxygenase, thereby reducing the activity of these enzymes in the arachidonic acid cascade. [12]

Berberine and several related alkaloids are bactericidal, in 1 study exceeding chloramphenicol (eg, *Chloromycetin*) against *Staphylococcus epidermidis*, *Neisseria meningitidis*, *Escherichia coli*, and other bacteria.[2] Another study reported that a methanolic extract (containing 80 mg of dried plant material) from the root of *M. aquifolium* exhibited antifungal activity against *Trichoderma viridae* and was considered more effective than nystatin.[13]

Several alkaloids (eg, berbamine, oxyacanthine) in Mahonia reportedly block the influx of calcium. For example, *M. aquifolium* root extract blocked calcium-induced contraction in an in vitro experiment on isolated rat aorta. The mechanism of the vasodilation is postulated to also involve alpha-adrenoreceptors. [14,15]

Berberine (100 mg 4 times/day), given alone or together with tetracycline (eg, *Achromycin V*), has been found to significantly improve acute watery diarrhea and excretion of vibrios after 24 hours, compared with placebo in patients with noncholera diarrhea. [16] Berberine does not appear to exert its antidiarrheal effect by astringency, and the mechanism of action has not been defined.[17]

Berberine has anticonvulsant, sedative, and uterine stimulant properties. Local anesthesia can occur following SC injection of berberine. [6] Berbamine also produces a hypotensive effect.[5]

TOXICOLOGY: Symptoms of poisoning are characterized by lethargy, stupor and daze, vomiting and diarrhea, and nephritis. [18] *M. aquifolium* is contraindicated during lactation and pregnancy because some of the alkaloids (eg, berberine, palmatine) may stimulant uterine contractions. [18] It is also contraindicated in patients with hypersensitivity to *M. aquifolium*. Burning, redness, and itching have been reported in some patients using the topical dosage forms. [8,9]

SUMMARY: Barberry has a long history of traditional use and continues to play a role in herbal medicinal practice today. Berberine, its best-studied alkaloid, has been shown to have significant pharmacologic activity, particularly in the management of bacterial-induced diarrheal conditions and psoriasis. Berberis species are among the highly regarded "alternative" herbs.

PATIENT INFORMATION — Barberry

Uses: The fruits have been used in jams, jellies, and juices. Plant alkaloids have been found to be antibacterial, antifungal, anti-inflammatory, antioxidant, and antidiarrheal. Berberine is a uterine stimulant.

Side Effects: Barberry can produce stupor, daze, diarrhea, and nephritis and is contraindicated during lactation and pregnancy. Hypersensitivity reactions (eg, burning, itching, redness) have occurred in some patients using topical dosage forms.

Dosing: Barberry berries and root bark have been used as an alternative source of berberine. Daily doses of 2 g of the berries have been used, but there are no clinical studies to substantiate barberry's varied uses. [19]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BARBERRY

BARLEY

DATE OF ISSUE: NOV 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Hordeum vulgare* L. Family: Gramineae

COMMON NAME(S): Barley, Hordeum[1]

BOTANY: Barley is a well-known cereal grain that is cultivated throughout the world.

HISTORY: The use of barley for food and medicinal purposes dates to antiquity. The Roman physician Pliny noted that if a person affected with a boil took nine grains of barley, traced a circle around the boil three times with each grain, and then threw the barley into a fire with his left hand, the boil would be immediately cured.[2] The mucilage derived from the cereal (known as ptisane by the ancient Greeks) was used to treat gastrointestinal inflammation. [3] Barley has served as a food staple in most cultures. Gladiators ate barley for strength and stamina and were called hordearii from the Latin word for barley, hordeum. [4] Although supplanted by wheat and rye in the baking process, barley is now used extensively in soups, cereals, animal feeds, and beer making. [5] Roasted seeds are used in coffees and seeds are fermented into miso. "Covered" barley is used for animal feed and malting. For human consumption, the barley hull is removed by abrasions producing "pearl" barley.

CHEMISTRY: Barley contains ß-glucan, a fiber also found in oat bran and reported to reduce cholesterol levels. It also contains the oil tocotrienol. Protein extracted from the leaves is said to be an adequate food supplement.[5]

Barley is the source of a natural sweetener known as malt sugar or barley jelly sugar, which is high in maltose. [5]

The root of the germinating grain contains the alkaloid hordenine, an aminophenol. [3]

"Pearling" removes essential amino acids and vitamins concentrated in the outer layers of the seed, although the grain retains its fiber content.

An oxalate oxidase that has commercial applications in monitoring oxalate levels in patients with hyperoxaluria, has been obtained from barley seedling plants. [8] Analogs of barley ribosomes and peptides are being used to enhance the potency and stability of in vitro immunoconjugate tests. [6,7]

PHARMACOLOGY: Hordenine is a sympathomimetic with a pharmacologic profile similar to that of epinephrine. [3] It stimulates peripheral blood circulation and has been used as a bronchodilator for bronchitis.

Barley's natural flavor may make it a more versatile grain for baking. In a taste test of muffins made with 100% barley flour, the barley muffins were rated more moist and flavorful than wheat bran muffins.[4]

The fiber content of barley suggests that it may be useful in reducing cholesterol levels and in controlling hyperglycemia in man. Ingestion by healthy subjects of barley-based breads resulted in lower glycemic and insulin indices than in subjects who ingested a control pumpernickel [9] or white bread.[10]

Of interest has been the finding of statistically significant reductions in total serum cholesterol and LDL-C in 79 hypercholesterolemic patients who supplemented their diet for 30 days with barley bran flour or barley oil. HDL-C also decreased significantly in the barley bran flour group, but not in the oil group. [11]

In a rat model of chemically-induced colon cancer, spent barley grain has been shown to protect against the risk of cancer, and this effect was greater than that observed with wheat bran and commercial barley bran.[12] This may be related in part to the ability of barley bran flour to decrease GI transit time. In 44 volunteers, barley bran significantly decreased transit time by 8.0 hours from baseline compared to 2.9 hours in the control group supplemented with cellulose. [13]

TOXICOLOGY: Because barley contains low levels of gluten, it should be ingested with caution by persons with celiac disease. [14] No other significant side effects have been associated with dietary ingestion of barley.

SUMMARY: Barley is a widely cultivated grain used as a food and in the brewing process. Interest has focused on the ability of components in the bran to reduce cholesterol levels and more extensive investigations into this effect are warranted.

PATIENT INFORMATION — Barley

Uses: Barley is a food staple also brewed to make beer, fermented to make miso, and processed to yield malt sugar. Studies indicate it may protect against colon cancer, reduce cholesterol and control hyperglycemia.

Side Effects: None of significant known, except that those with celiac disease should be cautioned about its low levels of gluten.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BARLEY

BARLEY GRASS

DATE OF ISSUE: JAN 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Hordeum vilgare*, *Hordeum distichon* Family: Poaceae (grasses)

COMMON NAME(S): Barley grass

BOTANY: Barley grass is the leaf of the barley plant, as opposed to the grain (for barley grain, refer to the "Barley" monograph). It is capable of growing in a wide range of climatic conditions. Barley grass has greater nutritional value if harvested at a young age. [1,2]

HISTORY: Barley is considered to be the first cereal grain cultivated by humans. Its medicinal and food use dates back to 7000 BC. Crop reports on barley date back to 2440 BC, and the Chinese were cultivating barley circa 2000 BC. Since biblical times, ancient Asian and Middle Eastern cultures reportedly included young wheat and barley grass plants in their diets. [1,2]

In the late 1920s, the role of vitamins gained increasing acceptance in human nutrition. Health researchers also studied the role of cereal grains in animal health. For example, in 1931, chickens fed a 10% mixture of cereal grass responded well in growth, appeared to have increased resistance to degenerative diseases, and increased winter egg production from 38% to 94%. Further studies concerning "grass juice factor," a water soluble extract of grass juice, found several beneficial growth and health effects from its supplementation in animal diets. In 1940, it was explained how the vitamins, minerals, and protein in the cereal grasses are essential to animals and humans. A dehydrated preparation of cereal grass called "cerophyl" was approved as an "accepted food" by the Council of Foods of the American Medical Association in 1939. Later, synthetic nutrients were added to a number of foods, and multivitamins gained popularity. [2]

CHEMISTRY: The juice of barley grass reportedly contains vitamins, including beta carotene, B_1, B_2, B_6, B_{12}, pantothenic acid, and folic acid. Minerals present include potassium, calcium, iron, phosphorus, and magnesium. Other constituents are chlorophyll, amino acids, protein, fiber, and enzymes (antioxidant enzyme, superoxide dismutase, and nitrogen reductase). [2,3]

PHARMACOLOGY: Although the claims mentioned are unreferenced, research from Japan suggests barley grass preparations are beneficial in treating certain skin diseases (dermatitis from P4D1 [a protein] fractions, skin rejuvenation, and inflammatory conditions), hepatitis, asthma, anemia, diabetes, arthritis, and obesity. The anti-inflammatory effects of the juice have been attributed to P4D1 fraction, which is also useful for the treatment of colitis, stomatitis, and pancreatitis. Other research has demonstrated that mice fed juice extracts of barley grass grew faster and had more energy compared with mice on control diets. [1]

Constituents in young barley leaves reportedly have antiulcer activity. Doses of 500 mg/kg appeared to protect the GI mucosa in stress- and acetic acid-induced stomach ulcers in rats. Furthermore, a multicenter clinical trial reported the usefulness of germinated barley foodstuff in treating patients with mild to moderate active ulcerative colitis. [4,5]

In hypercholesterolemic rats, beta-sitosterol, an active component in the juice, decreased plasma cholesterol within 1 week. [6]

Cobalamin or vitamin B_{12} deficiency may be avoided in vegetarian diets by supplementation with dehydrated barley grass juice. Barley grass is also available commercially as whole leaf powder capsules, caplets, and bulk powders. In an observational study, patients reported improvement in fibromyalgia syndrome from a dietary intervention that included barley grass. [7,8]

Barley grass may be considered an adjunctive therapy in the treatment of patients with type 2 diabetes because of the low glycemic and high insulinemic index. [9]

In 1979, data were presented suggesting cancer-preventative properties of wheat grass because of the presence of chlorophyll. Diets including wheat grass show decreased cancer in animal studies, thus barley grass may deactivate mutagenic compounds and stimulate cellular repair of damaged DNA. Superoxide dismutase, found in high concentrations in green barley juice, is a cellular antioxidant, protecting against radiation and free radicals. [1,10]

TOXICOLOGY: Barley grass has no reported side effects or toxicity. Barley grass products should not cause allergy in those sensitive to gluten because gluten is typically found in the seed of the plant, not in the grass. However, use is best avoided in patients with celiac disease. The barley grain dust may cause a respiratory allergic response in hypersensitive patients. [11,12]

SUMMARY: The use of barley as food dates back to 7000 BC. Barley grass is high in several vitamins and minerals. Both animals and humans have benefited from its effects in growth and nutrition. Barley grass may prove to be beneficial as an antiulcer and an anticholesterol agent as well as in vitamin B_{12} deficiency in vegetarian diets. Interest in other effects such as anticancer and anti-inflammatory activity has been reported in a small number of human clinical trials. Additional scientific studies are needed to determine any potential side effects.

PATIENT INFORMATION — Barley Grass

Uses: Historically, the plant species was used in the treatment of skin, liver, blood, and GI disorders.

Side Effects: Barley grass has no reported side effects or toxicity. Additional scientific studies are needed to determine any potential side effects.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BARLEY GRASS

BAYBERRY

DATE OF ISSUE: JUN 2001

REPLACES MONOGRAPH DATED: AUG 1991

SCIENTIFIC NAME(S): *Myrica cerifera* L. Family: Myricaceae

COMMON NAME(S): Bayberry, wax myrtle plant, candleberry[1]

BOTANY: The bayberry grows as a large evergreen shrub or small tree that is widely distributed throughout the southern and eastern US. It is known for its small bluish-white berries.[2]

HISTORY: The bayberry is best known for its berries, from which a wax is derived to make fragrant bayberry candles. In folk medicine, bayberry has been used internally as a tea for its tonic and stimulant properties and in the treatment of diarrhea. The dried root bark is often used medicinally. The plant is astringent, which may account for this latter use, as well as its topical use for wound healing. [2]

CHEMISTRY: A number of compounds have been identified in bayberry. Tannins account for the plant's astringency. The triterpenes myricadiol, taraxerol, and taraxerone are present, along with the flavonoid glycoside myricitrin. [2]

PHARMACOLOGY: Myricadiol has been reported to have mineralocorticoid activity. Myricitrin has choleretic activity, stimulating the flow of bile, and also exhibits antibacterial activity.[2] The dried root is reported to have antipyretic properties. [3] Bayberry has also been prepared as a gargle for treatment of sore throats.[4]

TOXICOLOGY: The elevated tannin concentration of the plant precludes its general internal use. The percutaneous injection of bark extracts in rats produced a number of malignant tumors following long-term (78-week) administration.[2,3] Ingestion of the plant may cause gastric irritation and vomiting. [5] The plant is said to be an irritant and sensitizer.[5,6] Use of bayberry gargle is contraindicated for dry and raw tissue such as dry sore throat. [7] Bayberry pollen has been documented as an aeroallergen.[8,9]

Large doses may cause typical mineralocorticoid side effects and may interfere with steroid therapy. [4]

SUMMARY: Bayberry is best known for its use in the production of a fragrance used in the preparation of scented Christmas candles. There is little evidence to support its use for the treatment of any disease, and because of its high tannin content, it should not be taken internally in any form.

PATIENT INFORMATION — Bayberry

Uses: Bayberry tea has been used as a tonic, stimulant, and diarrhea treatment. Plant parts are also used to heal wounds. Bayberry has been used as a gargle. Bayberry wax is used to make fragrant candles. There is little evidence to support its use for the treatment of any disease.

Side Effects: Bayberry should not be taken internally. Ingestion may cause GI distress. Long-term injection produced malignancies in rats. Bayberry pollen has been documented to cause allergic respiratory symptoms.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BAYBERRY

BEE POLLEN

DATE OF ISSUE: NOV 1995

REPLACES MONOGRAPH DATED: MAY 1990

SOURCE: Bee pollen consists of plant pollens collected by worker bees, combined with plant nectar and bee saliva. These are packed by the insects into small dust pellets which are used as a food source for the male drones. commercially, the pollen is gathered at the entrance of the hive by forcing the bees to enter through a portal partially obstructed with wire mesh, thus brushing the material off the hind legs into a collection vessel. Because of the increasing popularity of this health food, this means of pollen collection has been supplemented by the direct collection of the material from within the hives. Alternately, pollen is collected directly from the wind-pollinated plants by automated means, and the pollen is compressed into tablets, with or without added nutritional supplements. [1] Claims have been made that machine-collected pollen is safer and less likely to cause allergic reactions because pollen collected by bees may contain fungal or bacterial contaminants. There is no adequate evidence to support this claim.

HISTORY: The use of bee pollen increased during the late 1970s following testimonials by athletes that supplementation with this product increased stamina and improved athletic ability.

CHEMISTRY: Bee pollen is a good nutritional source for drone bees. It contains approximately 30% protein, 55% carbohydrate, 1% to 2% fat, and 3% minerals and trace vitamins.[2] Vitamin C concentrations of 3.6% to 5.9% have also been found in some pollen samples.[3] Promotional literature lists almost 100 vitamins, minerals, enzymes, amino acids and other compounds identified in bee pollen. The physiologic importance of many of these components is poorly understood. Bee pollen preparations often contain mixtures of pollens from diverse types of plants, and these pollens vary with the geographic origin of the material.

PHARMACOLOGY: Articles in the lay press reported that athletes could enhance their performance by ingesting bee pollen; however, an investigation conducted by the National Athletic Trainer Association with Louisiana State University swim team members found no beneficial effect. The 2-year double-blind study found bee pollen "absolutely not a significant aid in the metabolism, workout training of performance" of these athletes. [4] The results of a study conducted in track runners suggested that athletes who took bee pollen recovered faster after exercise and that bee pollen would therefore be of value in relieving common tiredness and lack of energy. Critics of the study found the test group to be small, the blinding to be inadequate and the conclusions to be premature. [5]

Pregnant Sprague-Dawley rats fed bee pollen were experimentally found to have fetuses with higher birth weights and decreased death rates, suggesting bee pollen is an effective prenatal nutrient. [6] Bee pollen administered to rats was also experimentally found to possibly display anti-aging effects. [7] Bee pollen has been recommended to immunologically strengthen multiple sclerosis patients being treated with prednisolone and *Proper-Myl*.[8] Bee pollen may relieve or cure cerebral hemorrhage, bodily weakness, anemia, weight loss, enteritis, colitis and constipation. [3] However, all of these certainly bear clinical verification.

TOXICOLOGY: Reports of adverse reactions to bee pollen have been related to allergic reactions after ingestion by sensitive persons. There is a popular, but unadvisable, home practice of using bee pollen to treat allergic disorders. Despite the usually limited response to oral hyposensitization techniques and the potential for severe allergic reactions, this practice has spread considerably.

In one report of anaphylaxis, a 46-year-old man with a history of seasonal allergic rhinitis took a teaspoonful of bee pollen to treat his hay fever symptoms. Fifteen minutes later he developed paroxysm of sneezing and by 30 minutes experienced generalized angioedema, itching, dyspnea and lightheadedness. He recovered following treatment with epinephrine, corticosteroids and diphenhydramine. [1]

Other investigators have reported similar allergic reactions after single doses among patients with a history of allergic rhinitis. The dose required to precipitate an acute allergic reaction was less than one tablespoonful of bee pollen. [9] By contrast, the development of hypereosinophilia, neurologic and gastrointestinal symptoms in a woman who ingested bee pollen for more than 3 weeks was also reported. [10] These chronic allergic symptoms resolved upon discontinuation of the preparation. Although infrequent, some reports of severe allergic reactions to bee pollen have been observed. A 33-year-old man with no prior allergies had an acute anaphylactic reaction 15 minutes after ingesting bee pollen. He recovered fully after emergency medical treatment with epinephrine, lactated ringer's solution and methylprednisolone sodium succinate.[11]

Several reports suggested that bee pollen may have been used as a vehicle to carry the biochemical warfare toxin, T-2 mycotoxin, in Asia and Afghanistan, but this theory has come under considerable criticism.[12]

SUMMARY: Bee pollen is an expensive source of carbohydrates and trace nutrients. Although claims have been made that it may increase stamina and provide a source of instant energy, there is little supportive evidence for these claims. It should be taken with caution by persons with a history of pollen-sensitive allergies. Bee pollen is sold as loose granules, compressed tablets, and in capsules in combination with vitamin E and other nutritional supplements. A 100 tablet bottle (500 mg) retails for approximately $5, but imported products can retail for more than $15.00 for 30 pollen pods (a 30-day supply).

PATIENT INFORMATION— Bee Pollen

Uses: Although bee pollen is nutritionally rich, claims that it enhances athletic performance have not been reliably verified. Some evidence indicates it may benefit a range of conditions, from constipation to aging.

Side Effects: Ingestion produces allergic reactions in sensitive individuals. Attempts to hyposensitize by administering bee pollen may produce severe anaphylaxis and other acute or chronic responses.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BEE POLLEN

BEE VENOM

DATE OF ISSUE: FEB 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Derived from *Apis Mellifera*

COMMON NAME(S): Bee venom, honeybee venom

SOURCE: Honeybee venom is obtained from *Apis Mellifera*, the common honeybee. Other venoms are derived from related members of the hymenoptera.

HISTORY: Anaphylaxis to insect stings is a relatively uncommon problem, believed to have affected only 0.4% of the general US population in the early 1990s. It is the cause of approximately 40 deaths per year in the United States.[1]

The allergic reactions are mediated by IgE antibodies directed at constituents of honeybee, yellow jacket, hornet and wasp venoms. In order to minimize the allergic reaction, hyposensitization immunotherapy techniques have been developed in which small doses of the venom are administered under controlled conditions over a period of months to years. Patients allergic to honeybee venom may be particularly sensitive to hymenoptera venoms in general and have been found to be at a significantly higher risk of developing systemic side effects to venom immunotherapy than patients who are sensitive to yellow jacket venom.[2]

More recently, it has been suggested that honeybee venom may alleviate the symptoms and slow the progression of immune-modulated diseases such as arthritis and multiple sclerosis.

CHEMISTRY: Bee venoms are complex mixtures of amino acids and polysaccharides. They are collected from the insects and diluted to standardized concentrations. Melittin, a phospholipase activating protein in bee venom, has been shown to induce neutrophil degranulation [3] and to both increase[3] and inhibit[4] the formation of superoxide. This difference in activity appears to be dependent upon the test method employed. Melittin induces neutrophil degranulation with subsequent superoxide formation;[3] however, melittin binds to calmodulin, and this effect is associated with an inhibition of the production of superoxide. [4]

The polypeptide adolapin isolated from bee venom inhibits inflammation in animals (carrageenan, prostaglandin and adjuvant rat paw edema models) and appears to inhibit the prostaglandin synthase systems.[5]

PHARMACOLOGY

Immunotherapy: Hypersensitivity to honeybee venom is mediated by a number of antibodies and immunomodulators, the most important of which appears to be IgE. The infusion of beekeepers' plasma has been shown to protect patients against systemic reactions that can occur during active immunotherapy. [6] Following infusion of this plasma, a decrease in the sensitivity to honeybee venom has been noted; in one study, this was accompanied by increases in the levels of anti-idiotypic antibodies and decreases in specific antibodies to honeybee venom (IgG and IgE). (The study was conducted over a 76-week period of immunotherapy with the venom.) These findings suggest that several mechanisms play an interrelated role in the development of immunity to honeybee venom.

Arthritis Therapy: For some time it has been speculated that honeybee venom may prevent the development or improve the status of patients with rheumatoid arthritis. This conclusion was based largely on anecdotal observations of a general lack of arthritis among beekeepers stung routinely during their lifetimes. In one survey of a random sampling of the general population, 83% of respondents believed that bee venom could be an effective treatment for arthritis based on information they had read in the popular press.[7]

Honeybee venom administered to rats with adjuvant arthritis resulted in a significant suppression of the disease. [8] Melittin has been shown to block the production of superoxide and hydrogen peroxide in human neutrophils. Melittin and other agents that bind calmodulin have been shown to decrease superoxide production. An elevated superoxide level has been suggested as a possible cause of oxidative damage to synovial fluid and other joint membranes. Therefore, agents that decrease the production of the superoxide may prevent or halt the progression of inflammatory diseases such as arthritis. Also, honeybee venom has been found to decrease the production of the inflammatory mediator interleukin-1 (IL-1) in rat splenocytes. [9] Honeybee venom treatment of rats with adjuvant arthritis inhibits certain macrophage activities and, thus, indirectly inhibits the activation of T and B cells. [9]

Other Uses: Other uses for bee venom, though poorly substantiated, include the treatment of diseases of the locomotor system, [10] particularly multiple sclerosis (MS). Despite widespread reports of true effectiveness of bee venom therapy for MS, there is no scientific consensus as to its safety and true effectiveness in the management of this disorder.

TOXICOLOGY: While single honeybee stings can cause anaphylaxis, the most severe reactions generally result from multiple stings. Signs and symptoms of multiple stings include urticaria (hives), nausea, vomiting, diarrhea, hypotension, confusion, seizures and renal failure. Treatment is supportive, with attention to blood pressure, renal function and maintaining an open airway. Stingers should be removed with gentle scraping to prevent further venom injection. [11] Because cardiac levels of noradrenaline have been found to increase dramatically in animals following injection with bee venom, it is suggested that all patients, regardless of sensitivity history, have cardiac monitoring if they are victims of multiple bee stings. [12] Rare cases of anuria and rhabdomyolysis/rhabdomyonecrosis have been reported.[13,14]

SUMMARY: Bee venom is used in hyposensitization immunotherapy for patients who are highly sensitive to the effects of bee stings. In addition, the venom finds use in the nontraditional treatment of arthritis and multiple sclerosis. The latter uses are based on observations of an anti-inflammatory and immunomodulating effect induced by bee venom.

PATIENT INFORMATION— Bee Venom

Uses: Bee venom is used to hyposensitize individuals highly sensitive to bee stings. There is some evidence it also helps inhibit or suppress arthritis and multiple sclerosis.

Side Effects: A single bee sting can produce anaphylaxis in sensitive individuals. Regardless of history, any patient with multiple stings should be monitored.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
      BEE VENOM

BERGAMOT OIL

DATE OF ISSUE: MAR 2004

REPLACES MONOGRAPH DATED: MAY 1993

SCIENTIFIC NAME(S): *Citrus bergamia* Risso et Poiteau. Family: Rutaceae

COMMON NAME(S): Bergamot, oleum bergamotte. Do not confuse with *Monarda didyma* L. Also known as scarlet bergamot or more commonly as oswego tea.[1] Do not confuse with the mints *Monarda didyma* L. (scarlet bergamot or oswego tea) or *M. fistulosa* L. (wild bergamot or horsemint).[2]

BOTANY: The bergamot is a small tree native to tropical Asia that is cultivated extensively on the southern coast of Italy. The peel of the fresh, nearly ripe fruit is the source of bergamot oil. The oil is obtained by cold expression. Further purification by vacuum distillation, solvent extraction, or chromatography yields terpeneless (rectified) bergamot oil.[3] It is synonymous with *C. aurantium* L. subspecies *bergamia*.

HISTORY: Bergamot oil is used as a citrus flavor and is often added to perfumes and cosmetics. Bergamot oil is used to flavor Earl Grey tea. It is also commonly used to flavor halva, a Middle Eastern sesame paste confection.

CHEMISTRY: Bergamot oil is a complex mixture of more than 300 compounds. The most prevalent compounds are linalyl acetate (30% to 60%), linalool (11% to 22%), and other alcohols.[3] The quality of bergamot oil is determined according to the amounts of oxygenated compounds (ie, linalool and linalyl acetate). [4] Furocoumarins include bergapten (approximately 0.4% 5-methoxypsoralen [5-MOP]) [5] , bergamottin (5-geranyloxypsoralen),[5,6] citropten (5,7-dimethoxycoumarin),[5,7] and others. Rectified bergamot oil contains lower concentrations of terpenes and has no coumarins. [3]

PHARMACOLOGY: The furocoumarins have been used therapeutically in conjunction with long-wave UV light therapy for the management of psoriasis and vitiligo.

TOXICOLOGY: Some furocoumarins (eg, bergapten and xanthotoxin, known as 5-MOP and 8-methoxypsoralen [8-MOP], respectively) have been shown to be phototoxic in humans.[3,8] Bergamottin accounts for about two thirds of the absorption of UVA and UVB light by bergamot oil. [9] Photosensitivity can reach its peak from 2 to 72 hours after topical administration of the oil followed by irradiation. [8,10] Hyperpigmentation of the face and other areas exposed to the sun is thought to be because of the photosensitizing effects of cosmetics that contain these compounds. Phototoxic reaction can be affected by a variety of factors, including vehicle, concentration, hydration of skin, skin site, interval between local application of bergamot oil and irradiation, degree of skin pigmentation, and ability to tan. [8] Inform patients of a potential phototoxic reaction caused by exposure to aerosolized bergamot aromatherapy oil with subsequent UVA exposure. [11]

Phytophotodermatitis is a nonimmunologic, chemical, and UVA radiation induced skin irritation. [12,13] Skin reaction induced by UVA radiation on bergapten is called berloque dermatitis. A concentration of less than 0.3% bergamot oil has been recommended. Use of bergapten-free bergamot oil, especially in the United States, has decreased the incidence of *berloque dermatitis*. However, bergamot oil in fragrance formulations is used in some countries. Although the chance of *berloque dermatitis* has become rare, cases are reported caused by the use of older versions of perfumes, fragrant waters, and colognes. [12,13,14]

Bergapten also has been shown to alter potassium channel currents, causing twitching and muscle cramps. There is a case report of a man 44 years of age who experienced muscle cramps, fasciculations, paresthesias, and blurred vision after consuming up to 4 L (approximately 1 gallon) of Earl Grey tea (flavored with bergamot oil) daily. All symptoms disappeared after switching to pure black tea.

The furocoumarins can induce genetic changes in cells exposed to UV light even in concentrations as low as 5 ppm. [15] These changes can be minimized by the application of a cinnamate-containing sunscreen, [16] but sunscreens in low concentrations (up to 1%) added to perfumes cannot suppress the phototoxicity of bergamot oil on human skin.[14] Studies suggest that many of the changes induced by bergamot oil and its components are malignant in nature. [15]

SUMMARY: Bergamot oil is used widely as a material that imparts a citrus flavor to foods and beverages. Consumption of large quantities of bergamot-flavored teas can cause muscle cramps and other symptoms. Its pleasant odor has made it a component of perfumes and cosmetics. Bergamot oil contains photosensitizing compounds that can induce rashes and pathologic cellular changes when applied topically and exposed to sunlight or other sources of UV radiation. Although caution must be maintained when using older versions of fragrances and items containing bergamot oil from foreign countries, use of bergapten-free bergamot oil in the United States has decreased instances of phytophotodermatitis.

PATIENT INFORMATION — Bergamot Oil

Uses: Bergamot oil is used widely as a flavoring and scenting agent. Some of its components might help with the management of psoriasis and vitiligo, but no clinical studies have been conducted to support these uses.

Side Effects: Photosensitizing components can induce rashes and pathologic cellular changes. Consumption of large quantities of bergamot oil-flavored tea may cause muscle cramps and other symptoms.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BERGAMOT OIL

BETA GLYCANS

DATE OF ISSUE: SEP 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Beta-1,3-glucan, beta-1,3/1,6-glycan

COMMON NAME(S): Beta glycans, beta glucans

SOURCE: Beta glycans are carbohydrates. They are natural substances that come from a variety of sources including mushrooms (eg, lentinan [see specific monograph]), oats, barley, baker's yeast, algae, and mannin.[1]

HISTORY: Beta-1,3/1,6-glycan has been studied for more than 30 years. It has immune system stimulant properties. In the 1980s, beta glycans were used to make salmon more disease resistant.[2]

CHEMISTRY: The chemistry of fungal beta-1,3-glucans has been reported. Structures were classified into triple helix, single helix, and random coil, which determined a variety of certain pharmacological characteristics. [3]

PHARMACOLOGY: In vitro testing demonstrated beta glycans induced non-specific macrophage-mediated tumor cell killing. [4] Beta glycans also increased hemagglutinin titers in certain cell lines. [5] Another report on soluble glycan demonstrates enhanced IL-1 and IL-2 production, which can be maintained 12 days post-glycan administration.[6] Beta glycans also cause a rapid decrease in tumor cells as shown in affected mice. [7] Fungal beta-1,3-glycan orally administered to mice inhibited tumor growth and potentiated immune response.[8] Another report confirms beta glycan's marked antitumor activity and enhanced ability of natural killer cell and macrophage activities in mice.[9] A review on mushroom beta glycans found differences in their effectiveness against certain tumors, primarily in cytokine expression and production.[10] Beta glycans were found to be immunostimulant in postsplenectomy sepsis in mice. Beta glycans increased survival by 75% in certain groups compared with 27% in the control group.[11] In mice with experimental colon and skin wounds, beta glycans increased tensile strength of the wounds by 42% and increased collagen biosynthesis as well.[12] Beta glycans obtained from oats were also found to possess immunostimulatory function in vitro and in vivo. [13] An overdose of a beta glycan preparation (sonifilan) failed to display antitumor activity in another report. [14]

Norwegian beta glycan is sold as an all-natural dietary supplement to boost the immune system and protect against colds and flu. It is claimed to strengthen the body's ability to fight disease-causing organisms. Because of its molecular shape, it binds specifically to macrophage surfaces, activating the immune system and increasing resistance.[2] In another product claim, beta glycans are said to be acid-resistant and pass through the stomach unchanged. Once in the intestine, macrophages attach to activate them.[1] Other product claims include beta glycans' ability to heal bed sores, nail fungus, and ear infections. [15]

Beta glycan's role in HIV appears promising in phase ? and ?? human trials but needs confirmation. [16]

TOXICOLOGY: Baker's yeast beta-1,3/1,6-glycan has a "GRAS" rating by the FDA, meaning "generally recognized as safe." [1] A report on Norwegian beta glycans noted that if a patient with an existing disease takes beta glycans, symptoms may actually worsen for a couple of days. [2] In a clinical trial testing beta glycans use in AIDS patients, side effects severe enough to be reported to the FDA were anaphylactoid reaction, back pain, leg pain, depression, rigor, fever, chills, granulocytopenia, and elevated liver enzymes (1 case each); 4 of 98 patients discontinued therapy because of side effects. [16] Beta glycans may potentiate airway allergic responses.[17,18]

A preclinical safety evaluation of soluble glycan in mice, rats, guinea pigs, and rabbits is available. Data from this report indicate that "administration of soluble glycan over a wide dose range does not induce mortality or significant toxicity." [19]

SUMMARY: Beta glycans are carbohydrates that come from mushrooms, oats, baker's yeast, and other sources. Reports in animals and a few in humans have shown that beta glycans have immunostimulant effects and antitumor actions. Beta glycans have a "GRAS" rating by the FDA, but some reports of toxicity exist, including allergy.

PATIENT INFORMATION — Beta Glycans

Uses: Although few studies in humans are available (primarily in HIV patients), beta glycans are sold as supplements to boost the immune system and have also been studied in animals for their antitumor actions.

Side Effects: The FDA classifies baker's yeast beta-1,3/1,6-glycan as "GRAS" (generally recognized as safe), but reports show beta glycans may potentiate airway allergic responses and worsen symptoms in patients with existing disease.

Dosing: In an HIV trial, patients were given 2 to 10 mg of the beta-glucan lentinan IV once a week for 8 weeks. In a second trial, 1 to 5 mg of lentinan was given IV twice a week for 12 weeks.[16]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BETA GLYCANS

BETA SITOSTEROL

DATE OF ISSUE: APR 2003

REPLACES MONOGRAPH DATED: NA

SCIENTIFIC NAME(S): *ß-sitosterol*

COMMON NAME(S): Plant sterol, phytosterol

SOURCE: Dietary consumption is the main source of plasma phytosterols. They are not synthesized endogenously. Fortified margarines used for lowering cholesterol contain 2 g of plant sterols per daily portion. [1] The sitosterols are usually obtained from soybean oil, [2] peanut oil (207 mg/100 g of unrefined oil), [3] and avocado oil (76 mg/100 g). [4] Preparations containing ß-sitosterol, derived from the South African star grass of *Hypoxis rooperi*or from species of *Pinus* and *Picea*, are available for the treatment of benign prostatic hypertrophy. [5] Saw palmetto berries also contain large quantities of beta-sitosterol and other plant sterols.

HISTORY: Plant sterols were chemically described in 1922. [6] Later in the 1950s, it was noted that these sterols lower serum cholesterol concentrations by reducing the absorption of cholesterol from the gut. However, by the 1980s, statins were introduced to the market, so the role of plant sterols in lipid lowering was diminished. Subsequently, it has been recognized that, as naturally occurring substances, plant sterols can be added to foods. Margarine appears to be an ideal vehicle. [1] Over the last 15 years, there also have been several reports in the literature indicating that phytosterols have some immunological activity. [6]

CHEMISTRY: Sterols are essential components of cell membranes, and both animals and plants produce them. The sterol ring is common to all sterols; the differences are in the side chain. They are 28- or 29-carbon alcohols. [7] ß-sitosterol is the most common plant sterol and is structurally similar to cholesterol. [1] Because of this structural similarity, ß-sitosterol can replace cholesterol in the human body. [2] ß-sitosterol is a 4-desmethyl sterol (containing no methyl groups at carbon atom number 4). [1,2] It has a double bond at the C-5 position in the ring, [7] and it is usually esterified with fatty acids in order for it to be incorporated into margarine. [2]

PHARMACOLOGY: ß-sitosterol has a limited number of pharmacological uses.

Cholesterol-lowering effects: Plant sterols in fortified margarine reduce the absorption of cholesterol from the gut by about half. This reduced absorption lowers serum cholesterol concentrations despite the compensatory increase in cholesterol synthesis that occurs in the liver and other tissues. Plant sterols are potentially atherogenic, like cholesterol, but atherogenesis does not occur because so little of the plant sterol is absorbed (approximately 5% of ß-sitosterol). [1]

A meta-analysis of 14 randomized controlled trials (N = 473) investigated the effects of plant sterols and stanols (when added to margarine) on cholesterol. Low density lipoprotein (LDL) cholesterol ranged from 116 to 174 mg/dL in the control groups in these studies. This is consistent with normal values in the general population. The margarine produced a reduction in the mean concentration of LDL cholesterol. The effect increased with age. In each age group, the dose response relation was continuous up to a dose of about 2 g of plant sterol or stanol per day. At doses of 2 g or higher, the average reduction in LDL cholesterol was 21 mg/dL for participants 50 to 59 years of age, 17 mg/dL for participants 40 to 49 years of age, and 13 mg/dL for those 30 to 39 years of age. At higher doses, no further reduction in LDL cholesterol is apparent. This trend was statistically significant ($P = 0.005$). [1]

Data suggest that in people 50 to 59 years of age, a reduction in LDL cholesterol concentration of 20 mg/dL would reduce the risk of heart disease by approximately 25% after 2 years. The effect is calculated to be superior to that expected if people merely ate less animal fat. For a person replacing butter with a plant sterol margarine, the reduction in cholesterol would be even greater. [1]

Immunomodulatory effects: Initial studies have shown that ß-sitosterol can increase the proliferation of peripheral blood lymphocytes and enhance the cytotoxic effect of natural killer cells. Further investigation revealed anti-inflammatory properties and has led to suggestions of a role in the control of chronic inflammatory conditions. [6]

Excessive physical stress such as that observed in marathon runners can cause subtle immunosuppression. This may be due, in part, to the fact that it disturbs the normal physiological equilibrium or homeostasis, including that of the immune system. Administration of ß-sitosterol (vs placebo) can prevent the typical neutrophilia, lymphopenia, and total leukocytosis. [8]

A randomized controlled trial of 47 patients with pulmonary tuberculosis investigated adjuvant ß-sitosterol therapy vs placebo. The ß-sitosterol (average dose of 60 mg/day) treatment group demonstrated increased weight gain, higher lymphocyte and eosinophil counts, and a generally faster clinical recovery. [9]

Anticancer properties: ß-sitosterol has demonstrated effects on tumor cell lines in vitro. Growth is inhibited in human colon, prostate, and breast cancer cell lines. It has been postulated that cell death (apoptosis) is initiated, probably by activation of the protein phosphatase A2 pathway. Studies using rat and mice models have shown ß-sitosterol to reduce the number of tumors. [6]

However, a cohort study performed in the Netherlands was unable to demonstrate any effect of plant sterols on the risk of colon and rectal cancers. For 6.3 years, 120,852 patients 55 to 69 years of age were followed. The average amount of plant sterols consumed by the participants was 285 mg/day. [7]

Benign prostatic hyperplasia: This nonmalignant enlargement of the prostate can lead to obstructive and irritative lower urinary tract symptoms. The majority of men over 60 years of age are considered to have urinary symptoms attributable to benign prostatic hypertrophy (BPH). The pharmacological use of plants and herbs for the treatment of BPH symptoms has been steadily growing in most countries. Nearly a quarter of men seen with previously treated BPH at a university urology clinic for urinary symptoms indicated they had tried phytotherapeutic agents. [5]

A Cochrane review of 4 randomized, controlled trials comparing ß-sitosterol with placebo (or other BPH medications) investigated the effects of ß-sitosterol on the outcomes of urinary symptom scores and flow measures. The treatment duration was short, with no study lasting longer than 26 weeks, and fewer than 600 men were evaluated. ß-sitosterol improved urinary symptoms and flow measures and was generally well tolerated. The authors of this review suggested that ß-sitosterol may be a useful treatment option for men with mild to moderate BPH, particularly those who would like to avoid or are at increased risk for adverse effects from alpha-adrenergic receptor blockers. [5] These agents (eg, prazosin) selectively block alpha-1-adrenergic receptors. The degree of smooth muscle tone in the prostate and bladder neck is mediated by the alpha-1-adrenergic receptor, which is present in high density in the prostatic stroma, prostatic capsule, and bladder neck. Blockade of the alpha-$_1$-adrenergic receptor decreases urethral resistance and may relieve the obstruction and improve urine flow and BPH symptoms.

TOXICOLOGY: On the basis of extensive safety evaluation studies, the plant sterols are generally recognized as safe when consumed in margarine at the recommended doses. The most important concern about plant sterols is that they reduce the absorption of some fat-soluble vitamins, ß-carotene, a-carotene, and vitamin E. No effects on vitamins A and K have been noted. No other side effects were evident in the randomized trials (1 of which lasted 1 year). [1] Increased concentrations of phytosterols in erythrocyte membranes may result in increased fragility; episodes of hemolysis have been reported. However, these were in patients with sitosterolemia. [10] Despite the lack of evidence of harm with beta-sitosterol use, it should be noted that hydrogenation into transfatty acids occurs with margarine ingestion. Therefore, margarine should be used in moderation only and cannot be recommended as the sole therapeutic option in the diseases mentioned in this monograph.

SUMMARY: Evidence from the literature supports positive outcomes of ß-sitosterol use for lowering cholesterol and symptom control in BPH. Effects on the immune system and a role in immunomodulation are still under investigation. Currently, there is no role for ß-sitosterol in cancer prevention.

PATIENT INFORMATION — Beta Sitosterol

Uses: Cholesterol lowering and symptom improvement in mild to moderate benign prostatic hypertrophy.

Side Effects: No major adverse effects at recommended dose. Reduced absorption of carotenes and vitamin E may occur.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BETA SITOSTEROL

BETEL NUT

DATE OF ISSUE: OCT 2002

REPLACES MONOGRAPH DATED: MAY 1992

SCIENTIFIC NAME(S): *Areca catechu* L. Family: Palmaceae

COMMON NAME(S): Betel nut, areca nut, pinlang, pinang

BOTANY: The areca tree is a feathery palm that grows to approximately 15 m in height. It is cultivated in tropical India, Sri Lanka, south China, the East Indies, the Philippines, and parts of Africa. The tropical palm trees bear the fruit all year. [1] The nut is about 2.5 cm in length[2] and may be used fresh, dried, or cured by boiling, baking, or roasting.[1]

HISTORY: The chewing of betel nut quids dates to antiquity. In the 1st century AD, Sanskrit medical writings claim "betel possesses thirteen qualities to be found in the region of heaven. It is pungent, bitter, spicy, sweet, salty and astringent. It expels wind, kills worms, removes phlegm, subdues bad odors, beautifies the mouth, induces purification and kindles passion." [3] It is widely cultivated in India, Bangladesh, Ceylon, Malaya, the Philippines, and Japan [1,4,5] and is used primarily as a mild CNS stimulant and digestive aid. The quid generally is composed of a mixture of tobacco, powdered or sliced areca nut, and slaked lime often obtained from powdered snail shells.[4] This mixture is wrapped in the leaf of the betel vine (*Piper betel* L. Family: Piperaceae). Users may chew from 4 to 15 quids a day with each quid being chewed for about 15 minutes.[6] A correlation exists between the betel quid or areca nut chewing habit and oral cancer. [4]

Because of its CNS stimulating effects, betel nut is used in a manner similar to the western use of tobacco or caffeine. [7] Chewing the nut stimulates salivary flow, thereby aiding digestion. Betel nut also has been used as an appetite stimulant. [4] The leaves have been used externally as a counterirritant and internally as an antitussive.

CHEMISTRY: The medicinal components are primarily associated with the nut and betel quid. The nuts contain at least 9 structurally related pyridine alkaloids including arecoline, arecaidine, arecaine, arecolidine, guvacine, isoguvacine, guvacoline, and coniine. [4,8] However, the most common is the parasympathetic stimulant alkaloid arecoline. The total alkaloid content can reach 0.45%. [9]

The methyl esters of arecoline and guvacoline are hydrolyzed in the presence of alkali to the respective acids, arecaidine and guvacine. The hydrolysis is catalyzed by lime, which is added to the quid. Arecoline most likely is present in the nut as a salt of tannic acid, and the lime facilitates the release of the base from the salt. [10]

Components of the betel quid, most likely from *P. betel*and not betel nuts, contain about 1% of a volatile oil, chalbetol, chavicol, cadinene, allylpyrocatechol, and safrole.[4,11]

PHARMACOLOGY: Nearly all of the scientific data involve animal or in vitro studies.

Arecoline is a parasympathetic stimulant and acts on muscarinic and nicotinic receptors. Arecoline is thought to be responsible for some of the claimed effects of betel quid chewing, such as alertness, increased stamina, a sense of well-being, euphoria, and salivation. [12,13] An antidepressant effect of the betel nut may be associated with the hexane and aqueous extracts. The extracts inhibit monoamine oxidase type A isolated from the rat brain. [14] The muscarinic cholinomimetic action of the alkaloids may also relieve symptoms associated with schizophrenia. [15]

The alkaloids of betel nut cause pupil dilation, vomiting, diarrhea, and in high doses, convulsions and death. These alkaloids have a cholinergic action, and it is believed that the central stimulating activity of arecoline is greater than that of pilocarpine. Consequently, extracts of the nut have been used for the management of glaucoma in traditional medicine.[16]

Betel nuts contain a tannin (eg, Areca ??-5-C) with angiotensin-converting enzyme (ACE) inhibitory activity in vitro. The activity of this tannin was comparable with that of captopril. Spontaneously hypertensive rats received oral doses of 100 to 200 mg/kg of the tannin extracts and the antihypertensive effects were similar to 30 to 100 mg/kg of captopril. The IV dose of the tannin was equivalent to 5 times the effect of an equivalent amount of captopril. [17]

Antibacterial activity is associated with the extracts of betel nuts. An ethanol extract inhibited *Staphylococcus aureus*, *Salmonella* sp., *Neisseria* sp., *Yersinia enterocolitica*, and *Listeria monocytogenes*.[18]

Arecoline is a basic oily liquid that has been used in veterinary medicine as a cathartic for horses and a vermifuge. Betel nut chewing induces a number of physiologic changes, including an increase in salivation, [12] gradual resorption of oral calcium induced by the lime, gingivitis, periodontitis, and chronic osteomyelitis. [19]

INTERACTIONS: Betel nut was reported to antagonize the anticholinergic effects of procyclidine in 2 patients, resulting in the occurrence of extrapyramidal symptoms.[20]

TOXICOLOGY: It is reported that nearly 10% to 25% of the world's population chews betel quid. [5,21,22] Betel nut chewing has been associated with significant cholinergic, neurological, cardiovascular, and GI manifestations. [10,23,24]

Leukoplakia, which is considered to be a precancerous lesion, and squamous cell carcinoma of the oral mucosa have been found with unusually high frequency in long-term users of betel nut. Studies in New Guinea also have shown that chewing a betel nut-slaked lime mixture has been associated with oral leukoplakia that is precancerous in up to 10% of the cases.[22,25,26,27,28] A recent study of users of areca products compared their degree of dependence and addiction to that of cocaine users, particularly if the product contains tobacco. [29,30]

Experimental evidence indicates that arecaidine and arecoline have the greatest carcinogenic potential. When tested by an in vitro cell transformation assay, both alkaloids gave a positive response, implicating both as suspected human carcinogens. [31] Other compounds, in particular 3-(N-nitrosomethylamino)propion-aldehyde (NMPA), are also highly active in decreasing mucosal cell viability, colony-forming efficiency, and in causing DNA strand breaks and cross-links in buccal cells in vitro. These effects indicate that these compounds may contribute to the oral carcinogenicity associated with chewing betel nut quid. [32]

To confirm the carcinogenic potential of the plant, mice were fed daily doses of aqueous extracts of betel nut or betel leaf, the polyphenolic fraction of the nut, or distilled water. Aqueous extracts of the nut induced tumors of the GI tract, liver, and lung in 58% of the treated mice. The polyphenolic fraction induced tumors in 17% of the mice. The aqueous extract of betel leaf and the water control did not induce tumors. Other studies by the same investigators indicate that betel leaf extract exerts an antineoplastic effect in mice when injected simultaneously with betel nut extract. [33]

The clinical implications of these animal data are poorly understood. The incidence of oral cancers increases among heavy long-term chewers of betel quids; whether this is due to the alkaloids, to the associated tannin (which accounts for 15% of the nut weight), or to carcinogens in the tobacco that is often added to the quid is unknown. What "protective" value chewing betel leaf has is also unknown.

The results of 1 small study of Filipino betel chewers found that dietary supplementation with retinol (100,000 IU/week) and beta-carotene (300,000 IU/week) for 3 months was associated with a 3-fold decrease (from 4.2% to 1.4%) in the mean proportion of oral cells with nuclear alterations suggestive of precancerous lesions. [6]

Arecaine is poisonous and affects respiration and heart rate, increases intestinal peristalsis, and can cause tetanic convulsions. Although doses of the seed in the range of 8 to 10 g have been reported to be fatal, it has been suggested that doses up to 30 g may have a low toxicity potential. [8]

Betel nut chewing has been associated with an aggravation of asthma. A dose-response relationship may exist between the use of this drug and the development of asthmatic symptoms.[34]

SUMMARY: Betel nut is used widely in many parts of the tropical world as a stimulant. In the United States, the nut is available through many Asian grocery stores. Most chewers are middle-aged or older women who spend several dollars per day on the product. Health professionals should suspect betel chewing as a cause of changes in the oral mucosa, particularly in people of Asian descent who may not readily discuss their use of the nut.

PATIENT INFORMATION— Betel Nut

Uses: Betel nut is a CNS and salivary stimulant. The leaves may act as an antitussive and topically as a counterirritant. Antihypertensive, antidepressant, and antibacterial activity has been reported in some in vitro studies.

Interactions: Betel nut was reported to antagonize the anticholinergic effects of procyclidine in 2 patients, resulting in the occurrence of extrapyramidal symptoms. [20]

Side Effects: Oral cancer and precancerous conditions are common among users, possibly because of other components of the quid. Betel may exacerbate asthma and cause periodontitis. It is contraindicated in patients with known hypersensitivity reactions to any of the components in the betel nut. The use of betel nuts during pregnancy is contraindicated.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BETEL NUT

BETONY

DATE OF ISSUE: SEP 1997

REPLACES MONOGRAPH DATED: JAN 1990

SCIENTIFIC NAME(S): *Stachys officinalis*(L.) Trevisan, also referred to as *Betonica officinalis* L. in some older texts. Family: Labiatae

COMMON NAME(S): Betony, wood betony, and bishop wort. The genus is often collectively referred to as hedge-nettles.

BOTANY: Betony is a square-stemmed, mat-forming perennial of the mint family. It is distributed widely throughout western and southern Europe. It has a rosette of hairy leaves and a dense terminal spike of pink, white or purple flowers that bloom from June to September. The plant reaches a height of 1 meter, and the above-ground parts are dried and used medicinally. It is native to Europe and is often cultivated as a garden ornamental. [1,2]

HISTORY: Few plants have as widespread a history as betony. Its use has been known since the Roman Empire, where it was considered a panacea for practically every disease. During the Middle Ages, the plant was ascribed magical powers. [3]

Today the plant continues to be used in traditional medicine. A weak infusion is sometimes taken as a tea. It is used as an astringent to treat diarrhea and as a gargle or tea for irritations of the mouth and throat. It has been given to treat anxiety and has been given as a tincture or smoked for the treatment of headache. [4] The name "betony" may derive from the Celtic form of "bew" (a head) and "ton" (good). [5]

CHEMISTRY: Betony contains about 15% tannins, which account for its astringency. A mixture of flavonoid glycosides has been isolated and found to have hypotensive properties. In addition to tannins, betony contains stachydrine, which is a systolic depressant and active against rheumatism. The plant contains about 0.5% betaine along with small amounts of numerous other compounds, none of which contribute to the activity of the plant. [4] A report lists six new phenylethanoid glycosides from the aerial parts of the plant. Phenylethanoid glycosides formerly known include acetoside, campneosides, forsythoside B and leucosceptoside B. [6]

PHARMACOLOGY: The high tannin content of the plant most likely contributes to the antidiarrheal effect. In large doses, the plant may have a purgative and emetic action. A powder of the dried pulverized leaves has been used to induce sneezing. [7] Betony possesses sedative properties, relieving nervous stress and tension. It is still used as a remedy for headache and facial pain. In combination with herbs such as comfrey or linden, betony is effective for sinus headache and congestion.[2] Other uses for betony include: Treatment of nosebleeds; use as a gargle for its positive effect on gums, mouth and throat; and treatment of diarrhea and irritations of mucous membranes. Folk remedies of betony include treatment of tumors, spleen and liver sclerosis, colds, convulsions, kidney stones, palpitations, stomachache and toothaches.[4] Betony is known to stimulate the digestive system and the liver, which may support some of these claims.[2]

TOXICOLOGY: Although there is little documented evidence of betony toxicity, caution suggests that overdosage may cause gastrointestinal irritation because of the tannin content.[4] Betony polyphenols were found to be toxic in animals.[8] Betony should not be taken during pregnancy.[2]

SUMMARY: Betony is an ornamental plant that has been used in traditional medicine for centuries. It possesses sedative properties, which may relieve stress, headache, facial pain and congestion. Because of betony's high tannin content, its treatment for diarrhea can be useful. Betony also stimulates the digestive system, but additional studies are needed to establish efficacy. The plant is non-toxic in small doses, but it may cause gastrointestinal irritation if taken in excess.

PATIENT INFORMATION — Betony

Uses: Betony is used as an astringent to treat diarrhea and as a gargle or tea for mouth and throat irritations. It has been used to treat anxiety and headaches.

Side Effects: Overdosage can cause stomach irritation, and betony should not be taken during pregnancy.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "B" MONOGRAPHS
  BETONY

BILBERRY FRUIT

DATE OF ISSUE: OCT 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Vaccinium Myrtillus,* Myrtilli fructus

COMMON NAME(S): Bilberries, bog bilberries,[1] blueberries (variety of),[2] whortleberries

BOTANY: Bilberry fruit originates from Northern and Central Europe and has been imported from parts of south-eastern Europe. These black, coarsely wrinkled berries contain many small, shiny brownish-red seeds. They have a somewhat caustic and sweet taste.[1]

HISTORY: The historical uses of dried bilberry fruit include being a supportive treatment of acute, non-specific diarrhea when administered as a tea and serving as a topical decoction for the inflammation of the mucous membranes of the mouth and throat.[1]

During World War II, British Royal Air Force pilots ate bilberry preserves before night missions in order to improve their vision. After the war, studies confirmed the folk beliefs that bilberry extracts could improve visual acuity and lead to faster visual adjustments between light (eg, glare) and darkness.[2] Some European physicians went on to recommend bilberry extracts for other eye complaints (eg, retinitis pigmentosa, diabetic retinopathy). Clinical studies, however, have not confirmed these therapeutic applications.

CHEMISTRY: According to older studies, bilberry consists of up to 10% tannins, most of which are catechol tannins. However, recent studies suggest that tannins constitute only 1.5%. In addition to tannins, bilberry contains anthocyans, flavonoids, plant acids, invert sugars and pectins. The fresh fruit does not have the antidiarrhetic effects; therefore, it must be dried to obtain the tannins which come about by the condensation of the monomeric tannin precursors during the drying process.[1]

PHARMACOLOGY: Dried bilberry fruit is used as an antidiarrhetic drug, especially in mild cases of enteritis. It is also used as a topical treatment for mild inflammation of the mucous membranes of the mouth and throat.[1]

Most clinical studies have concentrated on the fruit's anthocyanoside content. An experiment using a preparation of anthocyanosides from bilberry (equal to 25% of anthocyanidins) indicated vasoprotective and antiedema effects in experimental animals. Oral doses of 25-100 mg/kg increased the permeability of the skin capillary. Antiedema activity was discovered after intravenous or topical use.[3]

When vascular permeability is increased in rabbits by cholesterol-induced atheroma, a treatment of anthocyanosides from bilberry decreases vascular permeability. This is acheived when the drug interacts with collagen to increase its cross-links.[4] The administration of anthocyanosides before the induction of hypertension in rats maintains normal blood-barrier permeability and limits the increase in vascular permeability. This may also result from the interaction of the drug with collagens of the blood vessel walls to protect against the permeability-increasing action of hypertension.[5]

Vaccinium myrtillus anthocyanosides are effective in promoting and intensifying arteriolar rhythmic diameter changes which aid in the redistribution of microvascular blood flow and interstitial fluid formation.[6]

An investigation using an anthocyanidin pigment (IdB 1027) found in bilberries showed protective gastric effects without influencing acid secretion. The pigment was administered orally using 600 mg b.i.d. for 10 days in 10 laboratory animals. The results showed an increase in the gastric mucosal release of prostaglandin E2 which may explain the antiulcer and gastroprotective effects of IdB 1027.[7]

Anthocyans and vitamin E are natural antioxidants which produce a protective effect on liver cells damaged by injury.[8]

TOXICOLOGY: The effects of ingesting large doses of bilberry are not known. There are no known side effects or interactions with other drugs.

It is important that the fruit has not been attacked by insects and that it is free of mold. The berries should be as soft as possible or the long-stored drug will become hard and brittle.[1]

SUMMARY: The bilberry fruit is administered as a tea to treat acute, non-specific diarrhea. It may also be used topically for mild inflammation of the mucous membranes of the mouth and throat. Studies have shown various possible effects such as vasoprotectivity, antiedemic effects, decreasing vascular permeability, gastroprotectivity, hepatoprotectivity and intensifying arteriolar rhythmic diameter. However, further studies are need to prove these effects.

PATIENT INFORMATION— Bilberry Fruit

Uses: Dried bilberry tea is used internally to treat nonspecific diarrhea and topically to treat inflamed mouth and throat mucosa. Bilberry extracts demonstrably improve visual acuity and ability to adjust to changing light. Derivatives demonstrate vasoprotective, antiedema and gastroprotective effects.

Side Effects: None known.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
      BILBERRY FRUIT

BISHOP'S WEED

DATE OF ISSUE: MAY 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Trachyspermum ammi* (Linn.) Sprague, syn. *Carum copicum* Hiern, *Ptychotis ajowan DC*, *Trachyspermum copticum* (L.) Link Family: Apiaceae, Umbellifereae

COMMON NAME(S): Bishop's weed, Carum, Ajowan, Ajowan caraway, Ajowan seed, Ajava seeds, Yavani (Sanskrit), Ajowanj (Hindi), Omum

BOTANY: Bishop's weed is a smooth or slightly hairy branched annual (or perennial) reaching a height of 90 cm. It is an aromatic spice, resembling thyme in flavor. The plant is grown throughout India, mainly Rajasthan and Gujarat, preferring higher altitudes. Bishop's weed has small white flowers and leaves that are 2 to 3 pinnately divided. The fruit is harvested from February to March and is separated when dried. The oval fruits are one-seeded. The aromatic seeds are grayish-brown in color.[1]

HISTORY: The seeds of bishop's weed have long been used in India for GI ailments including diarrhea, dyspepsia, cholera, flatulence, and indigestion. [1] Its use as a household remedy for these conditions must have led to its use as a spice, as it imparts a specific taste to a wide variety of foods.

CHEMISTRY: The fruit of bishop's weed yields 2% to 4% brownish essential oil. Thymol is the main phenol comprising from 35% to 60%. It crystallizes easily and is sold in India as "flowers of Ajowan."[1] The nonthymol fraction is termed "thymene" (˜ 45%) and contains para-cymene, gamma-terpenine, alpha- and beta-pinenes, dipentene, alpha-terpinene, and carvacrol. [1] Minute amounts of caphene, myrcene, and ?^{3}-carene have also been found in the plant. Alcoholic extract of bishop's weed contains a highly hygroscopic saponin. From the fruits, both a yellow, crystalline flavone and a steroid-like substance have been isolated. The seeds also contain 6-O-beta-glucopyranosyloxythymol, a glucoside.[2] Several other chemical studies have reported 69% carvacrol in *T. ammi*,[3] a yield of 24.86% oleoresin containing 12.15% volatile oil (thymol, gamma-terpinene, para-cymene, and alpha- and beta-pinene) [4] ; the principal oil constituents of *T. ammi* are carvone (46.2%), limonene (38.1%) and dillapiole (8.9%)[5] ; the essential oil obtained by steam distillation of the fruits of *T. copticum*yielded thymol (61%), para-cymene (15%), and gamma-terpinene (11.9%).[6]

PHARMACOLOGY: Traditionally, bishop's weed has been used as a spice and as a preservative. The fruits (seeds) are used to flavor curries, pickles, biscuits, confections, and beverages.[2,4] The plant is also used in soaps and perfumes.[1] The oil, termed "Ajowan oil" is used in India as a powerful antiseptic (similar to thymol) to treat nasal catarrh and antifungal for skin diseases. It is used as a mouthwash, gargle, or toothpaste preparation in dentistry. Bishop's weed is also used as an insecticide and anthelmintic.[1] Other forms of the plant are solutions, ointments, lotions, powders, and deodorants. The plant has been shown to demonstrate antibiotic actions, as well, against *Salmonella typhosa*, *Micrococcus pyogenes* var. *aureus*, and *Escherichia coli*.

Aryuvedic use of bishop's weed has been to treat atrophy, cachexia, spasms, and rheumatism. Lung ailments, including bronchitis, the common cold, fever, cough, consumption, and emphysema are also said to benefit from bishop's weed. A paste of crushed fruit is applied on the chest for asthma and used for colic. Bishop's weed is also helpful in several GI disorders, including diarrhea, gastrosis, dyspepsia, cholera, flatulence, and indigestion. These carminitive, stimulative, tonic, antispasmodic, and parasympathomimetic actions have been proven in older animal studies. Bishop's weed produces contraction of isolated ileum, trachea, and bronchial strips in guinea pigs. Other reports demonstrated cardiac depression in frogs, decreased blood pressure in cats, and antidiuretic effects.

An extract of bishop's weed was found to inhibit platelet aggregation (mostly against arachidonic acid-induced aggregation). The mechanism, in part, may be due to redirection of arachidonic acid from the cyclooxygenase to the lipoxygenase pathway, reducing thromboxane B $_2$ formation.[7] The same report showed that the spice exhibits antiaggregatory effects and alters arachidonic acid metabolism in human platelets. [7] There also have been investigations with *T. ammi*, revealing antifungal properties.[8] The inhibitory effects of *T. ammi* extracts on hepatitis C virus (HCV) protease have been reported.[9] Others have identified a blood pressure-lowering action of the active principle (thymol) of *T. ammi* in animals. These results suggest that a channel blocker-like constituent (thymol) may explain the hypotensive and bradycardiac effects observed in in vivo studies. [10]

TOXICOLOGY: Bishop's weed is toxic in high doses and can lead to fatal poisoning. [2] Because of its ability to inhibit platelet aggregation, caution is warranted in pregnancy or with those taking drugs such as warfarin or NSAIDs.[8] The essential oils isolated from *T. ammi*seeds showed cytotoxic activity against P388 mouse leukemia cells.[11]

SUMMARY: Bishop's weed has been used traditionally in India as a spice and for GI complaints. It possesses antiseptic qualities and is said to be beneficial for lung ailments, skin diseases, and other conditions. The plant is toxic in high doses.

PATIENT INFORMATION — Bishop's Weed

Uses: Bishop's weed has been used in Ayurvedic medicine as an antiseptic, a spice, and a preservative, as well as for respiratory and GI ailments; however, there is limited information to support these uses.

Side Effects: In vivo studies demonstrate hypotensive and bradycardic effects. High doses may result in fatal poisoning. Use caution during pregnancy or when taking drugs such as warfarin or NSAIDs.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BISHOP'S WEED

BITTER MELON

DATE OF ISSUE: MAR 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Momordica charantia* L. Family: Cucurbitaceae

COMMON NAME(S): Bitter melon, balsam pear, bitter cucumber, balsam apple, "art pumpkin", cerasee, carilla cundeamor

BOTANY: Bitter melon is an annual plant growing to 6 feet tall. It is cultivated in Asia, Africa, South America, and India and is considered a tropical fruit. The plant has lobed leaves, yellow flowers, and edible (but bitter-tasting), orange-yellow fruit. The unripe fruit is green and is cucumber-shaped with bumps on its surface. The parts used include the fruit, leaves, seeds, and seed oil. [1,2,3]

HISTORY: Bitter melon has been used as a folk remedy for tumors, asthma, skin infections, GI problems, and hypertension. [4] The plant has been used as a traditional medicine in China, India, Africa, and southeastern US. [3] The plant has been used in the treatment of diabetes symptoms. In the 1980s, the seeds were investigated in China as a potential contraceptive. [1]

CHEMISTRY: Chemical constituents from whole plants, fruits, and seeds of bitter melon have been isolated and described. [5,6,7]

Specifically, bitter melon contains the glycosides mormordin and charantin. Charantin is a hypoglycemic agent composed of mixed steroids. [2,4] A pyrimidine glycoside has also been found.[8] The alkaloid mormordicine is also present, along with a fixed oil. [1] Leaves contain iron, sodium, and vitamins including thiamine, riboflavin, niacin, and ascorbic acid.[4]

An insulin-like, hypoglycemic peptide[1] "polypeptide-P"[2] is present in bitter melon. This has been isolated from the fruit, seeds, and tissue of the plant and has a molecular weight of 11,000 in 1 report.[9] An overview of specific antidiabetic constituents in bitter melon is available. [10]

Bitter melon seeds contain 32% oil, with stearic, linoleic, and oleic acids. [4] The seeds also contain the pyrimidine nucleoside vicine, [10] the glycoproteins alpha-momorcharin and beta-momorcharin (abortifacients) and lectins.[3] Amino acid composition in seeds is described as well.[11] Insulin-like molecules also have been found in the seeds.[12]

PHARMACOLOGY: Beneficial effects of bitter melon have been studied and reviewed. [3,13,14,15] These effects include hypoglycemic, antimicrobial, antifertility, and others.

The hypoglycemic effects of bitter melon have been clearly established in animal and human studies. [16,17] Constituents of the plant that contribute to its hypoglycemic properties include charantin, polypeptide P, and vicine. [2,10,18,19] Reduction of blood glucose and improvement of glucose tolerance are the mechanisms by which the plant exerts its actions.

Animal studies document the hypoglycemic effects and include reports in diabetic mice; [20,21,22] studies in rats,[23,24,25,26] including improvement in glucose tolerance,[27] sustained decrease in blood glucose levels even after 15 days of discontinuation of bitter melon treatment (as well as a decrease in serum cholesterol levels),[28] and a suggested oral hypoglycemic mechanism involving the presence of viable beta cells; [29] and a study in diabetic rabbits, which also confirmed the plant's consistent hypoglycemic effects.[30]

Other mechanisms for hypoglycemic effects include extrapancreatic actions such as increased glucose uptake by tissues, glycogen synthesis in liver and muscles, triglyceride production in adipose tissue, and gluconeogenesis. [31] Another report suggests the activity to be partly due to increased glucose use in the liver, rather than an insulin secretory effect.[32] Hepatic enzyme studies demonstrate bitter melon's hypoglycemic activity without glucose tolerance improvement in mice; [33] hypoglycemic activity by depression of blood glucose synthesis through depression of enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase, along with enhancement of glucose oxidation by enzyme G6PDH pathway;[34] and hypoglycemic actions involving hepatic cytochrome P450 and glutathione S-transferases in diabetic rats.[35] One report finds retardation of retinopathy (a diabetic complication) in diabetic rats administered a fruit extract of bitter melon. [36] At least 1 animal study finds no hypoglycemic effects in diabetic rats given a freeze-dried preparation of the plant for 6 weeks. [37]

Bitter melon improved glucose tolerance in humans.[27] Another study reported improved glucose tolerance in 18 type 2 diabetic patients with 73% success from a juice preparation of bitter melon.[38] Another report observed a 54% decrease in postprandial blood sugar, as well as a 17% reduction in glycosylated hemoglobin in 6 patients taking 15 g of aqueous bitter melon extract.[2] A report is also available on patients taking a powder preparation of the plant. [39] Clinical trials using fresh fruit juice in 160 diabetic patients controlled diabetes. Bitter melon did not promote insulin secretion but did increase carbohydrate use. [4] A review describing the antidiabetic activity of bitter melon discusses in vitro, animal, and human studies, mechanisms of action, and the phytochemicals involved. [10]

Antimicrobial effects of bitter melon have been documented. Roots and leaf extracts have shown antibiotic activity. [3,4] One study reports cytostatic activity from bitter melon aqueous extract,[40] as constituents momorcharins have antitumor properties and can inhibit protein synthesis. [41] Similarly, the plant also inhibits replication of viruses, including polio, herpes simplex 1, and HIV. [3,10] A study on antipseudomonal activity reports bitter melon to be effective, but not promising, in overall results. [42] Antiviral and other effects of bitter melon have been reviewed. [3]

Bitter melon exhibits genotoxic effects in *Aspergillus nidulans*.[43] It is cytotoxic in leukemia cells as a guanylate cyclase inhibitor.

Bitter melon's role in fertility has been reported. A protein found in the plant was found to show antifertility activity in male rats. [44] Oral administration of the fruit (1.7 g/day extract) to male dogs caused testicular lesions and atrophy of spermatogenic aspects. In female mice, the plant exhibited similar, but reversible, antifertility effects.[10] Momorcharins are capable of producing abortions.[41] Uterine bleeding has been induced in pregnant rats given the juice, as well as in rabbits, but not in nonpregnant females.[10] The ripe fruit has been said to induce menstruation. [1]

Other effects of bitter melon include the following: Dose-related analgesic activity in rats and mice, [45] anti-inflammatory actions,[10] and treatment for GI ailments, such as gas, ulcer, digestion, constipation, dysentery, [1,4] or hemorrhoids.[46] The plant has also been used for skin diseases (eg, boils, burns, infections, scabies, psoriasis),[4] and for its lipid effects[10] and hypotensive actions.[4,10] The plant has also been used as an insecticide. [3,4]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Bitter melon as an unripe fruit is commonly eaten as a vegetable [2,3] Bitter melon extract is said to be nontoxic.[3] The plant is relatively safe at low doses and for a duration of = 4 weeks.[1] There are no published reports of serious effects in adults given the "normal" oral dose of 50 ml. In general, bitter melon has low clinical toxicity, with some possible adverse GI effects.[10]

Because of the plant's ability to reduce blood sugar, some caution is warranted in susceptible patients who may experience hypoglycemia. [1] Two small children experienced hypoglycemic coma resulting from intake of a tea made from the plant. Both recovered upon medical treatment. [10] Another report concerning increased hypoglycemic effect noted an interaction in a 40-year-old diabetic woman between *M. charantia* (a curry ingredient) and chlorpropamide, which she was taking concurrently for her condition. [47]

The red arils around bitter melon seeds are toxic to children. The juice given to a child in 1 report caused vomiting, diarrhea, and death. [4]

Bitter melon's hepatotoxic effects have been demonstrated in animals, in which enzymes became elevated following plant administration. The momorcharin constituents may induce morphological changes in hepatocytes as well. [10]

The seed constituent, vicine, is a toxin said to induce "favism," an acute condition characterized by headache, fever, abdominal pain, and coma [3,10]

Bitter melon is not recommended in pregnant women because of its reproductive system toxicities (see Pharmacology, antifertility section), including induction of uterine bleeding and contractions or abortion induction. [3,10,41]

SUMMARY: Bitter melon is an edible tropical fruit used mainly as a traditional medicine in China, India, and Africa. Its effects are well documented in the area of hypoglycemia but also include antimicrobial and antifertility actions. Human studies to substantiate the plant's use as an antidiabetic drug are promising. Its toxicity profile in adults is low but may cause problems in children. Bitter melon use is not recommended in pregnant women.

PATIENT INFORMATION— Bitter Melon

Uses: Bitter melon's effects include hypoglycemic, antimicrobial, antifertility, and others.

Side Effects: Use with caution in hypoglycemic patients. The red arils around bitter melon seeds are toxic to children. The plant is not recommended in pregnant women because it may cause uterine bleeding and contractions or may induce abortion.

Interactions: Increased hypoglycemic effect when *M. charantia* and chlorpropamide are coadministered.

Dosing: Bitter melon juice has been recommended for diabetes at daily doses of 50 to 100 mL; 900 mg of fruit given 3 times/day also has been given for the same indication. There are no clinical trials available to substantiate these doses.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BITTER MELON

BITTERSWEET NIGHTSHADE

DATE OF ISSUE: SEP 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Solanum dulcamara* L. Family: Solanaceae

COMMON NAME(S): Bittersweet nightshade, deadly nightshade, bittersweet, bitter nightshade, felonwort, violet-bloom, woody nightshade, fellen, scarlet berry, snake berry, mortal,[1] fever twig,[1] dulcamara[2]

BOTANY: The bittersweet is a member of the same family as the potato and tomato. A number of members of the genus have been identified. This plant is found throughout Eurasia, the United States and Canada. Bittersweet is a vine-like perennial that grows to heights of 10 feet. It has alternating heart-shaped oval leaves that usually have two small ear-like segments at their bases. Its star-shaped flowers bloom from April to September; the flowers are pinkish-purple with bright yellow stamens. The flowers produce green berries that turn bright red upon maturing. [3]

HISTORY: The Latin name "dulcamara" refers to the flavor of the berries, which are first bitter, then unpleasantly sweet. [3] Although the plant has long been recognized as being highly toxic, it has been used as an external remedy for skin abrasions. Its use to treat "felons" (inflammations around nail beds) may be the source of the name "felonwort." The plant has been investigated for possible antirheumatic, diuretic, narcotic and sedative activity, but these actions are linked to the toxicity of the plant and therefore have not been exploited.

CHEMISTRY: Chemical investigations into the composition of bittersweet have identified an ever-growing number of alkaloids and other organic compounds in the leaves and fruits. The most widely recognized of these compounds are solanine and the glucoside dulcamarin. Related compounds include gamma-soladulcine, soladulcidine, solasonine, solamargine and lycopene. Other compounds include soladulcosides A and B. [4] Green and yellowing fruits contain a higher percentage of the glycoalkaloids than ripe fruits. [5]

PHARMACOLOGY/TOXICOLOGY: The FDA classifies bittersweet as an unsafe poisonous herb because of the presence of the toxic compounds solanine, solanidine and dulcamarin.

Solanine is poorly absorbed from the gastrointestinal tract and is rapidly eliminated in the urine and feces of animals. Because of its structural similarity to cardiac glycosides, solanine has weak cardiotonic activity. Like saponin, solanine causes hemolytic and hemorrhagic damage to the gastrointestinal tract. [6] Although a 200 mg oral dose of solanine has not been associated with toxicity in man, the oral LD_{50} in rats is about 590 mg/kg.[6] Solanine poisoning is often confused with bacterial gastroenteritis, with symptoms appearing only after a latent period of several hours following ingestion. The most common source of solanine poisoning has been the tuber of the potato.[6] Symptoms of solanine poisoning include headache, convulsions, cyanosis, stomach ache, scratchy throat, subnormal temperature, paralysis, dilated pupils, vertigo, vomiting, diarrhea, speech difficulties, shock, circulatory and respiratory depression and death.

Adults appear to be relatively resistant to the toxicity of solanine, but fatal intoxications are more common in children. [7]

Emesis, fluid replacement and supportive care as for gastroenteritis should be given. [7] Despite this typically aggressive therapy, the results of one study in mice fed ripened fruit suggested that because no gastrointestinal or neurologic toxicity was observed, aggressive treatment of children who ingest ripened berries may not be necessary.[8] Nevertheless, these investigators found significant neurologic and pathologic gastrointestinal toxicity when mice were fed unripened fruits, indicating that poisoning with this plant should be considered a critical situation. Other investigators have confirmed the pathologic changes in the gastrointestinal tract (glandular mucosal necrosis and necrosis of the small intestine) in hamsters fed ground bittersweet. [9]

Concern has emerged linking the glycosides of certain solanum species (ie, potato) to fetal malformations in animals and humans. Extracts of bittersweet have been shown to cause an elevated incidence of craniofacial malformations in hamsters, which was statistically significant compared to controls. [10] The alkaloids solasodine, soladulcine and related compounds were linked to the malformations.

SUMMARY: Bittersweet is a toxic plant that grows wild throughout most of the United States. Although the plant has been used in traditional medicine, its use was generally limited to external application. Ingestion of the unripened berries, particularly by children, constitutes a medical emergency; other parts of the plant are also toxic. The toxicity is caused by solanine and related glycoalkaloids.

PATIENT INFORMATION — Bittersweet Nightshade

Uses: Bittersweet has been used as a traditional external remedy.

Side Effects: The plant is toxic. Ingestion of unripened berries should be considered a medical emergency. Toxic symptoms may be delayed for several hours.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BITTERSWEET NIGHTSHADE

BLACK COHOSH

DATE OF ISSUE: MAY 1998

REPLACES MONOGRAPH DATED: SEP 1992

SCIENTIFIC NAME(S): *Cimicifuga racemosa*(L.) Nutt. Family: Ranunculaceae. Plants associated with the name include other *Cimicifuga* species, *Macrotys actaeoides* and *Actaea racemosa* L.

COMMON NAME(S): Black cohosh, baneberry, black snakeroot, bugbane, squawroot, rattle root[1]

BOTANY: Black cohosh grows in open woods at the edges of dense forests from Ontario to Tennessee and west to Missouri. This perennial grows to 8 feet and is topped by a long plume of white flowers that bloom from June to September. Its leaflets are shaped irregularly with toothed edges. The term "black" refers to the dark color of the rhizome. The name "cohosh" comes from an Algonquian word meaning "rough," referring to the feel of the rhizome.[2]

HISTORY: The roots and rhizomes of this herb are used medicinally. Traditional uses include the treatment of dysmenorrhea, dyspepsia and rheumatisms. A tea from the root has been recommended for sore throat. The Latin name cimicifuga means "bug-repellent" and the plant has been used for this purpose. American Indians used the plant to treat snakebites.

Old-time remedy "Lydia Pinkham's Vegetable Compound" (early 1900s) contained many natural ingredients, one of which was black cohosh.[3]

Remifemin, the brand-name of the standardized extract of the plant, has been used in Germany for menopausal management since the mid-1950s.[4]

CHEMISTRY: German reports from the late 1960s discussing the contents of black cohosh (eg, acetin) are available.[5,6,7]

Black cohosh contains alkaloids including N-methylcytisine and others, tannins and terpenoids. The terpenoid mixture consists of actein, 12-acetylactein and cimigoside. Other constituents found in the plant include acetic, butyric, formic, isoferulic, oleic, palmitic and salicylic acids, racemosin, formononetin (an isoflavone), phytosterols, acteina (resinous mixture) and volatile oil.[8]

An amorphous resinous substance called cimicifugin (macrotin) accounts for approximately 15% to 20% of the root. Cimigoside (cimifugoside) and 27-deoxyactein have also been isolated.[9,10]

PHARMACOLOGY: The purported estrogenic effects of the plant could not be reproduced in extensive tests in mice. In one study, there was no evidence of a direct or indirect influence on gonadal function.[11] However, other studies indicate that methanol extracts of *C. racemosa* contain substances that bind to estrogen receptors.[12] Intraperitoneal injection of the extract in ovariectomized rats caused a selective reduction in luteinizing hormone (LH) level with almost no effect on follicle-stimulating hormone (FSH) or prolactin levels.[13]

In women treated for 8 weeks with the commercial product *Remifemin* and luteinizing hormone but not follicle-stimulating hormone, levels were reduced significantly. This product is used for the management of menopausal hot flashes. Analysis of the commercial product identified at least three fractions that contribute synergistically to the suppression of LH and bind to estrogen receptors. These data suggest that black cohosh has a measurable effect on certain reproductive hormones.[14] The product may offer an alternative to conventional hormone replacement therapy (HRT). In patient populations with a history of estrogen-dependent cancer (although it possesses some estrogenic activity), *Remifemin* shows no stimulatory effects on established breast tumor cell lines dependent on estrogen's presence. Instead, inhibitory actions were seen. In addition, the product exerts no effect on endometrium, so there is no need to "oppose" therapy with progesterone as with conventional HRT. The plant extract's action proves to be more like estriol than estradiol, which is associated with higher risk for breast, ovarian and endometrial cancers. Estriol exerts its effects mainly on the vaginal lining rather than the uterine lining, as estradiol does. More studies are needed, however, to address osteoporosis and bone health with use of the product.[4]

One report finds no signs of uterine growth and vaginal cornification in ovariectomized rats given black cohosh extract. This helps to confirm that the plant's beneficial effects on menopausal discomfort cannot be explained as the traditional estrogenic type.[15]

A clinical and endocrinologic study has been performed in 60 patients under 40 years old who had hysterectomies. Four randomized treatment groups included estriol, conjugated estrogens, estrogen-gestagen sequential therapy or black cohosh extract. Results of this report showed no significant differences between groups in success of therapy.[16]

Other actions of black cohosh include: Constituent actein (it has been shown to have a hypotensive effect in rabbits and cats and causes peripheral vasodilation in dogs);[17,18] antimicrobial activity (both by black cohosh[19] and related species *Cimicifuga dahurica*);[8] in vivo hypocholesteremic activity; and therapy for patients with peripheral arterial disease (by causing peripheral vasodilation and increase in blood flow from constituent acteina).[8]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Overdose of black cohosh may cause nausea, vomiting, dizziness, nervous system and visual disturbances, reduced pulse rate and increased perspiration. The constituent acteina does not possess toxicity in animal studies.[8]

Large doses of the plant may induce miscarriage.[2] Black cohosh is contraindicated in pregnancy and may cause premature birth in large doses.[8]

A case report describes a 45-year-old woman who experienced seizures, possibly related to consumption of an herbal preparation containing black cohosh.[20]

SUMMARY: Black cohosh has been used to control symptoms of menopause as an alternative to conventional HRT therapy. The plant seems to have no effect on estrogen-dependent cancers and may even exhibit inhibitory effects against the disease. Black cohosh may also be useful in other areas such as treatment for hypercholesteremia or peripheral arterial disease. Overdose of the plant reportedly causes nausea, dizziness and nervous system disturbances. It is contraindicated for use in pregnant women.

PATIENT INFORMATION — Black Cohosh

Uses: Black cohosh has been used to help manage some symptoms of menopause and as an alternative to HRT therapy. It may be useful for hypercholesteremia treatment or peripheral arterial disease.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Overdose causes nausea, dizziness, nervous system and visual disturbances, reduced pulse rate and increased perspiration.

Dosing: The crude root has been administered at daily doses of 40 to 200 mg/day in clinical studies, although historically, higher doses of 1 g of root have been used. Standardized extracts such as *Remifemin*(Schaper & Brummer) standardized to 1 mg triterpene glycosides in 20 mg of extract, have been administered at doses from 2 to 8 mg/day of glycosides for menopause and related conditions.[14,16,21,22]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BLACK COHOSH

BLACK CULVER'S ROOT

DATE OF ISSUE: SEP 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Veronica virginica* = *Veronicastrum virginicum* (L) Farw. (syn: *V. sibiricum* L. Pennell, *V. Sibirica* L.) *Leptandra virginica* (Nutt.)[1] Fam: Scrophulariaceae

[1] Note: This plant was assigned by Linnaeus to the genus *Veronica*, but later was put in genus *Leptandra* by Nuttall, which is now used by present-day botanists. Different taxonomic names are confusing and a revision of the genus is needed. [1,2,3]

COMMON NAME(S): Black Root, Culver's Root, Culveris Root, Culvers Physic, Physic Root, Bowman's Root, Brinton Root, Hini, Leptandra, Leptandra-Wurzel, Oxadody, Tall Speedwell, Tall Veronica Whorlywort [1,2,3]

BOTANY: Black culver's root is a tall, herbaceous perennial consisting of a simple, erect stem growing from approximately 0.9 to 2 m tall. Whorled leaves (from 4 to 7) terminate in spikes of white flowers approximately 8 to 25 cm long, which bloom in July through August. The purple flower variety is termed *Leptandra purpurea*. Native to North America, but growing elsewhere, black culver's root prefers meadows and rich woodlands. The medicinal parts of the plant include the dried rhizome with the roots.[2,3]

HISTORY: The first documented use of culver's root was when Puritan leader Cotton Mather requested it as a remedy for his daughter's tuberculosis in 1716. Culver's root was used by early physicians as a powerful laxative and emetic. Native American tribes also used the plant and drank tea preparations to induce vomiting and to help cleanse the blood. Herbalists have used culver's root for its ability to increase the flow of bile from the liver. [2]

CHEMISTRY: Chemical analysis studies report constituents from genus *Veronicastrum* and *Veronica*,[4] and the presence of aucubin from *Veronica* species.[5] Culver's root is known to contain volatile oil, cinnamic acid derivatives (such as 4-methoxy cinnamic acid, 3,4-dimethoxycinnamic acid and their esters), tannins, and bitter principle leptandrin.[1,3] Asian studies involving *Veronicastrum sibiricum* list the constituents mannitol, resin, gum, phytosterols, glycoside, and saponins as also being present in the plants.[6,7,8,9]

PHARMACOLOGY: Black culver's root has been used for years as a liver tonic, for liver or gallbladder disorders, and to promote bile flow. Culver's root is also a stomach tonic, aiding in digestion. It is used both for diarrhea and chronic constipation, and hemorrhoids as well. [1,2,3] Anti-ulcer activity in rats given related species *Veronica officinalis* L. has been demonstrated.[10]

TOXICOLOGY: No health hazards have been associated with proper administration of culver's root. Avoid using with bile duct obstruction, gallstones, internal hemorrhoids, menstruation, and pregnancy.[11]

SUMMARY: Black culver's root has been used for centuries as a liver tonic and to increase the flow of bile. It may also be useful for GI problems such as indigestion, diarrhea, or constipation. No major toxicity from the plant has been reported. More studies are needed to confirm the plant's uses. A taxonomic revision of the genus is needed.

PATIENT INFORMATION— Black Culver's Root

Uses: Black culver's root has been used as a liver tonic, for liver or gallbladder disorders, and to promote bile flow. It has also been used for various GI problems; however, no studies are available to confirm these uses.

Side Effects: No health hazards have been associated with proper administration. Avoid using with bile duct obstruction, gallstones, internal hemorrhoids, menstruation, and pregnancy.[11]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BLACK CULVER'S ROOT

BLACK HAW

DATE OF ISSUE: MAY 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Viburnum prunifolium* L. Caprifoliaceae (honeysuckle family)

COMMON NAME(S): Black haw, sweet-haw, stagbush

BOTANY: Black haw is a large shrub or small tree with white flowers and shiny, juicy, blue-black berries that is native to the eastern and central United States. An extensive study of *Viburnum*botany and pharmacognosy was published in 1932.[1] The southeastern US species *V. alnifolium* Marsh. has been used to adulterate *V. prunifolium*,[2] as has mountain maple (*Acer spicatum*),[3] and confusion as to the identity of commercial samples muddled early research on black haw. The root bark is preferred to the trunk bark as the usual drug product.

HISTORY: Black haw was used by Cherokee and Delaware American Indian tribes as an antispasmodic for female reproductive complaints. It reputedly was used by slaveowners to forestall abortions in female slaves attempting to abort using cotton root bark.[3] Its use was sufficiently common that it was official in the *U.S. Pharmacopeia* from 1882 to 1926 and then in the *National Formulary*. It was popularized by the Eclectic movement as a mild sedative and uterine antispasmodic.

V. prunifolium also has been used for menstrual cramps and threatened miscarriage and as a "partus preparation."

CHEMISTRY: The bioflavonoid amentoflavone[4] and the coumarin scopoletin[5] have been isolated from black haw root bark. Much of the earlier chemistry was not definitive because the source material was widely adulterated, and reports of salicin from black haw have since been disproven.[6] The compounds isovaleric acid[7] and 1-methyl-2,3-dibutyl hemimellitate[8] also have been reported. Iridoid glycosides have been reported from stem bark of black haw.[9] Further investigation using modern phytochemical methods is warranted.

PHARMACOLOGY: Early pharmacologic studies on black haw failed to find an effect on isolated uterine tissues from guinea pig,[10,11,12] human,[13] and rabbit.[14] This may have been caused by the aforementioned adulteration with other species. Using well-defined plant material, a definite relaxant activity in isolated uterine tissue was detected in guinea pigs,[15] rats,[16,17] and humans.[16] However, the potency of commercial preparations was noted to vary widely,[18] and an active principle proved elusive. Then scopoletin and amentoflavone were isolated and shown to contribute to the uterine relaxant activity.[4,5,19]

No controlled clinical trials have been reported on black haw in dysmenorrhea or other conditions.

TOXICOLOGY: Extracts of the substituted species *V. alnifolium*were reported to be 10-fold more toxic to dogs than *V. prunifolium* and, therefore, unsuitable as a substitute.[2] Authentic black haw extracts were lethal to dogs at a 10 g/kg equivalent dose.

Black haw appears to be safe, although use in pregnancy and lactation should be discouraged because of insufficient safety data.

SUMMARY: Black haw has been used for dysmenorrhea, a use supported by its relaxant effect on isolated uterine tissue in experimental preparations. This use has not been validated by human clinical trials.

PATIENT INFORMATION— Black Haw

Uses: Black haw is used to treat dysmenorrhea.

Side Effects: Authentic black haw extracts were lethal to dogs at a 10 g/kg equivalent dose.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BLACK HAW

BLACK WALNUT

DATE OF ISSUE: FEB 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Juglans nigra* Family: Juglandaceae

COMMON NAME(S): Black walnut

BOTANY: There are about 15 species of Juglans. "Walnut" refers to several varieties, most commonly the English or Persian walnut (*J. regia*; see monograph) and the black walnut (*J. nigra*). Walnut trees have short trunks with round-topped crowns, and can grow to 45 m in height. The black walnut is native to the deciduous forests of the eastern United States (central Mississippi, Appalachian regions) and Canada. Its wood is valued for its rich beauty and yields valuable lumber, prized for furniture, cabinets, and gun stocks. The fruit is an elongated drupe, containing a 4-ribbed edible nut within a thick, hard, black shell (smaller in size than the English walnut).[1,2,3,4]

HISTORY: Walnuts have been found in prehistoric deposits dating from the Iron Age in Europe. They are mentioned in the Bible; King Solomon's nut garden dates back to 940 BC.[4] Black walnuts were an important food for American Indians and early settlers.[2] The genus name, "*Juglans*," comes from the Latin "*Jovis glans*," meaning "nut of Jupiter" or nut of the gods. Many legends have been associated with the walnut. Greeks and Romans regarded it as a symbol of fertility. In the Middle Ages, walnuts were thought to ward off witchcraft, the evil eye, and epileptic fits, from evil spirits lurking in the walnut branches. Medicinal uses of walnuts included treatments for swollen glands, shingles, and sores. The oil was used for intestinal discomfort. [4]

CHEMISTRY: Black walnuts contain juglone (5-hydroxy-1,4-naphthagulone) alpha hydro-juglone and its glycoside beta-hydrojuglone, caffeic acid, hyperin, kaempferol, and tannin.[3] Ellagic acid is also present. [3,5] Black walnuts contain 15 to 20 g of protein/100 g. Trace minerals present include 3 mg of iron and zinc, 2 mg of sodium, phosphorus, and magnesium.[2,3,6] Black walnuts contain 678 to 694 calories/100 g. Fat (oil) content is 60%. [2] Methyl 2-benzimidazolylcarbamate has been reported in black walnut fruit.[7]

PHARMACOLOGY: Aside from the use of its wood as a valuable lumber, black walnut has been employed in other ways; extract of black walnut was used to dye the hair,[1,3] skin, and clothing.[4] Black walnut as a food is common, including its presence in baked goods, candies, and frozen foods. [2,4] Even its shells, after hulling, have been used as fillers in glues, roofing materials, and tiles. They are also employed as stuffing for toys and as abrasives. Walnut shells are even burned for energy.[4]

The black walnut is important for its nutritional value (see Chemistry). The nuts are high in calories, a good protein source, and rich in dietary fiber and essential fatty acids (EFAs), which protect against heart disease and reduce cholesterol. EFAs reduce platelet adhesion and may also play a role in reducing arrhythmias and cardiac arrest.[8,9,10,11] Dietary fiber content not only helps reduce cholesterol but aids in relieving constipation. [11,12]

Black walnut is beneficial in certain skin problems, including eczema, pruritus, psoriasis, and blistering. [3,12] It has been used as an astrigent to shrink tissues and as a tonic restorative.[3] Black walnut has been shown to kill skin parasites due to its disinfectant qualities. Constituent juglone is antimicrobial and antiparasitic. [3,13] Black walnut has been used for warts. Eye irritations and styes have been relieved by black walnut as well. [3] Internally, black walnut is beneficial for these same conditions. It is mentioned by many sources as a vermifuge. The anthelmintic properties are said to be due to high tannin content. The bark (including kernel and green hull) has been used by Asians and certain American Indian tribes to expel worms. Other fungal and parasitic infections including ringworm and tapeworm have been eliminated by black walnut.[1,12] Other uses for black walnut include reduction of fluid secretion in glandular disturbances, treatment of gout and rheumatism, and for purported anti-cancer effects.[3,14] The toxic nature of juglone makes it a possible candidate for chemotherapy.[15]

No major human clinical trials regarding black walnut and its claimed uses have been found through a search of medical literature.

TOXICOLOGY: Juglone, the naphthaquinone found in black walnut and many others in the family Juglandaceae, is regarded as a toxin. Induced toxicosis in horses has been studied. Juglone 1 g orally administered in horses caused inconsistent mild signs of laminitis, in which inflammation of the feet around the hooves occurs, resulting in lameness from the pain.[16] Other studies have confirmed this type of toxicosis from black walnut,[17,18] including a detailed description in a case report. [19] In contrast, 1 report confirms the laminitis to be from black walnut but not from the constituent juglone, because the heartwood of black walnut, which is devoid of this component, was used.[20] Black walnut's effects on equine vasculature have been evaluated. [21,22,23] One mechanism suggested in another report is that black walnut increases capillary pressure, causing transvascular fluid movement, resulting in edema and possible eventual ischemia. [24]

Allergic reactions to black walnut in animals and humans have occurred. [25] Allergy studies involving skin testing with black walnut pollen (and other pollens) finds moderate allergic reactions in certain individuals. [26] Reports on dermatitis from black walnut[27,28] and on *E. coli* in black walnut[29] are available.

Black walnut is contraindicated in pregnancy because of possible cathartic effects at higher doses and in patients with chronic disease of the GI tract. [30,31]

SUMMARY: The use of black walnut dates back many thousands of years. Black walnut is not only used for its wood, but in foods and commercial products (shells) as well. Black walnuts are high in nutritional value, containing essential fatty acids known to protect against heart disease. It can be beneficial in certain skin disorders, for constipation, and as an anti-infectant or vermifuge. Constituent juglone is a known toxin. Laminitis in horses and allergies in humans can be caused by black walnut.

PATIENT INFORMATION— Black Walnut

Uses: Black walnut has been used as a wood source. It can also be beneficial in certain skin disorders, for constipation, and as an anti-infectant or vermifuge. It has nutritional value and its EFAs help protect against heart disease and reduce cholesterol. There are no human trials to support these effects.

Side Effects: Do not use during pregnancy or chronic GI tract disease. Juglone, the naphthaquinone found in black walnut and many others in the family Juglandaceae, is regarded as a toxin. Allergic reactions have occurred.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BLACK WALNUT

BLOODROOT

DATE OF ISSUE: JAN 2001

REPLACES MONOGRAPH DATED: JUL 1992

SCIENTIFIC NAME(S): *Sanguinaria canadensis*L. Family: Papaveraceae (poppies)

COMMON NAME(S): Bloodroot, red pucoon, red root, coon root, paucon, sweet slumber, tetterwort, snakebite, Indian paint

BOTANY: Bloodroot is an early spring wildflower that grows in woodlands of the eastern United States and Canada. Its single white flower emerges from the ground folded within a grey-green leaf and the delicate petals rapidly detach as the seed pod matures. The stout rhizome yields a bright red latex when cut, giving the plant its common name. The root and rhizome are collected in the fall for medicinal use.

HISTORY: Bloodroot was used by eastern Native American tribes as a red dye and in the treatment of ulcers, skin conditions, and as a blood purifier. All of these medicinal uses apparently derive from the appearance of the blood-red latex exuded from the fresh root. The juice was also used for coughs and sore throats, with the bitter taste masked by placing the juice on a lump of maple sugar that was then sucked. Higher oral doses were observed to have expectorant and emetic properties. The root entered 19th century medicine as a caustic topical treatment for skin cancers, polyps, and warts. In 1983 an extract of bloodroot was marketed in toothpaste and mouthwashes for prevention of gum disease and plaque (see Pharmacology).

CHEMISTRY: Sanguinaria root is an abundant source of isoquinoline alkaloids, with the major quaternary alkaloids sanguinarine and chelerythrine having been isolated in the 19th century. A dimeric isoquinoline, sanguidimerine, was isolated as a major constituent more recently. [1,2] Protopine is also a major constituent. Other minor alkaloids[3] possess similar structures. The biosynthesis of sanguinarine and related alkaloids was studied in a related plant, *Macleaya cordata* (papaveraceae), which is an alternate commercial source.[4] It was demonstrated that alkaloid biosynthesis in bloodroot cell cultures was induced by the flavonoids quercitin or rutin but not by related compounds baicalein, naringin, naringenin, catechin, caffeic acid, and benzoic acid, [5] and that this process appeared to require both protein kinase C and G protein signal transduction.[6]

The alkaloids have been characterized and quantified by a variety of methods. Detection in edible cooking oils (see Toxicology) was accomplished with thin-layer chromatography,[7] while saliva levels of sanguinarine have been determined by ion-pair HPLC. [8] More recently, FAB mass spectroscopy,[9] reversed-phase HPLC,[10] and capillary electrophoretic methods[11] have been reported.

PHARMACOLOGY

Biochemistry: Sanguinarine has been found to intercalate with DNA[12,13,14] favoring GC-rich sequences.[13,15] It has also been found to inhibit NaK-ATPase[16,17,18] in several systems, including human erythrocytes.[19] A431 cancer cells were found to undergo apoptosis at lower doses of sanguinarine than normal cells. [20] Other documented effects are inhibition of tubulin function by sanguinarine and chelerythrine, [21] and protein kinase C inhibition.[22] This latter effect has been shown to depend on reaction of the alkaloids with critical thiol groups. [22] Such a mechanism may also underlie some of these alkaloids' other diverse effects, including inhibition of liver aminotransferase,[23] inhibition of phosphorylation of a mitochondrial protein from rat heart, [24] inhibition of NF?B activation,[25] and induction of calcium release from sarcoplasmic reticulum.[26]

Antimicrobial activity: Sanguinarine has long been known to have antibiotic activity in vitro. [27] An ecological role in chemical defense of the plant against microorganisms and herbivores has been postulated;[28] given the broad variety of bioactivity noted above and the high concentration of alkaloids, this hypothesis is quite reasonable. The cholera bacterium, for example, is sensitive to sanguinarine. [29] More relevant are studies of oral cavity microbes. Virtually all isolates from human dental plaque were growth-inhibited by sanguinarine at 16 mcg/ml;[30] consequently, shifts in the spectrum of species in the oral flora were not observed. [31] Clinical studies using bacterial counts of saliva did not show reductions in *S. mutans*or *S. salivarius* with sanguinarine, while chlorhexidine was effective using the same measures.[32] Another similar clinical study of sanguinarine with zinc chloride found reductions in plaque bacteria over a 6-month trial compared to placebo. [33] A transient overgrowth of sanguinarine-resistant bacteria, but not fungi, in the mouth was observed in a further clinical study. [34] Consistent with this result, 6 yeast species were not efficiently killed by sanguinarine, while other mouthwash ingredients were effective. [35]

Antiplaque and gingivitis clinical studies: Early reports of small clinical studies indicated that sanguinarine might have use in plaque reduction. [36,37,38,39] Other studies using different methods questioned this efficacy, [40] while the addition of zinc was claimed to increase the efficacy of sanguinarine. [41] These studies were conducted over relatively short time periods. A 6-month, double-blind trial of sanguinarine toothpaste against plaque and gingivitis found no advantage over placebo.[42] When compared with a chlorhexidine mouthwash in a crossover trial, a sanguinarine-zinc mouthwash was less effective. [43] A direct comparison of sanguinarine with sodium fluoride toothpaste demonstrated equal activity against plaque and gingivitis. [44] A further 6-month trial showed moderate antiplaque and gingivitis activity for a sanguinarine mouthwash, but it was less effective than chlorhexidine. [45] A 6-month study of combined toothpaste and mouthwash in an orthodontic population showed benefit from sanguinarine by a variety of endpoints. [46] A review of studies from 1983 to 1990 suggested that the design of the clinical studies may have skewed results and proposed guidelines for improving further trials, including larger study populations, avoidance of crossover designs, and selection of appropriate controls.[47] Other studies have remained mixed. A small effect on plaque was seen for sanguinarine mouthwash compared with chlorhexidine[48] while safety and efficacy were reported in another study with combined sanguinarine toothpaste and mouthwash. [49] A further review concluded that sanguinarine was ineffective.[50] A comparison of sanguinarine-containing regimens with and without fluoride found a modest additional benefit for sanguinarine. [51] Attempts to market sanguinarine-containing products in the United Kingdom and Australia have met with skepticism. [52,53]

The most recent extensive trials of sanguinarine-containing dental products have used new delivery systems. A biodegradable matrix was used to achieve modest plaque and gingivitis control with sanguinarine; however, it was not more effective than supragingival mechanical plaque control. [54] A 9-month study of subgingivally delivered sanguinarine versus doxycycline in periodontitis found doxycycline superior to sanguinarine, [55,56] as did another study.[57] A French clinical study suggested combined use of chlorhexidine and sanguinarine.[58] In summary, the current clinical status of sanguinarine in dental plaque and gingivitis prevention and treatment is that while modestly effective, it is inferior to chlorhexidine, doxycycline, and other newer agents under development.

TOXICOLOGY: Short-term toxicity studies of sanguinarine and *Sanguinaria* extracts in rats found minimal oral toxicity (LD50 1200 to 1700 mg/kg), probably because of its very limited gastric absorption, while sanguinarine was considerably more toxic via acute intravenous administration (LD50 29 mg/kg). [59] A dermal LD50 of > 200 mg/kg in rabbits was estimated.[59] No reproductive or developmental effects in rats and rabbits were reported. [60] An expert panel reviewed the toxicological literature on bloodroot in 1990 and found no cause for concern. [61] Despite its DNA intercalating ability, sanguinarine was not mutagenic in the Ames test. [62] Phototoxic effects against mosquito larvae have been reported.[63]

Other cause for concern stems partly from reports of "epidemic dropsy" in India, where contamination of edible cooking oils with sanguinarine-containing *Argemone mexicana* seeds has been responsible for toxicity.[64,65,66,67] Further concerns were stimulated by reports of cytotoxicity of sanguinarine to cultured cells from oral tissue[68] and inhibition of neutrophil function. [69] Recent epidemiological work found a strong correlation of use of sanguinarine dental products with oral leukoplakia, a condition considered to be a possible precursor of oral cancer. [70,71] These concerns have been rendered somewhat moot by the removal of sanguinarine from the *Viadent* formulation, although some less widely promoted sanguinarine-containing products are still available in pharmacies.

Bloodroot is contraindicated during pregnancy and has uterine-stimulating action.

SUMMARY: Bloodroot is toxic in large doses. It has been widely studied as an antiplaque ingredient in toothpastes and mouthwashes; however, its modest efficacy is offset by concerns about its potential toxicity.

Sanguinaria was official in the *United States Pharmacopeia* from 1820 to 1926.

PATIENT INFORMATION — Bloodroot

Uses: Bloodroot was used historically as a treatment for skin cancers, polyps, and warts, although there are no clinical trials to support these uses. It was marketed in the early 1980s in toothpastes and mouthwashes for the prevention of gum disease and plaque; however, more recent studies have found it inferior to drugs such as doxycycline and chlorhexidine.

Side Effects: Recent studies have found a strong correlation between the use of sanguinarine dental products and oral leukoplakia, a possible precursor to oral cancer. Bloodroot is contraindicated during pregnancy.

Dosing: Bloodroot is emetic at doses of 30 to 125 mg in humans. It was formerly an ingredient in toothpastes and mouthwashes, but its use has been discontinued because of toxicity concerns.[71]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BLOODROOT

BLUE COHOSH

DATE OF ISSUE: APR 2000

REPLACES MONOGRAPH DATED: OCT 1992

SCIENTIFIC NAME(S): *Caulophyllum thalictroides* (L.) Michx. Family Berberidaceae (barberries)

COMMON NAME(S): Blue cohosh, squaw root, papoose root, blue ginseng, yellow ginseng

BOTANY: Blue cohosh is an early spring perennial herb whose yellowish-green flowers mature into bitter, bright blue seeds. It is found throughout woodlands of the eastern and midwestern United States, especially in the Allegheny Mountains. The matted, knotty rootstock, collected in the autumn, is used for medicinal purposes. The root of an Asian species, *C. robustum* Maxim., has also been used medicinally.

HISTORY: Blue cohosh was used by Native Americans; the name "cohosh" comes from the Algonquin name of the plant. It was used by Menomini, Meskawi, Ojibwe, and Potawatomi tribes for menstrual cramps, to suppress profuse menstruation, and to induce contractions in labor.[1] It was widely used in 19th century Eclectic medicine as an emmenagogue, parturient, and antispasmodic. It continues to be used for regulating the menstrual cycle and for inducing uterine contractions.

CHEMISTRY: The quinolizidine alkaloids anagyrine, baptifoline, and N-methylcytisine were isolated from blue cohosh rhizomes.[2] Other lupine alkaloids have been detected.[3] In addition to the quinolizidines, the aporphine alkaloid magnoflorine is found in substantial quantities.[2] Levels of the major quinolizidine alkaloids in herbal preparations have been determined by gas chromatography.[4] Blue cohosh root also contains triterpene saponins derived from hederagenin;[5] however, these saponins have not been purified or elucidated by modern chemical techniques. The saponins of the related species *C. robustum* have recently been more thoroughly characterized as a series of hederagenin bisdesmosides.[6]

PHARMACOLOGY: N-methylcytisine (caulophylline) was found to be a nicotinic agonist in animals[7] and to displace [3H]nicotine from nicotinic acetylcholine receptors with 50 nm potency.[8] It was essentially inactive at muscarinic receptors. Other quinolizidine alkaloids were considerably less potent nicotinic ligands, with anagyrine having IC50 values greater than 100 mcm in these test systems.[8]

Magnoflorine has its own pharmacological properties, decreasing arterial blood pressure in rabbits and inducing hypothermia in mice, as well as inducing contractions in the isolated pregnant rat uterus and stimulating isolated guinea pig ileal preparations in cell membranes.[9] The blue cohosh saponins have uterine stimulant effects, as well as cardiotoxicity presumably due to vasoconstriction of coronary blood vessels.[10] Extracts of *Caulophyllum* given to rats were found to inhibit ovulation and affect the uterus.[11] The saponins of the Siberian species *C. robustum* (caulosides) have antimicrobial activity.[12] A mechanism for cytotoxicity has been suggested for cauloside C involving formation of pH-dependent channels.[13]

TOXICOLOGY: Blue cohosh berries are poisonous to children when consumed raw although the roasted seeds have been used as a coffee substitute. The root can cause contact dermatitis.[14] The alkaloid anagyrine is a teratogen in ruminants,[15] causing "crooked calf syndrome." Another quinolizidine alkaloid in the plant, N-methylcytisine, was teratogenic in a rat embryo culture.[3] The skeletal malformations seen in calves have been postulated to be due to the action of the quinolizidine alkaloids on muscarinic and nicotinic receptors of the fetus, preventing normal fetal movements required for proper skeletal development.

A case was reported in which a newborn human infant, whose mother was administered blue cohosh to promote uterine contractions, was diagnosed with acute MI associated with CHF and shock. The infant eventually recovered after being critically ill for several weeks.[16] The FDA Special Nutritionals Adverse Event Monitoring System notes fetal toxicity cases of stroke and aplastic anemia following ingestion by the mother.

SUMMARY: Blue cohosh root is a dangerous product that can be toxic to humans. While it appears to be effective for inducing uterine contractions, its toxicity appears to outweigh any medical benefit.

PATIENT INFORMATION — Blue Cohosh

Uses: Blue cohosh has been used to induce uterine contractions. It is widely advertised on the internet but is dangerous (see Toxicology and Side Effects).

Side Effects: Blue cohosh root is a dangerous product. Its toxicity appears to outweigh any medical benefit.

Dosing: Blue cohosh has traditionally been used at doses of 0.5 to 3 g/day; however, its potential for teratogenicity makes it unsuitable for women who are or may become pregnant. Because its principal indications are for gynecological disorders, avoid its use.[17]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
      BLUE COHOSH

BOLDO

DATE OF ISSUE: JUN 2001

REPLACES MONOGRAPH DATED: MAY 1991

SCIENTIFIC NAME(S): *Peumus boldus* Molina also referred to as *Boldu boldus* [Molina] Lyons and *Boldea fragrans* Gay. Family: Monimiaceae

COMMON NAME(S): Boldo, boldus, boldoa, boldea

BOTANY: Boldo is an evergreen shrub or small tree native to central Chile and Peru.

HISTORY: In Chile, the yellowish-green fruit is eaten, its bark used in tanning, and its wood used for charcoal. [1] Boldo leaves have been used by South American natives against diseases of the liver and for the treatment of gallstones. [2] The plant is used in homeopathy in the treatment of digestive disorders, as a laxative, choleretic (a stimulant of bile secretion), diuretic, [3] and for hepatic diseases. [1] The leaves also have been used for worms, urogenital inflammations (eg, gonorrhea, syphilis), gout, rheumatism, head colds, and earaches. [4] Boldo extract is used as a flavoring for alcoholic beverages. An ethnobotanical survey is available, demonstrating boldo's importance in Guatemalan culture as a medicinal plant. [5]

CHEMISTRY: Several studies report a number of alkaloids present in boldo. Older reports list constituents norapophines, laurolitsine, [6] reticuline, isoboldine, [7] and others. Presence of alkaloid boldine has been confirmed by many reports. [8,9,10,11] Boldine content in leaves varies, with maximum amounts (0.29%) being reached in the summer. Pure boldine is 3.63% of the total alkaloid content. [12] Another report finds boldine to be a minor alkaloid, comprising 8.5% to 18.6% total leaf alkaloids. Other boldine-associated alkaloids were identified as isoboldine, N-methyllaurotetanine, laurotetanine, isocorydine, and nor-isocorydine. [13] Other isoquinoline alkaloids from boldo have been determined, some of which include (-)-pronuciferine and sinoacutine. [14,15] Other reported alkaloids include 6a,7-dehydroboldine and (R)- and (S)-coclaurine from the bark of the plant. [16,17]

Up to 46 compounds have been identified in the essential oil of boldo, with the main components being P-cymene, ascaridole, and 1,8-cineole. [18,19] Four major compounds in the essential oil, as reported in another study, include P-cymen-7-ol, transverbenol, thymol, and ascaridole. [20] Genetic variation of the essential oil, as well as alkaloid content, has been addressed. [21] Variability is dependent upon season, location, sex, canopy height, leaf age, and light intensity. [22,23]

Tannic acid (20 to 40 mg/g) has been reported from boldo. [24]

Other developments in boldo (and boldine) chemistry have been reported. [25,26]

PHARMACOLOGY: Boldine and boldo extracts are known to exhibit choleretic properties, stimulating bile flow. [7,27] Flavones boldoside and peumoside suppressed induced excitation in mice and demonstrated marked spasmolytic effect in rabbits experiencing gut spasm. [28] Boldine possesses cytoprotective and anti-inflammatory properties in experimental colitis models. [29] Dry boldo extract prolonged oro-cecal transit time when studied in 12 volunteers, explaining its medicinal use. [30] Boldo in combination with cascara has been used to treat constipation in the elderly. [31]

Besides its beneficial actions in the GI tract, boldine was shown to exert anti-inflammatory and antipyretic effects as well. Boldine is an effective inhibitor of prostaglandin synthesis. [32] Dried hydro-alcoholic extract of the plant reduced the inflammatory process in a carrageenan-induced edema test in rats. [33]

Boldine, in several reports, demonstrates cytoprotective and antioxidant actions. Boldine prevented free radical erythrocyte lysis in one report. [34] The plant also has been evaluated for its ability to protect against liver damage in rat hepatocytes, in CCl_4-induced toxicity in mice, [35] and in rat [35] and human liver microsomes. [36] Reduction of lethal effect in *Escherichia coli* submitted to reactive oxygen species was shown by presence of boldine. [37] Boldine demonstrated protective effects against oxidative mitochondrial damage in rats. [38] A review of the antioxidative properties of boldo over the last 4 decades finds boldo to be an effective antioxidant in biological and nonbiological systems. [39]

Essential oil of boldo has been shown to exhibit antimicrobial effects against a number of organisms, including *Streptococcus pyogenes*, *Micrococcus* sp., and *Candida* sp. [40]

Other studies performed with boldo/boldine describe its ability to demonstrate neuromuscular blockade in mouse phrenic nerve-diaphragm, [41] sensitize ryanodine receptor and induce calcium release from storage sites in isolated skeletal muscle, [42] and absorb UV radiation, suggesting possible use as a sunscreen. [43] A patent has been granted regarding the use of boldo in cosmetic/dermatological products to prevent the aging process. [44] Boldo also has been studied in the radioactive labeling of blood cells and plasma proteins, tracing uptake by certain cells. [45,46]

TOXICOLOGY: Oral doses of 0.5 mg/g killed mice, while doses of 15 g caused fatal intoxications in dogs. [2] Death was caused by respiratory depression. Physiologically, boldo stimulates the CNS, causing exaggerated reflexes, disturbed coordination, and convulsions. In large doses, boldo causes paralysis of the motor and sensory nerves and eventually the muscle fibers as well, causing death by respiratory arrest. [1]

Reviews on boldine report low toxicity in animal studies, which does not imply safety for use in humans. [35,39] In certain animals/cell lines, mitotic recombinant events such as crossover and gene conversion were induced by boldine, as were weak mutations in yeast cells. [47] However, boldine tested in vitro for clastogenic effect in human lymphocytes, and administration of up to 900 mg/kg given to mice, did not cause any significant increase in frequency of chromosomal aberrations in another report. [48] Hydro-alcoholic extract of boldo and boldine demonstrated abortive and teratogenic actions in a later study. This report also found changes in blood levels of bilirubin, glucose, cholesterol, ALT, AST, and urea in rats. [49] Serious health hazards exist with internal use in humans. Many boldo products contain ascaridole; patients with kidney disorders, liver disease, gallstones, and other medical illnesses should not use this herbal.

SUMMARY: Boldo is an evergreen shrub native to Chile and Peru. It contains several alkaloids, including boldine, which possess cytoprotective and anti-inflammatory actions. Certain extracts of the plant improve GI disorders. The essential oil was found to be antimicrobial. Toxicity of boldo involves CNS effects, genetic alterations, and blood level changes in enzymes, glucose, and cholesterol.

PATIENT INFORMATION — Boldo

Uses: Boldo has been shown to possess cytoprotective and anti-inflammatory actions and to improve GI disorders; however, there is limited data to support these uses.

Side Effects: Boldo is a CNS stimulant. Serious health hazards exist with internal use. Patients with kidney disorders, liver disease, gallstones, and other medical illnesses should not use this herbal. Large doses cause paralysis and death.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BOLDO

BONESET

DATE OF ISSUE: JAN 2004

REPLACES MONOGRAPH DATED: FEB 1993

SCIENTIFIC NAME(S): *Eupatorium perfoliatum* L. Family: Asteraceae (daisies)

COMMON NAME(S): Boneset, thoroughwort, vegetable antimony, feverwort, agueweed, Indian sage, sweating plant, eupatorium, crosswort, thoroughstem, thoroughwax, wild Isaac

BOTANY: Boneset is a ubiquitous plant found growing in swamps, marshes, and shores from Canada to Florida and west to Texas and Nebraska. The plant is easily recognized by its long, tapering leaves that join each other around a single stout stem giving the impression of one long leaf pierced at the center by the stem. Hence its name perfolia, meaning "through the leaves." The plant grows from July to October to a height of about 1 meter. It flowers in late summer with white blossoms that appear in small upright bunches. The entire plant is hairy and light green.

HISTORY: Boneset has been used as a charm and as a medicinal remedy for centuries by indigenous North Americans. As a charm, the root fibers were applied to hunting whistles with the belief that they would increase the whistle's ability to call deer. As an herbal remedy, American Indians used boneset as an antipyretic. [1] The early settlers used the plant to treat rheumatism, dropsy, dengue fever, malaria, pneumonia, and influenza. The name boneset was derived from the plant's use in the treatment of breakbone fever, a term describing the high fever that often accompanies influenza. [2] Boneset was official in the *US Pharmacopeia* from 1820 to 1900.

CHEMISTRY: Boneset leaves and roots contain a variety of sesquiterpene lactones [3,4] as well as a number of sterols and triterpenes, including sitosterol and stigmasterol.[5] The flavonoids quercetin, kaempferol, and eupatorin and their glycosides also have been identified in the plant. [6,7] Boneset has not been shown to definitively contain alkaloids; however, 2 of 7 samples screened in 1 program tested positive. [8] A number of related species of *Eupatorium* have been shown to contain unsaturated pyrrolizidine alkaloids of the type that can cause serious liver damage. [9] More recently, acidic polysaccharides containing principally xylose and glucuronic acid have been elucidated. [10]

PHARMACOLOGY: Based on data from early medical compendia, boneset is believed to have diuretic and laxative properties in small doses, while large doses may result in emesis and catharsis. The "usual" dose of boneset was the equivalent of 2 to 4 g of plant administered as a fluid extract. When used as a household remedy, the plant has been taken as a tea ranging in concentration from 2 teaspoonfuls to 2 tablespoonfuls of crushed dried leaves and flowering tops steeped in a cup to a pint of boiling water. Boneset had been used by physicians to treat fever, but its use was supplanted by safer and more effective antipyretics. It is not known which components of boneset reduce fever or how effective the plant is as an antipyretic.

An ethanolic extract of the aboveground parts of the plant was found inactive in a carrageenan-induced rat paw model of inflammation. [11] The isolated polysaccharides and an extract of *E. perfoliatum* combined with other herbs have been shown to stimulate phagocytic activity in vitro by a carbon particle clearance technique.[12,13] Compared with aspirin, a small double-blind clinical trial of a homeopathic preparation of boneset (N = 53) found the herbal treatment as effective in reducing symptoms of the common cold.[14] The ethanol extract of boneset leaves was shown to have modest antibacterial and cytotoxic activity; however, no fractionation to identify the constituents responsible for the activity was reported. [15]

TOXICOLOGY: Although few reports of adverse effects have been reported with the use of boneset, the FDA has classified this plant as an "Herb of Undefined Safety." The ingestion of large amounts of teas or extracts may result in severe diarrhea. The identification of pyrrolizidine alkaloids in related *Eupatorium* species is cause for concern until detailed phytochemical investigations are carried out on boneset. This class of alkaloids is known to cause hepatic impairment after long-term ingestion. While direct evidence for a hepatotoxic effect from boneset does not exist, there is sufficient evidence to indicate that any plant containing unsaturated pyrrolizidine alkaloids should not be ingested.

SUMMARY: Boneset is an old, popular remedy for fever; however, there are no controlled studies evaluating its safety or effectiveness in the treatment of fevers. Although its use was denounced by the editors of the 25th edition of the *Dispensatory of the United States of America* who noted that boneset "is never prescribed by the medical profession," a variety of unique pharmacologic activities have been informally characterized, which suggest that further studies are needed to establish the clinical value of this plant and its extracts. Until the occurrence of pyrrolizidine alkaloids in boneset is further investigated, discourage the oral use of this plant.

PATIENT INFORMATION — Boneset

Uses: Historically, boneset has been used to treat fevers. It also is believed to have effects as a diuretic, laxative, emetic, and cathartic. However, clinical trial data are lacking and its use should be discouraged.

Side effects: Boneset contains pyrrolizidine alkaloids, which are known to cause liver damage. Boneset also may cause severe diarrhea if taken in large amounts. The FDA has classified boneset as an "Herb of Undefined Safety."

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BONESET

BORAGE

DATE OF ISSUE: NOV 2001

REPLACES MONOGRAPH DATED: AUG 1992

SCIENTIFIC NAME(S): *Borago officinalis* L. Family: Boraginaceae (borage family)

COMMON NAME(S): Borage, burrage, common bugloss, bee-bread, bee fodder, star flower, ox's tongue, cool tankard.

BOTANY: Borage is an annual that grows to about 0.6 meters in height. The stem and leaves are covered with coarse, prickly hairs, and the flowers are large, star-shaped, and bright blue, with contrasting black anthers. It is a native of Europe but has been widely naturalized in other areas. The fresh plant has a salty flavor and a cucumber-like odor.

HISTORY: Borage leaves have been used as a potherb and in European herbal medicine since the Middle Ages, and are mentioned by Pliny, Dioscorides, and Galen. The name "borage" derives from the medieval Latin "burra," meaning rough-coated, which refers to the hairs. An alternative explanation suggests a corruption of the Latin "corago" (courage), as in Gerard's rhyme "ego borago gaudia semper ago" (I, borage, bring alwaies courage), in line with its reputation as an herb to dispel melancholy. Borage leaves and flowers were added to wine and lemon juice to make the popular beverages "claret cup" and "cool tankard." Borage leaves also have been used for rheumatism, colds, and bronchitis, as well as to increase lactation in women. Infusions of the leaves were used to induce sweating and diuresis. [1]

CHEMISTRY: The leaves and flowers contain mucilage, tannin, and a small amount of essential oil. The seed yields a fixed oil that has a high content (20% to 26%) of gamma-linolenic acid (GLA). This is about twice the content of evening primrose oil, another commercial source. [2] The triacylglycerol structure of borage oil has been compared with evening primrose oil and other GLA sources, with GLA attached at position sn-3 in evening primrose oil but sn-2 in borage seed oil. [3] This difference has been used to explain the apparently poorer bioavailability of GLA from borage seed oil compared with evening primrose oil. [4] Numerous methods for analysis of GLA and other polyunsaturated fatty acids (PUFA) from borage seed oil and leaves have been published. [3,5,6,7]

Because of the occurrence of toxic pyrrolizidine alkaloids in other members of the Boraginaceae, borage leaves, seeds, and seed oil have been carefully examined for their alkaloid content. The unsaturated, potentially toxic alkaloids lycopsamine and amabiline were found in borage leaves, stems, and roots in relatively low concentration.[8] The seeds and flowers were found to contain the saturated pyrrolizidine alkaloid thesinine, along with a trace of amabiline. Seed oil did not contain detectable amounts of alkaloids at the 5 ppm level.[9] More sensitive trace analyses to show that borage seed oils are free of unsaturated pyrrolizidine alkaloids at intake levels of < 1 mcg/day are required.

PHARMACOLOGY: The 18-carbon fatty acid linoleic acid is considered an essential fatty acid in human nutrition because it must be obtained from the diet. It is converted by the enzyme delta-6-desaturase to GLA, and this enzyme is considered rate-limiting in the pathway. GLA is further elaborated to the 20-carbon fatty acid dihomogamma-linolenic acid (DGLA), a key metabolite for the synthesis of the anti-inflammatory prostaglandins of the 1-series (eg, PGE1) and 15-(S)-hydroxy-8,11,13-eicosatrienoic acid (15HETrE) by different types of cells. [10] Therefore, supplementation with GLA might bypass the rate-limiting step in biosynthesis, providing more of these anti-inflammatory modulators. In addition, pathophysiological conditions have been found to alter the ability to convert linoleic acid to GLA.[10] The current commercial sources of GLA include borage seed oil, evening primrose oil, and black currant seed oil, with the oil from the fungus *Mucor javanicus* in development as well.[3] Cloning of delta-6-desaturase enzymes into plants not normally possessing them has been proposed as a means to increase dietary GLA.[11]

Extensive research has demonstrated that dietary supplementation with GLA can alter lipid fatty acid profiles in experimental animals. GLA itself is not always elevated; however, DGLA can be elevated several-fold by GLA supplementation. Macrophage phospholipids of mice showed altered ratios of 20-carbon PUFA when fed borage seed oil.[12] DGLA was selectively increased in the same system.[13] The particular phospholipid classes altered by GLA supplementation were examined in mice.[14] GLA and DGLA in cutaneous phospholipids were markedly increased in guinea pigs after an 8-week feeding experiment, as well as the metabolites PGE_1 and 15HETrE.[15,16,17] Borage seed oil and evening primrose oil were found to be equivalent sources of GLA in rats despite the higher GLA content in borage oil. [18] Upon stimulation with zymosan, isolated mouse peritoneal macrophages increased PGE1 synthesis when the mice had been maintained on high GLA diets. [19] Similar changes in hepatocyte PUFA were seen in Atlantic salmon smolts fed diets enriched with borage seed oil. [20] Analysis of the interaction of cholesterol metabolism with PUFA metabolism in rats showed that GLA had a smaller hypercholesterolemic effect than alpha-linolenic acid. [21] The effects of GLA supplementation in rats on PUFA were shown to be different in immune tissues as compared with other tissues.[22] Other effects of GLA supplementation in animal models include an increase in Mn-superoxide dismutase in rats,[23] decrease in rat liver fatty acid oxidation,[24] changes in mouse macrophage-vascular smooth muscle cell interactions,[4] and inhibition of serum cholesterol in aged rats on high cholesterol diets. [25]

Changes in these mediators of inflammation might be expected to have an impact on a variety of diseases and conditions. Animal model experiments have been reported for some of them. Borage seed oil protected mice from experimental autoimmune encephalomyelitis, with clinical, biochemical, and histological parameters improved.[26] Neovascularization of chemically burned rabbit corneas was favorably modulated by dietary GLA. [27] The use of enteral and parenteral feeding formulations supplemented with GLA and fish oil was investigated with rat models of acute endotoxin and burn injuries, as well as in pigs. Rats demonstrated increases in plasma GLA and DGLA;[28] however, lung microvasular permeability after endotoxin was not improved.[29] Pulmonary eicosanoids were altered in endotoxic rats,[30] but bacterial killing by macrophages was not changed.[31] In pigs, pulmonary surfactant function was not altered despite changes in PUFA composition of the surfactant.[32] GLA supplmentation in aged rats provided protection against ventricular fibrillation. [33] Thus, the link between dietary modulation of PUFA and functional changes remains tenuous in many cases.

Investigations in humans have followed a similar pattern. Borage seed oil increased plasma phospholipid GLA and DGLA levels, while augmenting the arterial baroreflex control of vascular resistance in healthy humans, actions that may be useful in the treatment of hypertension. [34] Proportions of different phospholipid types were unchanged but DGLA was increased in platelets when borage seed oil was administered for 42 days. [35] Neutrophils from subjects whose diets were supplemented with GLA mobilized 3-fold more DGLA after ionophore stimulation than controls. [36] In older subjects, GLA had no effect on natural killer cell activity, while fish oil reduced it by half. [37] T-lymphocyte proliferation, in contrast, was decreased by both GLA and fish oil in the same type of population. [38] This effect on lymphocytes was reproduced by a second group for GLA in borage seed oil, where increases in plasma GLA and DGLA were observed. [39] The release of pro-inflammatory leukotriene B_4 from neutrophils with ionophore stimulation was reduced, while DGLA was elevated in healthy adults. The effects were greater at the higher of 2 doses.[40]

Clinical trials have been performed with borage seed oil or purified GLA in several diseases. A 24-week randomized, double-blind, placebo-controlled trial of borage seed oil (1.4 g/day of GLA) in rheumatoid arthritis found clinically important reduction in symptoms compared with a cotton seed oil placebo. [41] A larger (n = 56) trial using a higher dose (2.8 g/day GLA) included a 6-month double-blind phase and a second 6-month single-blind trial. Improvement was found in arthritis symptoms for both groups, with the cohort receiving 12 months of GLA supplementation improving throughout both phases. [42] All of these regimens detected no adverse effects. Reviews of trials in rheumatoid arthritis have evaluated efficacy of GLA as beneficial, [43,44] an opinion shared by a Cochrane Review.[45]

A multicenter trial of borage seed oil in atopic eczema found modest improvement in the supplement group; however, the effect did not reach statistical significance. [46] The dose was 0.5 g/day GLA, given over 24 weeks, which may be too small to detect a significant effect. The trial also may have been confounded by varying use of steroids by some centers.[47,48]

A multicenter trial of fish oil and borage seed oil added to enteral feeding mixtures in patients with acute respiratory distress syndrome found significant improvement

in outcomes, with further major organ failures reduced, shorter intensive care unit stay, and less ventilator support required compared with controls. [49]

A pilot study of fish oil plus borage seed oil in elderly osteoporotic women found improved bone density in the treatment arm compared with placebo, and improvement after crossover to all treatment in both groups.[50] A review of trials of GLA for impaired nerve function in diabetics concluded that GLA may hold promise for treatment of diabetic neuropathy.[51]

TOXICOLOGY: Clinical studies of borage seed oil have not found adverse effects when doses up to 2.4 g/day of GLA equivalents were administered. The presence of unsaturated pyrrolizidine alkaloids in leaves, flowers, and seeds of borage [8,9] requires that seed oils be tested for content, and that other parts not be ingested to avoid the potential for hepatotoxicity.[52,53]

SUMMARY: Borage seed oil has shown promise in a limited number of clinical trials when used as a supplement providing GLA, in the treatment of rheumatoid arthritis, osteoporosis, diabetic neuropathy, and acute respiratory distress syndrome. Its usefulness in atopic eczema is marginal. Borage seed oil must be shown to be free of unsaturated pyrrolizidine alkaloids to prevent toxicity. Do not ingest the leaves and flowers because they may contain these hepatotoxic compounds.

PATIENT INFORMATION — Borage

Uses: Borage has been used in European herbal medicine since the Middle Ages and may be useful either alone or in combination with fish oil in the treatment of rheumatoid arthritis, atopic eczema, and osteoporosis, although limited information is available.

Side Effects: No adverse effects have been found. Do not ingest the leaves and flowers because they may contain hepatotoxic compounds.

Dosing: Borage seed oil has been given in doses of 1.4 to 2.8 g/day in several clinical trials for arthritis and other inflammatory conditions. [39] The content of gamma-linolenic acid is between 20% and 26% of the oil.[41,42]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BORAGE

BORON

DATE OF ISSUE: FEB 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Boron, an element

COMMON NAME(S): Boron

SOURCE: The element boron (B, atomic number 5) is found in deposits in the earth's crust at a concentration of about 0.001%. It is obtained in the form of its compounds and never in its elemental state.[1] Environmental boron is taken up by plants in trace amounts, thereby contributing to dietary boron intake. Boron was originally obtained in 1895 from the reduction of boric anhydride; today this remains a commercially important way to produce impure boron. Pure boron takes the form of clear red or black crystals, depending upon its crystalline shape. [1] The crystals can be as hard as diamonds. The chemistry of boron is extremely complex, with entire texts devoted solely to this topic.

HISTORY: Boron has been used in nuclear chemistry as a neutron absorber. It has also been added to other metals to form harder alloys. In medicine, boron is most commonly found in the form of boric acid, which is used as a topical astringent and anti-infective, as well as an ophthalmologic irrigant. Sodium borate is bacteriostatic and is commonly added to cold creams, eye washes and mouth rinses.

PHARMACOLOGY: Over-the-counter supplements containing boron compounds are purported to enhance mental power, sometimes citing poorly substantiated studies that found alterations in the electroencephalogram in the presence of a low-boron diet. These studies also reported a correlation between a low-boron diet and a decrease in mental alertness. There is no evidence, however, that diet supplementations of boron compounds, above the levels derived from a normal balanced diet, can enhance mental acuity or improve alertness.

Because of boron's ability to absorb electromagnetic radiation, boron-based compounds are used in conjunction with radiation therapy to enhance the selective killing of neoplastic cells, particularly those of resistant neoplasia such as glioblastoma. [2]

Boric acid solutions for topical use are generally used in diluted concentrations. A 2.2% solution of boric acid is isotonic with lacrimal fluid. Because boric acid has weak antifungal and antibacterial activity, it is employed as a mild disinfectant in concentrations ranging from 2% to 10%. [3]

Bori acid powder has been used as an insect and rodent repellent, being sprinkled in corners and along floor boards. This use, however, should be avoided because of the serious toxicity that can occur if ingested orally by small children or pets.

TOXICOLOGY: Boric acid and borates are toxic when ingested or absorbed through broken skin. An oral dose of 0.3 g/kg can be fatal, and serious toxicity can occur following the ingestion of as little as 5 g in infants and 15 to 20 g in adults. [4] Boric acid solutions should be labeled not to be used on broken skin or on severely irritated or inflamed mucous membranes in order to prevent toxicity as a result of its topical absorption.

Fatalities have been reported because of confusion between boric acid and similar-looking powders (ie, baking soda, dextrose). Stringent controls should be maintained in hospitals, nursing homes and other public facilities to prevent possible intoxications due to boron-containing products.

There is no effective antidote to boron poisoning, and treatment is symptomatic and supportive. Symptoms of toxicity include irritation and sloughing of skin, gastrointestinal irritation, restlessness, weakness, kidney and liver damage, convulsions, coma or death.

SUMMARY: The element boron is distributed throughout the earth's crust and found in trace quantities in normal diets. Compounds containing boron are used medicinally, but all pose a potential toxic hazard if ingested or absorbed through nonintact skin.

PATIENT INFORMATION — Boron

Uses: Boric acid is a topical astringent, mild disinfectant and eye wash. Sprinkled in crevices and corners, boric acid powder controls rodents and insects. Sodium borate is used in cold creams, eye washes and mouth rinses. Boron compounds are used to enhance the cell selectiveness of radiation therapy.

Side Effects: Boric acid and borates are toxic and potentially fatal when ingested or absorbed through broken skin. Solutions should not be used on broken skin or severely affected mucous membranes.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BORON

BOVINE COLOSTRUM

DATE OF ISSUE: JAN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Bovine colostrum

COMMON NAME(S): Cow milk colostrum

SOURCE: Colostrum is the premilk fluid produced from mammary glands during the first 2 to 4 days after birth. It is a rich natural source of nutrients, antibodies, and growth factors for the newborn.[1]

CHEMISTRY: Colostrum contains immune factors, immunoglobulins, antibodies, proline-rich polypeptides (PRP), lactoferrin, glycoproteins, lactalbumins, cytokines (eg, interleukin 1 and 6, interferon ?), growth factors, vitamins, and minerals. [1,2,3,4,5] Specific bovine colostrum growth factor has been purified, stimulating synthesis of certain cell lines, for example.[6] Colostrokinin is also a constituent isolated from bovine colostrum, responsible for uterine and intestinal contraction, and lowering of blood pressure.[7]

PHARMACOLOGY: Bovine colostrum, with its rich pool of nutrients, has successfully supported and maintained a variety of cell cultures. [8,9,10,11,12] Various concentrations of bovine colostral constituents, including certain immunoglobulins, have been studied in calves fed colostrum or colostral supplement products.[13,14,15,16,17] Certain immune factors and antibodies also fight a variety of organisms, allergens, or toxins including pneumonia, candida, and flu. Constituent lactoferrin prevents pathogens from getting the iron they need to flourish. Lactalbumins and cytokines (interleukin 1 and 6, interferon ?) are also important as antivirals and anticancer agents.[5]

Several studies show how bovine colostrum concentrates, including G immunoglobulin isolates, are highly successful alternative agents used to improve GI health and to treat diarrhea caused by a variety of pathogens. In > 50% of AIDS patients, diarrhea and subsequent weight loss pose a problem. The severity of symptoms in some cases and sometimes unidentifiable pathogens unaffected by antibiotics welcome alternative therapy with bovine colostrum.

In one study, 29 AIDS patients received a bovine colostrum preparation. The average stool per day decreased from 7.4 before therapy to 2.2 after treatment. [18] Another report finds similar results in animals, including high capacity for neutralization of bacterial toxins and high effectiveness in treating severe diarrhea, using a specialized colostrum preparation.[19] A 25- patient study of HIV subjects with chronic diarrhea administered bovine colostrum preparation also confirms therapeutic effectiveness, resulting in 64% of patients experiencing complete (40%) or partial (24%) remission of diarrhea. [20] *Cryptosporidium*, a human GI parasite, can also cause life-threatening diarrhea in immunodeficient patients when antibiotics or other anti-diarrheals may be ineffective. Bovine colostrum therapy has reduced significantly oocyst excretion of pathogen in stools vs placebo and relieved a previously untreatable AIDS patient of severe *cryptosporidium*-associated diarrhea.[21,22] *Lactobin*, a registed bovine colostral product, shows antibody reactivity and neutralization against certain *E. coli* strains and shiga-like toxins.[23] Immunoglobulin preparation supplementation was found to protect against *Shigellosis* (*S. flexneri*), and suggests its usefulness in high-risk groups including travelers and military personnel during *Shigella* outbreaks.[24] Bovine colostrum use against organisms *Yersinia enterocolitica*and *Campylobacter jejuni* has also been reported.[25] Bovine colostrum also inhibits *Helicobacter pylori* and *Helicobacter mustelae* by binding to certain lipid receptors, which may modulate the interaction of these pathogens to their target sites.[26] One report investigates the bovine colostral immunoglobulin proteins and how they are subject to degradation by gastric acid and intestinal enzymes under certain conditions.[27] Bovine colostrum supplementation, in another report, has been shown to prevent NSAID-induced gut injury in various in vivo and in vitro models, suggesting its possible usefulness for certain ulcerative bowel conditions. [1]

The immune-boosting properties of bovine colostrum have been greatly proclaimed as performance enhancers and anti-aging/healing supplements. Certain Web pages, for instance, promote significant fitness gains for athletes, noting its "anabolic effects" and claiming it can "promote muscle growth." [28] One clinical trial finds bovine colostrum supplement to increase serum IGF-1 concentration in athletes.[29] IGF-1 is a growth factor that speeds up protein synthesis and slows catabolism.[23]

TOXICOLOGY: A few symptoms, including mild nausea and flatulence, were seen in certain trials, but most have reported bovine colostrum to be well tolerated.[18,19,20] At least 2 allerginicity studies have been performed in humans.[30,31]

SUMMARY: Bovine colostrum is rich in nutrients, immune factors, immunoglobulins, antibodies, and other important constituents, all of which benefit the immune system. Many studies have been performed resulting in its successful use for severe diarrhea in certain populations such as the immunocompromised. Bovine colostrum also has other positive GI effects and may help rebuild muscle and other tissue. There is no major toxicity associated with bovine colostrum supplementation. Continued studies will further elucidate its true benefits.

PATIENT INFORMATION— Bovine Colostrum

Uses: Bovine colostrum has been used to treat diarrhea, to improve GI health, to boost the immune system.

Side Effects: Bovine colostrum appears to be safe and effective.

Dosing: Bovine colostrum is a difficult preparation to standardize because its antibody content may vary widely. Some clinical studies have been performed with hyperimmune colostrum, which may have a specific antibody titer; however, most products do not meet this criterion. Studies administering 25 to 125 mL of liquid formulations or 10 to 20 g of dry powder have been reported.[32,33,34,35]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BOVINE COLOSTRUM

BRAHMI

DATE OF ISSUE: JAN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Bacopa monnieri* (L.) Wettst. Family: Scrophulariaceae (figworts); also known as *Bacopa monniera*, *Herpestis monniera*, or *Moniera cuneifolia*

COMMON NAME(S): Brahmi, Jalnaveri, Jalanimba, Sambrani chettu, thyme-leaved gratiola

BOTANY: *Bacopa monnieri* is a creeping herb that grows in marshy places and is frequently planted in freshwater aquaria. It is native to India but has spread throughout the tropics. The name brahmi has also been applied to *Centella asiatica* (better known as *gotu kola*), as well as *Merremia gangetica*, however most authorities consider it most appropriate for *B. monnieri*.[1] A tissue culture method has been developed for the plant.[2]

HISTORY: Brahmi is a well-known drug in the Ayurvedic medical tradition in India, and is used in many Ayurvedic herbal preparations. It has been traditionally used to treat asthma, hoarseness, insanity, epilepsy, and as a nerve tonic, cardiotonic, and diuretic.[1] It was prominently mentioned in Indian texts as early as the 6th century A.D.[3]

CHEMISTRY: The principal constituents of *B. monnieri* are triterpene saponins of the dammarane class, which have been named bacosides[4] and bacopasaponins,[5,6] and which contain 2 or 3 sugars each. The saponins are considered to be primarily responsible for the bioactivity of the plant. Due to the proclivity of the sapogenins to rearrange on acid hydrolysis,[7] the correct structures of the saponins have been difficult to elucidate, despite many chemical investigations.[8,9,10,11,12] An analytical HPLC method for the quantitation of bacoside A3 has been published.[13] The structure of 4 saponins of *B. monnieri* have also been determined by HPLC coupled to 2-D NMR, mass spectrometry, and an anthelmintic bioassay.[14] While alkaloids were initially suspected to be the CNS-active agents in brahmi,[15] the very small amounts of nicotine and other simple alkaloids are no longer considered to be of pharmacologic importance.[16] A free triterpene, bacosine, has been reported from *B. monnieri*.[17] Other reported constituents include mannitol, common plant sterols, and betulinic acid,[4] as well as glutamic and aspartic acids.[18]

PHARMACOLOGY: In mice, the ethanolic extract of *B. monnieri* was found to increase cerebral levels of GABA 15 minutes after administration.[19] Oral treatment of rats with the extract of *B. monnieri* for 24 days facilitated their ability to learn mazes.[20] A saponin fraction of *B. monnieri* reduced spontaneous motor activity in rats, and lowered rectal temperatures in mice.[21] The same extract showed tranquilizing effects in rats but did not block the conditioned avoidance response. It also protected against audiogenic seizures.[22] More recently, the extract was found to improve the performance of rats in various behavioral models of learning.[3] Furthermore, the purified bacosides A and B showed dose-dependent effects in the same rat models, as well as in a taste aversion response test.[23] Bacosine, a free triterpene isolated from the aerial parts of *B. monnieri*, was found to have analgesic effects operating through opioidergic pathways.[17] The ethanolic extract of *B. monnieri* relaxed smooth muscle preparations of guinea pig and rabbit pulmonary arteries, rabbit aorta, and guinea pig trachea by a mechanism that was postulated to involve prostacyclins.[24] The same investigators found spasmolytic effects of the ethanol extract in guinea pig ileum and rabbit jejeunum to be nonspecifically mediated through calcium channels.[25] The saponins were found to have anthelmintic activity using *C. elegans* as a test organism.[14] They are also reported to be hemolytic.[26]

TOXICOLOGY: Brahmi appears to be free of reported side effects. Its CNS actions do not include serious sedation, although the potentiation of chlorpromazine's effect on conditioned avoidance responses may indicate caution with phenothiazine coadministration.[22]

SUMMARY: Brahmi is an extract of *Bacopa monnieri* used in Ayurvedic medicine as a nerve tonic and aid to learning. Animal studies lend support to these indications, however no human trials have been reported to date. It is not monographed in any of the European or American compendia.

PATIENT INFORMATION — Brahmi

Uses: Brahmi is used as a nerve tonic and an aid to learning.

Side Effects: Brahmi has no reported side effects.

Interactions: Use caution when coadministering with phenothiazine.

Dosing: A single clinical trial of brahmi's effects on cognition reported a daily dose of 300 mg of extract.[27]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BRAHMI

BROOM

DATE OF ISSUE: FEB 1996

REPLACES MONOGRAPH DATED: SEP 1989

SCIENTIFIC NAME(S): *Cytisus scoparius* (L.) Link, sometimes referred to as *Sarothamnus scoparius* (L.) Wimm. Family: Fabaceae (Papilionaceae or Leguminosae)

COMMON NAME(S): Bannal, besenginaterkraut (German), broom, broom top, ginsterkraut (German), herbe de genet a balais (French), herba genistac scopariae, herba spartii scoparii, hog week, Irish broom top (English) [1] , sarothamni herb, scoparii cacumina (Latin); scotch broom, Scotch broom top (English). Scotch broom should not be confused with Spanish broom (*Spartium junceum*), which also is pharmacologically active. The related *Cytisus laburnum* (golden chain) contains the toxic alkaloid cytisine.

BOTANY: Broom is native to central and southern Europe. It grows throughout the United States along the Eastern coastline and across the Pacific Northwest. The plant grows as a deciduous bush up to 1.8 m tall and possesses 5-sided, greenish, rod-like twigs with small leaves. On flowering, it show yellow, butterfly-like flowers that bloom from May to June.[1] It is often used as an outdoor ornamental to hold steep, barren banks in place. The crude drug is made up mostly of short fragments (2.5 to 5 cm) of the woody twigs.[1]

HISTORY: In early American traditional medicine, a fluid extract of broom was used as a cathartic and diuretic. Large doses of the extract were used as an emetic. [2] An alkaloid derived from the plant (sparteine) was once used to induce labor and as an antiarrhythmic, but has now been abandoned for safer compounds.

The plant has been touted as a potential drug of abuse or "legal high." In describing the preparation of the drug, some counter-culture magazines suggest that the flowers be collected and aged for about 10 days in a closed jar. [2] The moldy, dried blossoms are then pulverized, rolled in cigarette paper and smoked like marijuana.

Before the advent of hops, the tender green tops were used to impart bitterness and to increase the intoxicating effects of beer. In homeopathy, extracts of the plant are used for the management of arrhythmias, congestion of the head and throat, and occasionally for diphtheria. [3]

CHEMISTRY: The main alkaloid in the plant is l-sparteine found in the floral parts of the plant in concentrations ranging up to 0.22%, but may exceed 1.5% in other parts of the plant. In addition, the alkaloids sarothamnine, [4] genisteine,[4] lupanine[5] and oxysparteine[6] have been identified. A number of minor alkaloids and other componenets have also been isolated.[7] The flavone glycoside scoparoside has also been isolated, primarily from the flowers. Apparently, the toxic alkaloid cytisine is not present in this species.[8]

The plant alkaloids are mainly found in the stem, but are also in the epidermis and sub-epidermis. Also present are flavonoids (spiraeoside, isoquercitin, genitoside, scoparoside) as well as other kaempferol and quercetin derivatives. Isoflavones such as sarothamnoside have also been reported. Broom also contains caffeic-acid derivatives and small amounts of essential oil. The seeds contain phytohaemagglutinins or lectins. [1] Fresh flower essential oils contain cis-3-hexan-l-ol, l-octen-3-ol, benzyl alcohol, phenethyl alcohol and various phenols and acids. [9]

PHARMACOLOGY: Sparteine is a powerful oxytocic drug once used to stimulate uterine contractions. Sparteine slows the cardiac rate and shares some pharmacologic similarities with quinidine [10] and nicotine.[3] It also has antiarrhythmic effects.[11]

Scoparoside is an active diuretic and may exert a pharmacologic effect if ingested in sufficient quantities.

A number of lectins have been isolated from broom seeds and these are being used as pharmacologic probes. [12]

Broom has long been used as a tea in Europe for improved regulation of the circulation. This activity is related to the alkaloidal content, particularly sparteine. It possesses an antiarrhythmic property, based on its ability to inhibit the transport of sodium ions across the cell membrane. The alkaloid reduces overstimulation of the system that conducts the nerve impulse. Hence, impulses arising in the auricle are normalized. Sparteine extends diastole, but does not show a positive inotropic effect. With low blood pressure, this property can lead to normalization.

TOXICOLOGY: Sparteine is an oily liquid that vaporizes readily when heated. Therefore, persons who smoke broom cigarettes may inhale significant amounts of the alkaloid. One such cigarette is said to produce a feeling of relaxation and euphoria lasting about 2 hours. However, some studies indicate that doses in excess of that which one would obtain by smoking the leaves would be needed to induce euphoria; the same studies concluded that "apparently this plant is not very toxic and the use of it as a 'legal high' probably would not precipitate a severe toxic episode." [8]

Smoking broom cigarettes may pose a number of health hazards. These include adverse cardiac effects such as headaches, uterine stimulant effects and residual effects. The inhalation of moldy plant material cannot be recommended as this may be associated with the development of pulmonary aspergillosis or similar fungal infections.

Broom tea is contraindicated during pregnancy because it can increase the tonus of the gravid uterus. For similar reasons (tonus increasing properties), it is not recommended with hypertensive individuals.[1]

The FDA considers broom an unsafe herb. Symptoms of toxicity suggest nicotine poisoning and are characterized by tachycardia with circulatory collapse, nausea, diarrhea, vertigo and stupor. The seeds have been used as a coffee substitute, a dangerous and unwarranted practice. [3]

SUMMARY: Broom is a traditional medicinal herb that is found throughout many regions of the United States and Europe. Broom contains the pharmacologically active alkaloid sparteine, which has oxytocic and antiarrhythmic properties. The plant has been touted as a "legal high," but the authenticity of these experiences has been doubted. The German Commission E monograph on this herb lists its uses as an effective agent for functional disorders of the heart and circulation. [1] Nevertheless, broom is considered an unsafe herb by the FDA and should not be used in modern therapeutics.

PATIENT INFORMATION— Broom

Uses: Extracts have been used for cathartic, diuretic, emetic, antiarrhythmic and labor-inducing effects. Tender plant tops have been used to flavor beer and increase its intoxicating effect. Leaves and aged flowers have been smoked to produce euphoria.

Side Effects: Although broom appears an effective agent for heart and circulatory disorders, the FDA has designated broom an unsafe herb.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "B" MONOGRAPHS
  BROOM

BUCHU

DATE OF ISSUE: FEB 1998

REPLACES MONOGRAPH DATED: MAY 1990

SCIENTIFIC NAME(S): *Agathosma betulina* (Berg.) Pillans (syn. *Barosma betulina* [Berg.] Bartl. & Wendl.) (short buchu); *B. serratifolia* (Curt.) Willd. (long buchu); *B. crenulata* (L.) Hook. (ovate buchu). Family: Rutaceae. These plants should not be confused with "Indian buchu" (*Myrtus communis* L.), which is native to the Mediterranean regions.

COMMON NAME(S): Bookoo, buku, diosma, bucku, bucco.[1]

BOTANY: Buchu is harvested from the dried leaves obtained from three species of *Barosma*. The species derive their common names from the shape of the aromatic leaf.[2] The buchus grow up to 6 feet tall as low, bushy, drought-resistant shrubs with colorful blossoms. The leaves are described as yellowish green to brown, glossy and leathery, revealing oil-glandular dots on the underside. The three species produce oval, serrated leaves with the leaf of *B. serratifolia* being the longest and most slender. Harvesting of the leaves occurs in summer. Most commonly, *B. betulina* is used in commerce. Native to South Africa, buchu undergoes hillside cultivation. Odor and taste of the plants is described as spicy, resembling black currant but also reminiscent of a mixture between rosemary and peppermint.[3,4] Buchu oil is sometimes added as a component of black currant flavorings.

HISTORY: The Hottentots employed the leaves for the treatment of a great number of ailments. Early patent medicines sold in the United States hailed the virtues of the plant and its volatile oil for the management of diseases ranging from diabetes to nervousness. The drug had been included in the US National Formulary and was described as a diuretic and antiseptic. Its use has since been abandoned in favor of more effective diuretics and antibacterials. Buchu remains a popular ingredient in over-the-counter herbal diuretic preparations. [5]

Buchu was first exported to Britain in 1790. In 1821, it was listed in the *British Pharmacopoeia* as a medicine for "cystitis, urethritis, nephritis and catarrh of the bladder."[4]

CHEMISTRY: Buchu leaves contain from 1.5% to 3.5% volatile oil. Over 100 components exist in the oil, [1,5] including diosphenol (the main component in distilled oil, also called buchu camphor, barosma camphor or 1-pulegone), limonene, methone, pulegone, terpinen-4-ol and p-menthan-3-on-8-thiol (responsible for the aroma of the plant).[2,3,6]

Flavonoids include diosmetin, quercetin, diosmin, quercetin-3,7-diglucoside and rutin. Other constituents include mucilage, resin, thiamine and sulfur compounds. Coumarins have been reported from other *agathosma* species.[4,6]

PHARMACOLOGY: No scientific evidence is available to justify buchu's herbal uses, but its diuretic and anti-inflammatory effects may be attributed to the volatile oil and flavonoid's irritant nature. [6] Diosphenol, the flavonoids and terpinen-4-ol may contribute to the plant's diuretic activity, but this action of buchu teas is probably no greater than that of the xanthine alkaloids in coffee or tea. [7] Buchu is listed in the German Commission E Monographs to treat inflammation, kidney and urinary tract infections and is also used as a diuretic, but the monograph explains that the plant's activity in these claimed uses has not been substantiated. [3]

Other reported uses of buchu include carminative action, treatment for cystitis, urethritis, prostatitis, gout and as a stomach tonic. [8]

An infusion of the leaves has been used gynecologically as a douche for leukorrhea and for yeast infections. [4] Diosphenol may be responsible for buchu's antibacterial effects.[3]

Despite the lack of evidence, buchu is still used today in western herbal medicine for urinary tract ailments, cystitis or urethritis prophylaxis and prostatitis. It is also used in combination with other herbs such as cornsilk, juniper and uva-ursi. [4]

TOXICOLOGY: There is little evidence to suggest that the casual intake of teas brewed from buchu are harmful. [9] Poisoning has not been reported.[3,6] Essential oil components diosmin and pulegone can cause GI and renal irritation. [3,6] Pulegone is known to be an abortifacient and to increase menstrual flow; therefore, use is not recommended during pregnancy. Pulegone is also a hepatotoxin, present in the plant "pennyroyal," in larger quantities. [4,6]

SUMMARY: Buchu leaves and extracts are recognized in herbal medicine as diuretics and weak antiseptics. Their use is a popular treatment of kidney and urinary tract infections and prostatitis. More clinical trials are needed to substantiate these claims. There is little known toxicity associated with the plant, but because some of its components are associated with uterine stimulation, it is not recommended during pregnancy.

PATIENT INFORMATION— Buchu

Uses: Buchu has been used to treat inflammation and kidney and urinary tract infections; as a diuretic and as a stomach tonic. Other uses include carminative action and treatment of cystitis, urethritis, prostatitis and gout. It has also been used for leukorrhea and yeast infections.

Side Effects: Buchu can cause stomach and kidney irritation and can be an abortifacient. It can also induce increased menstrual flow.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BUCHU

BUGLEWEED

DATE OF ISSUE: MAR 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Lycopus europaeus* L. or *L. virginicus* L. Family: Lamiaceae (mints)

COMMON NAME(S): *L. europaeus*: Bugleweed, wolfstrappkraut, bitter bugle, water horehound. *L. virginicus*: Paul's betony, water bugle, Virginia water horehound, gypsywort, sweet bugle, purple archangel, wolf foot, carpenter's herb, green archangel.

BOTANY: Bugleweed is an herbaceous perennial mint that grows in wet habitats. The leaves are toothed, and the small white flowers surround the square stem at the leaf axils in dense clusters. The plant has little odor; the European species has a bitter taste, while the American species is not bitter. The whole herb is used medicinally.

HISTORY: Traditional uses of bugleweed include treatment of nosebleeds, heavy menstrual bleeding, coughs, as a sedative, astringent, and mild narcotic, and for consumption (tuberculosis, characterized by bleeding from the lungs). Its current uses are primarily for mild hyperthyroid conditions and for premenstrual syndrome including breast pain (mastodynia), with its actions mediated by thyroid hormones and gonadotropins, respectively.

CHEMISTRY: The phenolic compounds lithospermic acid,[1] rosmarinic acid,[2] chlorogenic acid, and caffeic acid[3,4] have been identified in both *Lycopus* species. The metabolism of these phenolics in rat liver has been analyzed by HPLC and capillary electrophoresis. [3] The flavonoids luteolin 7-glucoside, luteolin 3´,7-diglucoside, luteolin 7-glucuronide, and apigenin 7-glucoside have also been isolated from bugleweed. [5,6,7,8,9] Several isopimarane diterpenes have been isolated as well.[10,11,12] An automated thin layer chromatography method for analysis of *Lycopus* and other plants has been published.[13]

PHARMACOLOGY

Thyroid: Extracts of *L. europaeus* administered to normal rats were found to reduce the weight of the thyroid, decrease thyroid hormone activity, and increase absorption and storage of iodine. The extract retarded goiter formation in propylthiouracil-treated rats. All animals treated with the extract demonstrated reduced metabolism.[14] Similarly, humans treated with *Lycopus*extracts showed inhibition of serum thyrotropic hormone and thyroxine.[15] More recent studies in rats have shown similar effects after oral administration.[16] Freeze-dried extracts of bugleweed and other related plants showed a dose-dependent inhibition of bovine thyrotropin (TSH) binding to human thyroid membranes, with simultaneous inhibition of TSH-stimulated adenyl cyclase activity. [17] The inhibition of cyclase activity also was demonstrated in cultured rat thyroid cells stimulated with forskolin. [18] Antithyroid activity initially was attributed to lithospermic acid; [1] however, a more complex mechanism has developed since that early work. The oxidation of phenolics to unstable orthoquinones by plant enzymes has been proposed to be required for antithyroid activity. Thus, caffeic acid, rosmarinic acid, and lithospermic acid are inactive without some form of oxidation. This enzymatic oxidation usually has been reproduced experimentally using potassium permanganate as oxidant. Formation of covalent adducts with TSH amino acid residues was postulated; however, the evidence is not conclusive.[19] The effect of extracts on Graves' disease immunoglobulin also was suggested as a potential mechanism. [20] A review of the thyroid pharmacology of *Lycopus* has been published.[2]

Gonadotropin: In parallel with the work on thyroid hormones, effects of *Lycopus* extracts on gonadotropin function have been discovered. A similar requirement for enzymatic or chemical oxidation was found.[21] As above, the phenolic compounds caffeic acid, chlorogenic acid, and rosmarinic acid served as precursors to bioactive oxidation products.[22,23,24,25] The elucidation of 2 cyclolignans with antigonadotropic activity following oxidation of caffeic acid suggested that quinones may not be the ultimate active species.[23,24] The flavonoid luteolin-7-glucuronide was shown by the same group to possess antigonadotropic activity similar to the phenolics despite its chemical dissimilarity.[5] Extracts showed inhibition of human chorionic gonadotropin binding to rat testis membranes, but not of insulin to liver membranes, thus demonstrating a measure of selectivity.[17]

A catechol oxidase thought to be responsible for the in situ oxidation of *Lycopus* phenolics has been purified from *L. europaeus*.[26] The substrate specificity and products of oxidation have been characterized as neolignans produced by oxidative dimerization of caffeic acid derivatives. [27]

The observation of a reduction of prolactin levels by *Lycopus* extract administration to rats is thought to be secondary to reduction in TSH because thyroid status is known to influence prolactin production.[28]

The bioactivity of *Lycopus* phenolics appears to be limited to the family of glycoprotein hormones, which includes TSH and gonadotropin. Because these hormones share a common alpha subunit,[29] it is possible that *Lycopus*phenolic oxidation products interact with this subunit in producing their effects. Further research on the pharmacologic and biochemical targets of *Lycopus* is warranted.

TOXICOLOGY: The potential for serious toxicity appears to be low; however, very high doses of bugleweed can cause thyroid enlargement, as can abrupt discontinuation. Because of its endocrine effects, bugleweed is clearly contraindicated in pregnancy and lactation.

SUMMARY: Bugleweed has been used for the treatment of mild hyperthyroid conditions and for premenstrual syndrome and breast pain; however, no formal clinical studies have been conducted. Typical doses are 1 to 2 g per day. The potential for toxicity appears low, but do not use bugleweed in hypothyroid conditions, when thyroid function is being evaluated, or in pregnancy. Bugleweed is approved by the *German Commission E*.

PATIENT INFORMATION— Bugleweed

Uses: Bugleweed is used to treat mild overactive thyroid conditions, premenstrual syndrome, and breast pain, although there have not been any studies done.

Side Effects: Bugleweed taken in high amounts or stopped suddenly can cause thyroid enlargement. Do not use bugleweed if you are pregnant, breastfeeding, have an underactive thyroid condition, or are having your thyroid examined by a physician.

Dosage: 1 to 2 g/day.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BUGLEWEED

BUPLEURUM

DATE OF ISSUE: APR 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Bupleurum chinense* DC., related species include *B. falcatum* L., *B. scorzoneraefolium* , *B. fruticosum* L., *B. ginghausenii*, *B. rotundifolium* L., *B. stewartianum*. Family: Umbelliferae[1]

COMMON NAME(S): Thoroughwax, hare's ear root, chai hu (Chinese)

BOTANY: Bupleurum is a perennial herb that grows mainly in China, but also is cultivated in other areas. The plant grows to ˜ 1 m in height and requires plenty of sun to flourish. The leaves are long and sickle-shaped with parallel veining. Terminal clusters of small, yellow flowers appear in autumn. [2,3]

HISTORY: Bupleurum is a traditional Chinese herb dating back to the first century B.C. It is one of China's "harmony" herbs purported to affect organs and energy in the body. Bupleurum has been used as a liver tonic, with spleen and stomach toning properties as well. The plant has also been said to clear fevers and flu, promote perspiration, and alleviate female problems.[1,2,3]

CHEMISTRY: Bupleurum contains triterpene saponins or saikosides, also known as saikosaponins. [1,2] The highest levels of these saikosaponins are found in species *B. falcatum* (2% to 8%) and *B. chinense* (1.7%).[4] Saikosaponin content varies depending on certain growing periods and also between wild and cultivated species.[5] Root parts of bupleurum have been analyzed, resulting in the discovery of many saikosaponins. [6] Saponins, along with 8 flavonoid compounds, have also been found in the aerial parts of 6 species. [7] Saikogenins A, B, C, and D are also present in the plant. Spinasterol, stigmasterol, and rutin have also been found, as well as pectin-like polysaccharides (bupleurans). [1,4]

PHARMACOLOGY: Bupleurum's traditional role as a liver tonic has been substantiated by research. The saikosides are known liver protectants, and bupleurum has been found to be beneficial in both acute and chronic liver disease. [2,4] Doses of saikosaponins demonstrate marked hepatoprotective activity in several animal models.[8,9,10,11] IV injection of bupleurum provided beneficial therapeutic outcomes in 100 cases of infectious hepatitis in adults and children. [12] Saikosaponins increase hepatic protein synthesis both in vitro and in vivo. [4]

Bupleurum's effects on the immune system have been widely reported. Traditional use of the plant for acute infection, cold with chills and fever, headache, vomiting, and malaria treatment have been discussed.[3,4] Bupleurum was also found to possess antitussive effects.[13] The saikosides stimulate corticosteroid production, thus increasing the anti-inflammatory effects.[2] Bupleurum inactivated enveloped viruses including measles and herpes, but had no effect on nonenveloped viruses such as polio.[14] Bupleurum demonstrated cytotoxic effects in certain human cell lines in vitro.[4] Mitogenic activity has been shown from certain extracts of the plant.[15] Other immune problems may benefit from bupleurum including SLE, inflammatory disorders, and autoimmune disease.[4]

Improvement in certain GI conditions has also been seen with bupleurum. Constituents bupleurans and saikosaponins have been shown to decrease gastric ulcer development.[4] Bupleurum in combination has been reported to inhibit gastric secretion and acid output. [16] One study reports improved integrity of gastric mucosa in rats.[17]

A Chinese medicinal treatment including *B. chinense* was found to be comparable to methylphenidate (eg, *Ritalin*) in a 100-patient study of children 7 to 14 years of age with minimal brain dysfunction (MBD). The group that was administered the Chinese combination had far fewer side effects, as well as more improvement in parameters such as intelligence or enuresis than the methylphenidate group. [18]

Bupleurum is often used as part of the popular Japanese herbal remedy Sho-saiko-to (Tj-9, Xino-chai-hu-tang), which is used extensively for the treatment of various liver diseases. In one study, this product was found to reduce the incidence of hepatocellular carcinoma in patients. [19]

Other ailments for which bupleurum is used include irregular menstruation, PMS, hot flashes, prolapsed uterus, [1,3] kidney problems (protectant), high cholesterol (saponins decrease cholesterol by increasing excretion in bile), [4] and hemorrhoids.[2]

TOXICOLOGY: Limited pharmacokinetic information is available in humans, but in mice it was determined that certain saikosaponins are transformed into ˜ 30 compounds for potential absorption. Saikosaponin metabolites undergo enterohepatic recycling. Crude saikosaponins show medium toxicity after intraperitoneal administration and low toxicity if taken orally (LD_{50}= 4.7 g/kg in mice).[4] One report regarding bupleurum in combination finds no effects on CNS, respiratory, cardiovascular, or blood coagulation systems in mice, concluding that no important adverse events occur at pharmacologically effective doses. [16]

Bupleurum has produced sedative effects in some patients, along with increased flatulence and bowel movements in large doses. Some combinations with bupleurum may have certain undesirable effects such as induction of pneumonitis, or nausea and reflux in sensitive patients. Some reports are unclear as to whether or not the ill effects are due specifically to bupleurum.[4]

SUMMARY: Bupleurum has been used in China for over 2000 years as a liver tonic. Research finds bupleurum beneficial as a liver protectant. It also has positive effects on the immune system, including treatment for cold and flu, inflammatory disorders, and certain cancers. Bupleurum is also useful in GI ailments, certain brain disorders, and gynecological problems. The toxicity profile is low, with no important adverse effects being reported in animals.

PATIENT INFORMATION— Bupleurum

Uses: Bupleurum has been found beneficial as a liver protectant and possesses positive effects on the immune system, including treatment for cold and flu, inflammatory disorders, and certain cancers. It is also useful in GI ailments, certain brain disorders, and for gynecological problems.

Side Effects: Bupleurum has caused sedative effects in some patients, along with increased flatulence and bowel movements in large doses. Some combinations with bupleurum may have certain undesirable effects such as induction of pneumonitis, or nausea and reflux in sensitive patients.

Dosing: Dosage of bupleurum root is 1.5 to 6 g/day; however, no clinical trials have been performed to validate this range as safe and effective.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BUPLEURUM

BURDOCK

DATE OF ISSUE: DEC 1996

REPLACES MONOGRAPH DATED: JUL 1991

SCIENTIFIC NAME(S): *Arctium lappa* L. (Synonymous with A Majus Bernh, great burdock as well as A munus Bernh., lesser burdock.) Family: Asteraceae or Compositae.

COMMON NAME(S): Bardana, beggar's buttons, clotbur, edible burdock, great bur, great burdocks, lappa

BOTANY: Budock is considered to be native in Europs and Northern Asia; it is neutralized in the US. Burdock is widely cultivated in Eastern Europe especially former Yugoslavia, Poland, Bulgaria and Hungary. The plant is a perennial or biennial herb, growing up to 3 meters (about 9 feet), with large ovate, acuminate leaves, broad pinkish flowers made up of reddish-violate tubular florets, surrounded by many involucral bracts ending in a stiff spiny or hooked tip. Overall, these are rounded and spiny in appearance. The root pieces are used in teas and are very hard, minimally fibrous, longitudinally wrinkled and grayish brown to balck in color. [1,2]

HISTORY: In traditional medicine, the fruits (seeds), roots and leaves of burdock have been used as decoctions or teas for a wide range of ailments including colds, catarrh, gout, rheumatism, stomach ailments, cancers and as a diuretic, diaphoretic and laxative. It has even been promoted as an aphrodisiac. Externally, it has been used for various skin problems.

CHEMISTRY: Burdock root yields a wide variety of compounds on analysis that include inulin (up to 50%), tannins, polyphenolic acids (caffeic and chlorogenic), volatile acids (acetic, butyric, costic, 3-hexenoic, isovaleric, 3-octanoic, propionic, etc), polyacetylenes (0.001% to 0.002%, dry-weight basis), and a crystalline plant hormone, glamma-guanidino-n-butyric acid. Studies conducted have isolated and characterized a xyloglucan from the 24% KOH extract of edible burdock. [3] The seeds of burdock yield 15% to 30% fixed oils; a bitter glycoside (arctiin), two lignans (lappaols A and B), chlorogenic acid, a germacranolide and other materials. Other studies have isolated six compounds from burdock seeds including daucosterol, arctigenin, arctiin, matairesinol, lappaol and a new lignan named neoarctin. [4] The levels of arctiin and arctigen in the fruits of burdock that are used in Chinese medicine for the treatment of common colds have also been studied. [5] Others have also reported on the fruit constituents, [6] and even the fruit pulp (pomace). The fruit pulp contains 11% proteins, 19% lipids and 34% inulin.

PHARMACOLOGY: Several researchers have reported on the various biological acitivites of burdock which include antipyretic, antimicrobial, antitumor, diuretic, and diaphoretic properties. [2] Beyond these effects are reported fruit extracts with hypoglycemic activity in rats and fresh root juices with antimutagenic effects probably due to a lignan. [2] Some cosmetic and toiletry type products used for skin-cleaning, antidandruff and hair tonic applications are given in the recent literature. It should be noted that burdock root is fairly commonly used as a food in Asia. [2] Occasionally, US health food stores carry fresh burdock root for sale as a food and nutraceutical (medical food). Among the more recent studies are the uses of burdock in the treatment of urolithiasis, [8] potential inhibition of HIV-1 infection in vitro, [9] metabolism of burdock lignans in rat gastrointestinal tract, [10] platelet activating factor (PAF) antagonism by burdock, [11] effects of burdock dietary fiber in digestion, [12] lack of effectiveness of burdock in treating streptozotocin diabetic mice, [13] potential antitumor activity of burdock extract [14] and a desmutagenic factor isolated from burdock. [15]

TOXICOLOGY: While burdock is generally considered a safe and edible food product, a few reports have appeared on burdock root tea poisoning [16] due to adulteration (subsequently shown to be extraneous atropine), and allergic contact dermatitis due to burdock. [17]

SUMMARY: Burdock root is generally considered an edible food product with some potential medical benefits as a mild diuretic, diaphoretic, antipyretic, antimicrobial and possible antitumor product. Many of the recent chemical and pharmacological studies verify some of these activities. Further investigations are warranted, particularly as a potential medical food or nutraceutical.

PATIENT INFORMATION — Burdock

Uses: Treatment of fever, infection, cancer, fluid retention and kidney stones. Effectiveness and safety for these have not been adequately evaluated. In addition, burdock has been used topically to cleanse the skin and treat dandruff.

Side Effects: Oral: Root tea poisoning due to extraneous atropine (blurred vision, headache, drowsiness, slurred speech, loss of coordination, incoherent speech, restlessness, hallucinations, hyperactivity, seizures, disorientation, flushing, dryness of mouth and nose, rash, lack of sweating, fever).

Topical: Allergic skin irritation.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BURDOCK

BURR MARIGOLD

DATE OF ISSUE: NOV 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Bidens tripartita* Family: Asteraceae/Compositae

COMMON NAME(S): Burr marigold, water agrimony, three-lobe beggarticks, sticktights, water hemp, bastard hemp, bastard agrimony.[1,2]

BOTANY: The burr marigold flowers in the late summer and autumn. It is mostly found in wet areas and near fresh water. The root contains several fibers. The stem may grow > 0.6 m and is somewhat smooth, solid, and highlighted with small brown spots. The plant contains several dark green leaves about 5 to 7 cm in length. The uppermost leaves may be undivided or divided, smooth and pointed at the ends, and normally divided into 3 or occasionally 5 segments. The brownish-yellow flowers may have 8 outer leaflets. The fruits have 4 ribs ending in spiky projections.[1]

HISTORY: Internally, burr marigold was valued for its protective effects in the liver (eg, yellow jaundice),[1,2] blood (eg, infections),[1] and GI disorders (eg, peptic ulcerations, diarrhea)[2] and also was used to reduce fevers.[1] Externally, burr marigold has been used in the treatment of alopecia.

CHEMISTRY: One report indicates that burr marigold contains flavonoids, xanthophyllis, volatile oil, acetylenes, sterols, and tannins.[2] Antimicrobial activity is believed to be associated with phenylheptatriyne, linolic acid, and linolenic acid. Friedelin and friedelan-3-beta-ol and many of the flavonoids (eg, quercetin) are associated with anti-inflammatory activity.[3]

PHARMACOLOGY: *B. tripartita* contains the alkyne derivative phenylheptatriyne, which is believed to be the main active ingredient for its astringent (treatment of wounds and ulcers) and dermatological aid (treatment of eczema) properties.[4] Several other species within the genus have reported activity.

Antihyperglycemic activity has been reported with *B. pilosa*[5] and *B. leucantha*.[6] Blood glucose levels decreased in mice using an in vivo bioassay of 2 polyacetylenic glucoside extracts from the aerial parts of *B. pilosa*. Although not clinically important, in vitro results using *B. leucantha* aqueous extracts demonstrated glycolytic properties.

The genus also is associated with antimicrobial activity. An MIC of 50 mcg/mL for *Candida albicans* was obtained from a sesquiterpene phenol in *B. cernua*[7,8] and phenylheptatriyne in *B. pilosa*has reported activity against a wide variety of bacteria, yeast, and molds.[9] Results of an in vitro antimalarial study concluded that *B. pilosa* extracts at concentrations of 50 mcg/mL inhibited growth of *Plasmodium falciparum*.[10]

Antiulcerogenic activity has been studied in *B. aurea*. The results of an in vitro experiment in rats revealed *B. aurea* flavonoid extracts provided a higher level of gastric protection (ie, increased mucus secretion) as compared with ranitidine and omeprazole.[11,12,13]

Anti-inflammatory activity has been studied in *B. bipinnata* and *B. campylotheca*. Compared with dexamethasone, the flavones of *B. bipinnata* demonstrated greater anti-inflammatory activity in an in vitro experiment using mice.[14] Another study revealed that 5 isolated polyacetylenes from *B. campylotheca*inhibited the activity of cyclooxygenase and 5-lipooxygenase.[15]

An in vitro experiment involving rats evaluated the hepatoprotective effects of 3 *Bidens* species on acetaminophen-induced acute hepatic lesions. The results indicated that *B. chilensis* exhibited the greatest hepatoprotective effect.[16]

TOXICOLOGY: Insufficient information is available on toxicology. However, an allergic reaction may occur in patients hypersensitive to the Asteraceae/Compositae family.

SUMMARY: Although the genus *Bidens* has a history of traditional use, it currently plays a minor role in herbal and conventional medicine. Most of the scientific studies in animals or in vitro for the genus *Bidens* are statistically but not clinically significant; additional scientific studies are recommended to determine clinical efficacy.

PATIENT INFORMATION — Burr Marigold

Uses: Historically, the plant species was used in the treatment of liver, blood, and GI disorders. However, there are no human studies to support these uses.

Side Effects: Allergy may occur in patients sensitive to the Asteraceae/Compositae family. Additional scientific studies are recommended to obtain a profile of any potential side effects.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BURR MARIGOLD

BUTCHER'S BROOM

DATE OF ISSUE: FEB 2003

REPLACES MONOGRAPH DATED: SEP 1991

SCIENTIFIC NAME(S): *Ruscus aculeatus* L. Family: Liliaceae

COMMON NAME(S): Butcher's broom, box holly, knee holly, pettigree, sweet broom,[1] Jew's myrtle[1]

BOTANY: Butcher's broom is a low-growing common evergreen shrub. It is widely distributed, from Iran to the Mediterranean [2] and the southern United States.[3] The plant develops edible shoots from rhizomes that are similar to asparagus in form.[4] Butcher's broom has tough, erect, striated stems with false thorny leaves called cladophylles.[5] The nomenclature of this plant should not be confused with broom (*Cytisus scoparius*L.) or Spanish broom (*Spartium junceum*L.).

HISTORY: *R. aculeatus* was given its common name, butcher's broom, because its stiff twigs were bound together and used by butchers in Europe to keep their cutting boards clean. The plant has a long history of use; more than 2000 years ago, it was noted as a laxative, diuretic, and a phlebotherapeutic agent. [1] Extracts, decoctions, and poultices have been used throughout the ages, but the medicinal use of this plant did not become common until the last century. Early investigations during the 1950s indicated that extracts of the rhizomes of butcher's broom could induce vasoconstriction and therefore may have use in the treatment of circulatory diseases. The increasing popularity of natural and herbal remedies in Europe in the 1970s reaffirmed its position in modern medicine. Novel uses for this plant have included its use as an anti-inflammatory agent and to prevent atherosclerosis. Butcher's broom is the active component in several drug formulations and topical treatments for venous disease. Structural elucidation of active compounds and the discovery of new pharmacological activity, particularly as a cytotoxic agent, demonstrate the need for continued research on butcher's broom.

CHEMISTRY: A variety of compounds have been isolated from butcher's broom. The 2 primary saponin compounds are ruscogenin and neoruscogenin. [6] The ruscogenin content in underground and aboveground parts is approximately 0.12% and 0.08%, respectively. [7] The plant also contains numerous furanostanol and spirostanol saponins.[8,9] Two bisdesmosidic spirostanol saponins, aculeoside A and aculeoside B, also have been isolated. [9] In addition, a variety of flavonoids, a fatty acid mixture composed primarily of tetracosanoic acid and related compounds, chrysophanic acid, sitosterol, campesterol and stigmasterol, have been isolated from the roots.[3] Butcher's broom also contains triterpenes, coumarins, sparteine, tyramine, and glycolic acid. [10] The benzofuran euparone[7] and the phenolic ruscodibenzofuran[11] have been isolated. Plant extracts have revealed the presence of sulfated steroid saponins [12] and the steroid glycosides, rusin and ruscoside.[5]

PHARMACOLOGY: Extracts of *Ruscus* have been included in commercial therapeutic agents designed for the management of venous insufficiency. The most commonly known oral formulation, *Cyclo 3 Fort*, is composed of *R. aculeatus* extract, hesperidin methylchalcone, and ascorbic acid. In France, *Ruscus*extract is the standard treatment in preventing postoperative thrombosis.[1] *Ruscus* has venotonic properties, such as reducing venous capacity and pooling of blood in the legs. It also has a protective effect on capillaries, the vascular endothelium, and smooth muscle. [1]

In dogs, an extract of the root was shown to cause a dose-dependent increase in the contraction of isolated veins. These contractions were inhibited by the alpha-adrenergic blocking agent phentolamine, suggesting that compounds in *Ruscus* activated alpha-1 and alpha-2 receptors in smooth muscle. *Ruscus* had no influence on prostaglandin levels in these tests. [13] Prazosin, an alpha-1-adrenoceptor antagonist, also reduced the activity of *Ruscus* extract.[14] Topical application of the extract on hamster cheek pouch microvasculature displayed concentration- and temperature-dependent responses in the vessels. [15] In humans, *RAES*, a venotropic drug containing *Ruscus* extract, has been shown to be effective in improving the signs and symptoms of lower limb venous disease in patients with chronic phlebopathy.[16] *RAES* is composed of 16.5 mg *Ruscus* extract, 75 mg hesperidin, and 50 mg ascorbic acid.[16] The effectiveness and tolerability of this product was evaluated during a 2-month, double-blind, placebo-controlled, crossover trial involving 40 patients with chronic phlebopathy of the lower limbs. A trend toward improvement was noted among treated patients, although statistical significance was not reached. In particular, edema, itching, and paresthesias improved, as did a feeling of limb heaviness and cramping. In another randomized, double-blind study, 18 healthy volunteers applied 4 to 6 g of a cream containing 64 to 96 mg of *Ruscus*extract to their legs; a reduction in the diameter of the femoral vein was noted ($P = 0.014$).[17]

Researchers have found that when a *Ruscus*extract is applied topically, a dose-dependent inhibition of the macromolecular permeability-increasing effect of histamine occurs.[18] *Ruscus* extract given IV (5 mg/kg) inhibits the macromolecular permeability-increasing effect of bradykinin, leukotriene B4, and histamine. [18] Ruscogenins are ineffective on hyaluronidase activity but show exceptional antielastase activity. [19]

Ruscus is used to treat orthostatic hypotension and does not cause supine hypertension like other related drug therapies. [1] As orthostatic hypotension generally worsens under hot environmental conditions, *Ruscus*extract is unique in that under these conditions, the response of cutaneous veins improves greatly. [14] It is noted in several references that treatment of venous diseases is best accomplished using *Ruscus* extracts along with other nonpharmacologic therapies.

Several studies indicate that compounds found in butcher's broom may possess cytotoxic activity. Researchers have found cytotoxic activity in aculeoside A; it exhibited inhibitory activity against HL-60 cancer cell growth with an IC_{50} of 0.48 mcg/mL.[20] A furanosterol and its corresponding spirostanol have exhibited inhibition of HL-60 cells in vitro. The presence of acetyl and 2-hydroxy-3-methyl pentanoyl groups attached to the diglycoside moiety is suspected to contribute to the observed cytostatic activity.[21]

Cytotoxic activity also has been demonstrated with *Ruscus* diglycoside and its corresponding saponin in culture. [8]

The combined action of flavonoids, sterols, and proteolytic enzymes found in the root has been shown to reduce dextran and carrageenan-induced rat paw edema, indicating that the extract has some anti-inflammatory activity.[22] This mixture of compounds was administered intraduodenally, thereby reducing the possibility of inactivation by stomach acids. Glycolic acid found in the plant is credited for short-term diuretic activity. [1]

Formulations of suppositories containing 100 mg of dry *Ruscus* extract are being investigated for the treatment of hemorrhoids and other venous diseases. A 100 mg extract contains 0.5 mg of active ruscogenins.[23]

TOXICOLOGY: Butcher's broom has not been associated with toxicity. The rhizomes and shoots have been eaten in a manner similar to asparagus in some early cultures. In a clinical trial, no adverse events were attributable to therapy by the 40 patients evaluated. [16] It is a safe, inexpensive botanical medicine. The German Commission E approves oral use of the rhizome for supportive therapy for discomforts of chronic venous insufficiency and complaints of hemorrhoids and reports no known interactions.[24]

SUMMARY: Butcher's broom has been used in traditional medicine and in culinary applications for centuries. Components of the plant may be useful in the management of circulatory disorders. Several compounds also show potential as a cytotoxic agent. However, there is limited information from clinical trials to verify these potential uses. The plant does not appear to be associated with toxicity.

PATIENT INFORMATION— Butcher's Broom

Uses: Butcher's broom has been used in many forms as a laxative, diuretic, treatment for circulatory disease, and cytotoxic agent, although limited results from clinical trials are available.

Side Effects: Not known to be toxic.

Dosing: *Ruscus* extract has been given IV (5 mg/kg).

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BUTCHER'S BROOM

BUTTERBUR

DATE OF ISSUE: APR 2002

REPLACES MONOGRAPH DATED: MAR 1999

SCIENTIFIC NAME(S): *Petasites hybridus* (L.) Gaertner, Meyer & Scherb. Family: *Asteraceae*(daisies)

COMMON NAME(S): Butterbur, pestwurz (German), pestilence-wort, blatterdock, bog rhubarb, butter-dock, bogshorns, butterfly dock, exwort

BOTANY: Butterbur is a perennial shrub native to Europe that has very large, downy leaves. It commonly grows in wet, marshy ground or on sandbars of streams. The distinctive pink-lilac flowers grow on large spikes, and appear before the leaves in spring. The related species *P. albus*is also native to Europe and has been used medicinally. The Japanese species *P. japonicus* is used as a rhubarb-like vegetable and in medicine.

HISTORY: The generic name *Petasites* is derived from the Greek word petasus, a type of broad-brimmed hat worn by shepherds, referring to the broad, downy leaves. The name butterbur relates to the use of the leaves to wrap butter. During the Middle Ages, butterbur leaves and roots were used to treat plague (hence *pestwurz*) and fevers. Other traditional uses include the treatment of cough, asthma, and gastric ulcer. [1]

CHEMISTRY: Butterbur contains senecionine and other toxic pyrrolizidine alkaloids in the leaf and root; a competitive immunoassay has been developed for determination of alkaloid content.[2] High-performance liquid chromatography (HPLC) analyses of both plant parts indicate that, on average, leaves have lower alkaloid levels than roots.[3]

A large number of sesquiterpenes have been isolated from butterbur, with petasin and related eromophilanes being the most pharmacologically important. [4,5,6,7,8] The distribution of sesquiterpenes in different plant parts, in different seasons, and in different locations, has been studied. [3,9,10] HPLC methods for quantitative determination of petasin have been reported,[11,12] and the existence of a distinct chemovar with furanoeremophilanes has been noted. The petasin series of compounds is unstable on storage, with rearrangements occurring in dry plant materials and in stored extracts. [9] The biosynthesis of petasin has been elucidated. [13] Differences in sesquiterpene profiles of various European *Petasites* species have been studied.[14] Other constituents of butterbur include the flavonoid glycosides isoquercitrin and astralagin. [15]

PHARMACOLOGY: Petasin was initially isolated as the antispasmodic constituent of butterbur. [5] In isolated guinea pig trachea, the sulfur-containing S-petasin was the most potent antagonist of histamine, carbachol, KCl, and LTD-4-induced contractions.[16] The iso- series of compounds was less potent than the parent compounds. Since the iso- series is thermodynamically more stable, rearrangement during storage would lead to lower potency. [9] The mechanism of action was described as nonspecific;[17] however, later studies by the same group found that S-petasin blocked calcium channels in vascular smooth muscle cells. [18]

In rat gastric ulceration models, a butterbur extract was found to block the effects of ethanol and indomethacin. Further investigation of mechanism found inhibition of peptido-leukotriene synthesis in macrophages (a calcium-dependent process) without an effect on prostaglandins. [19] Isopetasin and 3 oxopetsan esters were found to be responsible for this effect, while petasin was inactive as a peptido-leukotriene synthesis inhibitor. [20] On the contrary, anti-inflammatory assays in primed human eosinophils and neutrophils found that petasin was able to block early events leading to leukotriene generation. [21]

Two randomized double-blind clinical trials have demonstrated efficacy for butterbur extracts. In the first, a supercritical fluid (SCF) carbon dioxide extract of butterbur was found to have equal efficacy against seasonal allergic rhinitis (hayfever) compared with the antihistamine cetirizine, with butterbur having no sedative side effects.[22] The extract was standardized to 8 mg of petasin per tablet. A second trial, also with an SCF extract, found butterbur to be superior to placebo in migraine prophylaxis over a 12-week period.[23]

TOXICOLOGY: Pyrrolizidine alkaloids are known liver toxins, and the *German Commission E* set upper limits of pyrrolizidine dosage to a maximum of 1 mcg/day. Because butterbur roots normally contain as much as 100 mcg/g, while leaves contain considerably less, [2,3] using the leaves is one method for reducing toxicity. The use of SCF extraction to produce extracts with little or no pyrrolizidine content is another promising possibility.

SUMMARY: Butterbur extract has been shown to be active against hayfever and for prevention of migraines in 2 small studies; however, dosage forms must be certified as free of hepatotoxic pyrrolizidine alkaloids. Typical dosage is 5 to 7 g of plant material. The *German Commission E*set upper limits of pyrrolizidine dosage to a maximum of 1 mcg/day.

Butterbur root was approved by the German Commission E for urinary spastic pain, with limits on pyrrolizidine alkaloid content. A summary of a recent research symposium is available.[24]

PATIENT INFORMATION— Butterbur

Uses: Butterbur extract has shown activity against hayfever and migraines in 2 small studies.

Side Effects: Pyrrolizidine alkaloids are known liver toxins. Dosage forms must be certified as free of hepatotoxic pyrrolizidine alkaloids.

Dosing: Butterbur cannot be recommended for human use because of the presence of hepatotoxic pyrrolizidine alkaloids. An extract was used in a clinical trial for migraine at 100 mg/day; however, unless a product is demonstrated to be free of alkaloids, its use would be contraindicated. [25]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "B" MONOGRAPHS
    BUTTERBUR

"C" MONOGRAPHS

CALABAR BEAN

DATE OF ISSUE: OCT 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Physostigma venenosum*. Family: Leguminosae (Fabaceae)[1]

COMMON NAME(S): Calabar bean, physostigma, ordeal bean, chop nut, esere nut, faba calabarica [2]

BOTANY: The calabar bean is the dried ripe seed of the *P. venenosum*, a perennial woody climbing plant found on the banks of streams in West Africa. Vines of the plant extend more than 50 feet in the air, climbing high among the trees.[3] The plant bears showy purple flowers and seed pods that grow to about 6 inches in length. [3] Each pod contains from 2 to 3 seeds.[4] The dark brown seeds are about 1 inch wide and thick and have an extremely hard shell.

HISTORY: This plant is native to an area of Africa around Nigeria once known as Calabar. The plant is widely known in Africa because the seeds had been used as an "ordeal poison" to determine if a person was a witch or possessed by evil spirits. [5] When used for this purpose, the victim was made to ingest several beans; if the person regurgitated the beans and survived the "ordeal," his innocence was proclaimed. Western settlers who were captured by native tribes and who underwent the "ordeal" soon learned not to chew the bean, but to swallow the kidney-shaped bean intact, thereby not permitting the release of the toxic constituents. The plant has been long recognized as a commercial source of the alkaloid physostigmine, first isolated in 1864.

CHEMISTRY: The seeds contain the alkaloid physostigmine (eserine) in a concentration of about 0.15%, along with the related alkaloids eseramine, physovenine, calabatine, and geneserine, among others. These alkaloids are derived from a tryptophan precursor. On exposure to air, physostigmine oxidizes to a reddish compound, rubreserine, and therefore should be protected from air and light.

PHARMACOLOGY: Physostigmine (usually as the stable salicylate salt) (*Antilirium*) is an acetylcholinesterase inhibitor, that prolongs the neuronal activity of acetylcholine. It is used clinically to contract the pupil of the eye, often to counter the dilating effects of mydriatic drugs, reverse the CNS toxicity of anticholinergic drugs, including tricyclic antidepressants, and to manage intraocular pressure in patients with glaucoma. Physostigmine and related drugs have been investigated for their ability to increase cognition, particularly in demented patients, but these therapies have met with minimal success. Physostigmine and the related synthetic agent neostigmine (eg, *Prostigmin*) have been used for the diagnosis and treatment of myasthenia gravis.[6]

Physostigmine is extremely toxic, with an oral LD50 of 4.5 mg/kg in mice. The maximum reported number of beans eaten followed by survival of a human is 35.[5] Physostigmine kills by affecting heart contractility and inducing respiratory paralysis.

SUMMARY: The use of the calabar bean as an "ordeal bean" has long been outlawed in Africa, although its use persists in tribal ritual. The bean is the source of physostigmine, a medically valuable drug that prolongs the activity of the neural transmitter acetylcholine. Physostigmine is highly toxic.

PATIENT INFORMATION— Calabar Bean

Uses: Originally consumed in African ritual ordeals which killed many subjects, the bean produces alkaloids clinically used to contract the pupil, manage ocular pressure in glaucoma, reverse toxicity of certain other drugs, and treat myasthenia gravis.

Side Effects: Toxic principle affects heart and induces respiratory paralysis.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CALABAR BEAN

CALAMUS

DATE OF ISSUE: MAR 1996

REPLACES MONOGRAPH DATED: JUL 1989

SCIENTIFIC NAME(S): *Acorus calamus* L. At least four subtypes have been identified and are differentiated by their content of the compound isoasarone. Family: Araceae

COMMON NAME(S): Calamus, rat root, sweet flag, sweet myrtle, sweet root, sweet sedge

BOTANY: Calamus is a perennial that is found in damp, swampy areas. It has sword-shaped leaves and grows to 6 feet tall. It is similar in appearance to the iris. It is found throughout North America, Europe, and Asia,[1] and is often imported from India and the former Yugoslavia and USSR.[2]

HISTORY: The fragrant underground portion (the rhizome) has been used medicinally since biblical times. Popular European books on medicinal plants touted calamus as a "wonder drug." It was commonly used in folk medicine as a "nervine," most likely linked to the tranquilizing effect of cis-isoasarone (the major component of the oil).[2] It has been used in traditional medicine for the treatment of digestive disorders and childhood colic. Infusions of the rhizome have been suggested for the treatment of fever, and chewing the rhizome has been said to relieve irritated throats and to remove the odor of tobacco.

The ground rhizome is used as a spice and commercial flavoring in drinks, cosmetics, and toothpastes. However, because of an association with isoasarone and the development of tumors in animals, the use of calamus and its extracts is prohibited in the US.[1]

CHEMISTRY: Calamus contains from 1.5% to 3.5% of a volatile oil responsible for the plant's characteristic odor and taste.[1] A major component of the oil (up to 75%) from some types of calamus is beta-asarone (also referred to as cis-isoasarone).[2] More than a dozen additional fragrant compounds have been identified in the oil.

Acorus calamus has recently been classified into four separate varieties which grow in different locations worldwide. The virtually isoasarone-free plant grows in North America (drug type ?). Western Europe is home for yet another type of calamus, the oil of which contains less than 10% isoasarone (drug type ??). The two other varieties, however, have been found to contain oils which are composed of up to 96% isoasarone (drug types ??? and ?V).[1]

Calamerone, a bicyclic sesquiterpene, has been discovered in the roots of *A. calamus* Calamendiol and isocalamendiol, two known sesquiterpenes, were isolated from the same plant.[3] The essential oil consists of sesquiterpenes and phenylpropanes. The composition of the oil varies depending upon the degree of the ploidy of the plants. Other constituents are acorone, a sesquiterpene diketone, tannins, mucilage, and small startch grains.[2]

PHARMACOLOGY: A variety of studies have been conducted to evaluate the pharmacologic effects of calamus and its extracts. The crude drug has been found to possess sedative properties and to potentiate barbiturate and ethanol-induced sedation in mice; calamus potentiates the CNS effects of reserpine.[4] Doses of 10 to 100 mg/kg intraperitoneally of calamus oil to rats, mice, dogs, cats, and monkeys resulted in a dose-dependent reduction in spontaneous movement; at the 100 mg/kg dose, spontaneous motor activity was reduced by 95% compared to a control. No deaths occurred at any dose. The depressant effect did not induce hypnosis, but was characteristic of sedation induced by reserpine or chlorpromazine.[4]

In low doses, calamus oil has an acetylcholine-like action on smooth muscle; at high doses, it has an antispasmodic and relaxant effect.[4] It boasts stomachic, carminative, and (externally) rubefacient indications.[2] When tested *in vitro*, calamus oil abolished drug-induced contractions of isolated animal intestine, aorta, and uterus; its action was about 10 times less potent than that of papaverine.[5] The oil induced hypotension when administered parenterally to dogs.[1]

This sedative activity has been ascribed to asarone, which in part is chemically related to the reserpine molecule. The sedative effects of intraperitoneal doses of asarone in mice lasted 4 to 6 hours.[6]

Although calamus oil inhibits monoamine oxidase in vitro, this effect occurs primarily at doses higher than are required for usual pharmacologic activity. It has been suggested that the effects of the drug are mediated through 5-hydroxytryptamine[4] or norepinephrine; however, this mechanism has been disputed. Some experts suggest that asarone may mediate its effect through depression of hypothalamic function.[6]

When tested in vitro, it was found that isoasarone-free oil (type ?) had a pronounced spasmolytic action comparable to that of a standard antihistamine. However, at a similar dose, isoasarone-rich oil (type ?V) showed no spasmolytic action at all.[7] Researchers also noted that the oil decreased the mortality of guinea pigs caused by histamine.[5]

Such results suggest that the isoasarone-free oil from type ? (North American) calamus plants can be an effective herbal remedy for dyspepsia and similar spasmodic gastrointestinal complaints.[1]

The essential oil of calamus has also been used as an insecticide. Several studies have found that the vapors of the oil are sufficient to control the hatching and molting of several types of common pests in doses of approximately 10 ml of a 100 ppm dilution.[8]

TOXICOLOGY: The primary toxicologic concern focuses on the carcinogenic effect of isoasarone, a major component of the volatile oil of calamus. Feeding studies conducted more than 20 years ago provided evidence for the mutagenic potential of this compound. Subsequently, all calamus-containing products were removed from the US marketplace.[1] However, a recent study found extracts of *A. calamus* to exhibit no mutagenic activity in the salmonella mutagenicity screen.[9] The plant and its extracts continue to find use throughout the world.

The LD_{50} of asarone in mice is 417 mg/kg (oral) and 310 mg/kg (IP).[10] Although *A. calamus* exhibited no mutagenic activity in the salmonella mutagenicity screen, recent experiences showed that calamus oil exhibited genotoxic effects on Swiss mice.[11] Another experiment showed that calamus oil was strongly mutagenic.[12]

SUMMARY: Calamus is a fragrant plant that grows throughout many parts of the world and has been used in traditional medicine since biblical times. Although used in many countries as a flavoring, the oil contains asarone, a compound which has been considered to be mutagenic. Hence, calamus and its derivatives are not used in foods in the US. The oil has a strong sedative and antispasmodic action that appears to resemble the activity of the phenothiazine tranquilizers.

PATIENT INFORMATION — Calamus

Uses: Traditionally used as a tranquilizer and general "wonder drug," calamus also is used as a flavoring. The oil is a sedative, hypotensive, and muscle relaxant.

Side Effects: Because of mutagenic properties, calamus derivatives are not used in foods in the US.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CALAMUS

CALANOLIDE A

DATE OF ISSUE: JUN 2000

REPLACES MONOGRAPH DATED: NA

SCIENTIFIC NAME(S): Originally isolated from species *Calophyllum lanigerum* var. *austrocoriaceum*

COMMON NAME(S): Calanolide A

BOTANY: Calanolide A is a compound isolated from the latex of the tree, *Calophyllum lanigerum* var. *austrocoriaceum*, that grows in the rain forest of the Malaysian state of Sarawak on the island of Borneo. There are at least 200 species in the genus *Calophyllum*.[1,2]

HISTORY: Rain forests are a very promising source of natural medicines because of their vast diversity. It has been estimated that more than half of the world's 250,000 plant species exist in tropical rain forests. Searching for natural drugs in these areas, the National Cancer Institute (NCI) contracts scientists to gather specimens for analysis. In 1987, an Illinois team obtained samples from many trees, one of which was *Calophyllum lanigerum*. Four years later, the NCI discovered that a preparation from this gum tree was very effective against the human immunodeficiency virus type 1 (HIV-1).[1,3] Confirmation of species was performed by comparison to Arnold Arboretum species and samples from the Singapore Botanic Garden.[3]

CHEMISTRY: Plants from the genus *Calophyllum*have been shown to contain xanthones, steroids, triterpenes, coumarins, and benzopyrans. Calanolide A falls into the category of a dipyranocoumarin.[2] It is classified as a nonnucleoside HIV-1 specific reverse transcriptase (RT) inhibitor.[2,4] Many studies in this area discuss findings from the genus *Calophyllum*, and offer structural representations, related compounds and their derivatives, modifications of the molecule, etc.[2,4,5,6,7,8,9] Calanolide A has been synthesized in the lab and was found to have similar actions to the natural product.[10]

PHARMACOLOGY

HIV: This recently discovered natural product has been found to specifically inhibit the DNA polymerase activity of HIV-1 RT, but not HIV-2 RT.[11] This information warrants further investigation in human clinical trials. Calanolide A has been found to inhibit a wide variety of HIV-1 strains, drug-resistant strains, and HIV disease in various stages. Calanolide A appears to act early in the infection process similar to dideoxycytidine.[12] Calanolide A's complex biochemical mechanism of inhibition has suggested the presence of 2 binding sites, 1 competitive, 1 noncompetitive. Calanolide A binds near the active site of the enzyme and interferes with deoxynucleotide triphosphate binding.[13] Many RT inhibitors bind to a common site on HIV-1 RT; whereas calanolide A may bind to a different site or sites on the enzyme.[14] Changes in the nonnucleoside inhibitor binding site itself may also alter effects. One report discusses cross-resistance of certain viral strains. Single mutations at certain amino acids can yield virus with either higher or lower resistance.[15]

In vivo, calanolide A has suppressed (HIV) viral replication in both IP and SC compartments in the hollow fiber mouse model. When combined with zidovudine, calanolide A had a synergistic effect.[16]

Other related compounds from the genus *Calophyllum* possess HIV-inhibitory actions. Examples include costatolide,[17,18] dihydrocalanolide,[18] and certain cordatolides.[19] Calanolides, their derivatives and/or structural analogs from *C. lanigerum* and other *Calophyllum* species, and their anti-HIV activities have been reported.[5,6,7,8,9,20,21] HIV RT inhibitors of natural origin, including calanolide A, have been reviewed.[22]

TOXICOLOGY: It has been mentioned that substance from *C. lanigerum* destroys the HIV virus without killing healthy cells,[1] but toxicology information is limited because of its recent discovery.

SUMMARY: Calanolide A offers promising treatment for HIV-1, although most studies have been performed in vitro. Clinical investigation and human trials are underway to further evaluate the effects of *Calophyllum*, a natural substance found in the tropical rain forest.

PATIENT INFORMATION— Calanolide A

Use: Initial studies show promise for treating HIV-1.

Side Effects: Because this product is a relatively new discovery, no data are available.

Dosing: Calanolide A is an investigational anti-HIV drug that has been given in early clinical trials at an oral dose of 200 to 800 mg; however, it is not available for use. Its safety and efficacy remain to be defined.[23]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CALANOLIDE A

CALENDULA

DATE OF ISSUE: JAN 1995

REPLACES MONOGRAPH DATED: AUG 1992

SCIENTIFIC NAME(S): *Calendula officinalis* L. Family: Compositae

COMMON NAME(S): Calendula, garden marigold, gold bloom, holligold, marygold, pot marigold, marybud [1]

BOTANY: Believed to have originated in Egypt, this plant has almost world wide distribution. There are numerous varieties of this species, each one varying primarily in flower shape and color. Calendula grows to about two feet in height and the wild form has small, bright yellow-orange flowers that bloom from May to October. It is the ligulate florets, mistakenly called the flower petals, that have been used medicinally. This plant should not be confused with several other members of the family that also carry the "marigold" name.

HISTORY: The plant has been grown in European gardens since the 12th century and its folkloric uses are almost as old. Tinctures and extracts of the florets had been used topically to promote wound healing and to reduce inflammation; systemically, they have been used to reduce fever, to control dysmenorrhea and to treat cancer. The dried petals have been used like saffron as a seasoning and have been used to adulterate saffron. [2]

The pungent odor of the marigold has been used as an effective pesticide. Marigolds are often interspersed among vegetable plants to repel insects. [3]

CHEMISTRY: A number of studies have been reported describing the chemistry of calendula. Almost all of the investigations regarding this plant have been conducted in Eastern Europe. The plant contains a number of oleanolic acid glycosides. [4] Flavonol-2-O-glycosides have been recovered from *C. officinalis* via high pressure chromatography.[5] Calendulin (also known as bassorin) has been identified in the plant. [1] Sterols and fatty acids, such as calendic acid, are present in the plant.[6,7,8] In addition, the plant contains triterpenoids, [9] tocopherols,[10] mucilage and a volatile oil. The carotenoid pigments have been used as coloring agents in cosmetics and the volatile oil has been used in perfumes. [11]

PHARMACOLOGY: Despite the history of use of calendula and the rather detailed studies of its chemistry, there are almost no studies regarding its efficacy in the treatment of human disorders.

Calendula extracts have been used topically to promote wound healing, and experiments in rats have shown that this effect is measurable. An ointment containing 5% flower extract in combination with allantoin was found to "markedly stimulate" epithelialization in surgically-induced wounds. On the basis of histological examination of the wound tissue, the authors concluded that the ointment increased glycoprotein, nucleoprotein and collagen metabolism at the site. [12]

Russian investigators found that sterile preparations of calendula extracts alleviated signs of chronic conjunctivitis and other chronic ocular inflammatory conditions in rats;[13] the extracts also had a systemic anti-inflammatory effect. Other Russian investigators have used plant extract mixtures containing calendula for the treatment of chronic hyposecretory gastritis. Extracts of the florets are uterotonic in the isolated rabbit and guinea pig uterus.

Calendula extracts have in vitro antibacterial, antiviral [14,15] and immunostimulating properties.[16] Published reports of small clinical trials conducted in Poland and Bulgaria suggest that extracts of the plant may be useful in the management of duodenal ulcers, gastroduodenitis and periodontopathies.

TOXICOLOGY: Despite its widespread use, there have been no reports in the Western literature describing serious reactions to the use of calendula preparations. A report of anaphylactic shock in a patient who gargled with a calendula infusion has been reported in Russia.

Allergies to members of the family Compositae (chamomile, feverfew, dandelion) have been reported, in particular to the pollens of these plants. Users of calendula preparations should consider the potential for allergic reactions to occur.

In animals, doses of up to 50 mg/kg of extract had essentially no pharmacologic effect and induced no histopathologic changes following either acute or chronic administration.[17] Saponin extracts of *C. officinalis* have not been found to be mutagenic.[18]

SUMMARY: Calendula is one of the many plants used persistently despite no clear evidence that its components exert any consistent pharmacologic effect. Some support in the form of animal studies exists for its topical wound healing and anti-inflammatory uses, and these properties should be investigated further. The plant appears to have a low potential for toxicity, but nevertheless, cannot be recommended at this time for the systemic treatment of any disease.

PATIENT INFORMATION — Calendula

Uses: Calendula has been used in folk medicine topically to treat wounds and internally to reduce fever, treat cancer and control dysmenorrhea. Extracts have proved antibacterial, antiviral and immunostimulating in vitro. Petals are consumed as a seasoning. The plant has been used to repel insects.

Side Effects: Allergic reactions to the botanical family and one case of anaphylaxis have been reported.

Dosing: One to 4 g of herb has been used to make a tea for sore throat and peptic ulcer; however, clinical trials have not validated this dose. An ointment containing 2% to 5% flower extract is used for topical wound healing. [19]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CALENDULA

CANAIGRE

DATE OF ISSUE: APR 2003

REPLACES MONOGRAPH DATED: JUL 1991

SCIENTIFIC NAME(S): *Rumex hymenosepalus* Torr. Family: Polygonaceae

COMMON NAME(S): Canaigre, ganagra, tanner's dock, wild rhubarb[1,2]

BOTANY: Canaigre is native to the deserts of the southwestern United States and Mexico. It is a member of the dock (sorrel) family and can attain a height of 0.9 m.

HISTORY: Canaigre has been known as a practical source of tannin. The common name is derived from the Spanish "Cana Agria" or "sour cane." [2] Extracts of the plant were used in the tanning industry. It was also the source of a mustard-colored dye. Canaigre does not have an extensive history of use in herbal medicine. It became popular during the later half of the last century and today is promoted for the treatment of a variety of ailments. It has been suggested that canaigre may be used as an inexpensive alternative to ginseng because of its ability to manage various disease states. Canaigre is not related botanically to ginseng, and there is no evidence of any beneficial effects associated with its use.

CHEMISTRY: The root of canaigre contains up to 25% tannin.[2] The plant contains small amounts of anthroquinones (about 1%) as well as starch and resin. [3] Several compounds have been isolated from the plant, including the anthroquinoids emodin, chrysophanol, and physcion, as well as beta-sitosterol. [4] Canaigre also contains the anthocyanins leucodelphinidin and leucopelargonidin. [5] There is no evidence that the plant contains any of the panaxoside-like saponin glycosides responsible for the pharmacologic activity of ginseng. In the past, canaigre was used to adulterate rhubarb powders.

PHARMACOLOGY: There are no reports of any pharmacological activity associated with canaigre. The high tannin content may provide an astringent effect when applied topically. The leucoanthocyanin fraction of the plant may have antitumor activity. [5,6] A review of clinical research from PubMed and ChemAbstracts suggests that the plant is not actively under investigation, as there are no new pharmacological data.

TOXICOLOGY: Although the leaf stalks are edible like rhubarb, this practice is not widespread and no reports of clinically significant toxicity have been associated with canaigre. The high tannin concentration may pose a considerable carcinogenic risk. [3] Consequently, avoid the ingestion of canaigre.

SUMMARY: Canaigre has been promoted for the treatment of a variety of disease states. However, there is little new pharmacological data to support its use. The plant contains high concentrations of tannin but appears to be otherwise devoid of important pharmacologic activity. There is no evidence that canaigre contains the same pharmacologically active compounds as ginseng. Its high tannin content may pose a carcinogenic risk; avoid ingestion of the plant.

PATIENT INFORMATION — Canaigre

Uses: Roots contain up to 25% tannin. The plant yields a mustard-colored dye. It has been promoted as an alternative to ginseng, although there is no evidence of any beneficial effects associated with its use.

Side Effects: High tannin content may pose carcinogenic risk; avoid ingestion.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CANAIGRE

CAPERS

DATE OF ISSUE: FEB 2003

REPLACES MONOGRAPH DATED: APR 1992

SCIENTIFIC NAME(S): *Capparis spinosa* L. Family: Capparidaceae

COMMON NAME(S): Caper, cappero

BOTANY: *C. spinosa* is a dicotyledonous perennial shrub found throughout the Mediterranean countries of Europe, Asia, and North Africa. [1,2] The plant has been used for erosion control because the roots grow up to 3 m into the soil. [3] From mid-April to the end of September, capers may grow 1 to 1.5 m in height, spread 2 to 3 m, and bud white flowers up to 7.6 cm across.[1,2,3] The fruit is a round berry. Two forms of the caper can be found, a spiny and a nonspiny variety. Capers thrive best in dry soil.

HISTORY: The caper has a long history of use as a culinary spice and remains widely used as a spice today. In commercial operations, the unopened flowered buds are collected by hand and pickled to produce the characteristic pungent taste and smell. [4] Leaves of related species are used as rubifacients and to treat skin disorders.

CHEMISTRY: The plant contains the flavonoids rutin, kaempferol-3-glucoside, kaempferol-3-rutinoside, and kaempferol-3-rhamnorutinoside. [5] Other components contained within the plant include quercetin 3-O-glucoside, [6] quercetin 3-O-glucoside-7-O-rhamnoside, [6] a new flavonoid quercetin 3-O-(6-alpha-L-rhamnosyl-6-beta-D-glucosyl)-beta-D-glucoside, [6] and 2 novel (6S)-hydroxy-3-oxo-alpha-ionol glucosides. [7] One article alluded to the anti-inflammatory activity of the polyprenol cappaprenol-13. [8]

PHARMACOLOGY: Preliminary investigations have found that extracts of capers may be an effective treatment for improving the function of enlarged capillaries and for improving dry skin.[4]

The aqueous extracts from *C. spinosa* completely prevented the growth of *Microsporum canis* and *Trichophyton mentagrophytes*.[9]

p-Methoxy benzoic acid, from an aqueous extract from *C. spinosa*, protected against in vitro hepatotoxicity in rats caused by thioacetamide and galactosamine as well as in vivo hepatotoxicity resulting from carbon tetrachloride and paracetamol. [10]

TOXICOLOGY: The topical application of wet compresses soaked in fluid containing capers has been associated with the development of contact dermatitis. Therefore, patients with sensitive skin should be aware of the irritating potential of this plant when used topically. [11] The related species *C. fasicularis* and *C. tumentosa* are reported to be poisonous.[4]

SUMMARY: Capers are best known as spices used in Mediterranean cooking. Although they have not been used widely in herbal medicine, extracts of the buds and plant have been used for the treatment of some skin disorders. Capers may induce dermatitis.

PATIENT INFORMATION — Capers

Uses: Pickled flower buds are used as a condiment. Extracts of this or related species may improve dry skin and the function of enlarged capillaries, but this has not been confirmed in clinical trials. Some preliminary studies allude to the plants' antifungal and antihepatotoxic activity.

Side Effects: Topical use of capers may cause contact dermatitis; avoid use in patients hypersensitive to the plant species as well as during pregnancy and lactation.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CAPERS

CAPSICUM PEPPERS

DATE OF ISSUE: AUG 2001

REPLACES MONOGRAPH DATED: JUL 1993

SCIENTIFIC NAME(S): *Capsicum frutescens* L., *Capsicum annuum* L., or a large number of hybrids or varieties of the species. Family: Solanaceae

COMMON NAME(S): *C. frutescens*: capsicum, cayenne pepper, red pepper, African chillies, green pepper; *C. annuum*, var. *conoides*: tabasco pepper, paprika, pimiento, Mexican chilies; *C. annuum*, var. *longum*: Louisiana long pepper or hybridized to the Louisiana sport pepper.

BOTANY: *C. frutescens* is a small spreading annual shrub that is indigenous to tropical America. It yields an oblong, pungent fruit, while *C. annuum* (the common green pepper) yields paprika. At one time, it was believed that all peppers derived from *C. frutescens*, *C. annuum*, or their hybrids. However, it is now recognized that approximately 5 species and their hybrids contribute as sources of "peppers." [1] Capsicum peppers should not be confused with the black and white pepper spices derived from the unripened fruit of *Piper nigrum*.

HISTORY: Capsicum was first described in the mid-1400s by a physician who accompanied Columbus to the West Indies. The plants derive their names from the Latin capsa, meaning box, referring to the partially hollow, box-like fruit. Capsicum has been highly desired as a spice and has been cultivated in some form in almost every society. Peppers are among the most widely consumed spices in the world, with an average daily per capita consumption in some Southeast Asian countries approaching 5 g of red pepper (approximately 50 mg of capsaicin). [2] Preparations of capsicum have been used as topical rubefacients, and extracts have been ingested as a stomachic, carminative, and GI stimulant.

CHEMISTRY: Capsicum contains about 1.5% of the irritant oleoresin. The major component of the oil is capsaicin (0.02%), a very pungent phenolic chemical. Along with several closely related compounds, it is responsible for the pungency of the fruit. [3] The structure of capsaicin (8-methyl-*N*-vanillyl-6-nonenamide)[4] is similar to that of eugenol, the active principle in oil of cloves, which also can induce long-lasting local analgesia. [5] The pungency appears to be related to the presence of a 4-hydroxy-3-methoxyphenyl substituent.[5] It has been noted that the more tropical the climate, the more pungent the fruit. [6] The characteristic flavor of capsaicin in aqueous solutions can be detected in concentrations as low as 1 part in 11 million.

PHARMACOLOGY

Irritant: Capsicum is a powerful irritant because of the effect of the oleoresin and capsaicin. Solutions of capsaicin applied topically can produce sensations varying from warmth to burning, depending on the concentration; with repeated applications, an apparent desensitization to the burning occurs. This effect has been studied in detail and has resulted in the elucidation of capsaicin's mechanism of action.

In one study, 4 applications of a 0.1% solution of capsaicin were applied topically to the skin of healthy subjects and compared with untreated skin. Histamine was injected intradermally at the application site to test for chemical responsiveness. As expected, injection at the untreated area evoked a wheal, flare, and itching. The capsaicin-treated areas developed a wheal but no flare. The flare response, also called axon reflex vasodilation, is believed to be mediated by the release of the vasoactive compound, substance P. This compound is involved in the transmission of painful stimuli from the periphery to the spinal cord. Following an initial application, substance P is released, causing the sensation of pain. However, upon repeated administration, the compound is depleted and a lack of pain sensation ensues. This effect usually occurs within 3 days of regular application. Pretreatment with capsaicin also abolishes airway edema and bronchoconstriction induced by cigarette smoke and other irritants.[5]

Pain treatment: Capsaicin has become a valuable "pharmacologic probe" for the evaluation of nociception, the reception and transmission of painful or injurious stimuli. Because capsaicin-evoked mechanical allodynia and hyperalgesia cross nerve territories, organic and psychogenic mechanisms must be considered in the differential diagnosis of chronic pain. [7] The use of capsaicin ointments for the treatment of pain caused by herpes zoster (shingles) has been of more practical importance. In patients affected with shingles, often excruciating pain may persist around the infected nerve tracts for months to years after the initial flare. *Zostrix*cream (Bioglan Pharma, Inc.), containing either 0.025% or 0.075% capsaicin, has been found to be effective when applied topically in the management of postherpetic neuralgia.[8,9] It also has been found to be effective in the management of trigeminal and diabetic neuralgia, causalgia, postmastectomy, postsurgical neuralgias, rheumatoid arthritis, and osteoarthritis. A preliminary study using high-dose (5% to 10%) topical capsaicin brought relief to patients with intractable pain, thus warranting further investigation.[10]

Pruritus: Topical capsaicin has been shown to effectively treat pruritus associated with psoriasis, [11,12] pityriasis rubra pilaris,[13] PUVA (photochemotherapy with psoralen),[14] and prurigo nodularis.[15]

Densitization of nasal nerves: The inhalation of a capsaicin solution can desensitize nasal nerves that cause runny nose, sneezing, and congestion. In a small study at Johns Hopkins Asthma & Allergy Center, such symptoms were alleviated in 8 volunteers who received repeated nasal sprays of capsaicin. [16] In a placebo-controlled study, intranasal capsaicin was shown to be effective in reducing nasal symptomatology in nonallergic, noninfectious perennial rhinitis without affecting cellular homeostasis up to 9 months after treatment.[17,18]

Tonsillitis/Cough: In Germany, *C. annuum* in a fixed combination with *Guajacum officinale* and *Phytolacca americana* has been successfully used to treat tonsillitis;[19,20] and used along with other homeopathic remedies to treat otitis media in children. [21]

Cough response to capsaicin (concentration that caused 5 coughs) has been used to assess the cough susceptibility in a wide range of diseases. [22]

Decreased bladder pain/Hyperreflexia: Intravesical capsaicin has decreased frequency and nocturia of patients with severe bladder pain. [23] Repeated instillations of intravesical capsaicin were shown to be effective for 3 to 5 years in treating detrusor hyperreflexia because of spinal cord disease. [24] Intraureteric capsaicin instillation was shown to provide dramatic symptomatic relief in some patients with loin pain hematuria syndrome.[25]

Birdseed use: Capsaicin has been used in birdseed to discourage squirrels, as birds do not have capsaicin receptors, while squirrels do.

INTERACTIONS: A study using antipyrine to assess oxidative metabolizing enzyme activity of the liver found that when rats were given capsaicin, it caused impaired elimination of antipyrine but had no effects on the pharmacokinetics of theophylline or quinine. [26] Studies in humans are necessary to investigate whether capsaicin interferes with the cytochrome P450 hepatic drug metabolizing enzymes.

TOXICOLOGY: The most well-known adverse effect of peppers is the often intolerable burning sensation that occurs following contact with moist mucous membranes. For this reason, it is a common component of many self-defense sprays. When sprayed into an attacker's eyes, it causes immediate blindness and irritation for up to 30 minutes, with no permanent damage. If mucous membranes come in contact with capsicum, they should be flushed with water. Anecdotal reports suggest that flushing the area with milk may be beneficial.

Topical irritation is common, particularly with the use of commercial creams. One clinical study in patients with postherpetic lesions was terminated early because approximately one-third of the patients experienced "unbearable" burning. [27]

The toxicity of Tabasco brand red pepper sauce was evaluated in rats. [28] The acute oral $LD_{50}$was 24 mL/kg. After 90 days of diet supplementation with the sauce, no signs of toxicity were noted. Mild eye irritation was observed when instilled, but vinegar, an ingredient in the sauce, was shown to contribute to this effect. [29]

The intense GI burning that often accompanies the ingestion of peppers may be reduced by removing the seeds from the pepper pods before ingestion [30] or by ingesting bananas along with the peppers. [31] One study found no difference in the healing rate of duodenal ulcers among patients who ingested 3 g of capsicum daily compared with untreated controls,[32] and another study found that chili protects against aspirin-induced gastroduodenal mucosal injury, [33] disproving a commonly held idea that peppers always exacerbate GI problems. Low-dose capsaicin may stimulate the swallowing reflex and prevent aspiration pneumonia in elderly patients with swallowing disorders.[34] Capsaicin has been referred to as a "double-edged sword" because it enhances postprandial heartburn; however, capsaicin decreases gastric liquid emptying, which could provide mucosal protection. [35] Although capsaicin has shown inhibitory action on *Helicobacter pylori* in vitro, an in vivo study does not support this action.[36] The validity of the study has been questioned because of the small number of subjects and the short study duration. [37,38]

Allergic reaction to paprika has been seen in patients with "mugwort-celery-spice-syndrome." [39] These patients exhibit allergy to mugwort, birch-pollen, celery, anise, coriander, cumin, fennel, and green and black peppercorns, along with fresh bell peppers and dried bell-pepper fruits (paprika). [39]

Patients sensitive to latex, banana, kiwi, chestnut, and avocado can also exhibit sensitization to peppers. [40]

"Hunan hand" is a contact dermatitis resulting from the direct handling of capsaicin found in chili peppers. [41] Controversy exists regarding capsaicin's mutagenicity and tumorigenicity.[42,43]

A review of the literature, including a study that showed lack of tumor promoting activity in mouse skin, concluded that capsaicin is a carcinogen, cocarcinogen, and anticarcinogen.[42,43]

SUMMARY: Peppers are some of the most common spices known, and their distribution is worldwide. Pungent peppers contain the highest concentration of the active principle capsaicin, a compound known to deplete neuronal stores of the pain transmitter, substance P. Capsaicin is applied topically in the management of topical neuritis syndromes and skin conditions such as psoriasis. Intravesical capsicum has been effective in patients with spinal cord disease who suffer from detrusor hyperreflexia. Topical, mucosal, and GI irritations are common.

PATIENT INFORMATION — Capsicum Peppers

Uses: Many varieties are eaten as vegetables and spices. The component capsaicin is an irritant and analgesic, used in self-defense sprays, and in pain treatments for postsurgical neuralgia, shingles, and others.

Interactions: When given to rats, capsaicin caused impaired elimination of antipyrene but had no effects on the pharmacokinetics of theophylline or quinine. Human studies are necessary investigate whether capsaicin interferes with the cytochrome P450 hepatic drug metabolizing enzymes.

Side Effects: Topical, mucosal, and GI irritations are common. Allergies to latex, bananas, kiwi, chestnut, avocado, or having "mugwort-celery-spice-syndrome" may predispose people to capsicum (pepper) allergy.

Dosing: For internal use, a typical dose of cayenne powder is 30 to 120 mg as a digestive aid. The pungency of hot peppers can vary widely, influencing the dose required, and much higher doses (1 to 20 g) occasionally have been recommended; [33,44] however, high doses of pungent peppers may induce gastritis. For external uses, capsaicin and capsicum creams are available in several strengths, from 0.025% to 0.075% capsaicin. [45]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CAPSICUM PEPPERS

CARROT OIL

DATE OF ISSUE: JUN 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Daucus carota* L. Subsp. *carota*. Family: Umbelliferae or Apiaceae

COMMON NAME(S): Oil of carrot, Queen Anne's lace, wild carrot

BOTANY: The carrot is an annual or biennial herb, having an erect multi-branched stem, growing up to 1.5 m (4 ft) in height. The wild carrot is commonly seen in fields and roadsides throughout most of temperate North America and is seen with an intricately patterned flat flower cluster (Queen Anne's lace). The main cluster is made up of some 500 flowers, each showing at the center a single, small red-to-purplish flower. The wild carrot has an inedible tough white root. It is native to Asia and Europe, having been brought to America from England. The common cultivated carrot [*Daucus carota* L. subspecies *sativus*(Hoffm.) Arcang.] possesses an edible, fleshy, orange taproot. The parts that are used pharmaceutically are the dried fruit which yields carrot seed oil upon steam distillation and the orange carrot root which yields root oil by solvent extraction.[1,2]

CHEMISTRY: Carrot seed oil is made up of a-pinene (up to 13.3%), ß-pinene, carotol (up to 18.29%), daucol, limonene, ß-bisabolene, ß-elemene, *cis*-ß-bergamotene, ?-decalactone, ß-farnesene, geraniol, geranyl acetate (up to 10.39%), caryophyllene, caryophyllene oxide, methyl eugenol, nerolidol, eugenol, *trans*-asarone, vanillin, asarone, a-terpineol, terpinene-4-ol, ?-decanolactone, coumarin, ß-selinene, palmitic acid, butyric acid and other constituents. The seed oil varies in content from 0.005% to 7.15% of the plant.[2]

The chemical composition of the edible carrot root is 86% water, 0.9% protein, 0.1% fat, 10.7% carbohydrate, 1.2% fiber, trace elements and vitamin A (2,000 to 4300 I.U. in 100 grams).[1] Several tissue culture studies on *D. carota* identify new ingredients in the vegetative tissue (eg, enthocyanins,[3,5] chlorogenic acid,[3] flavonoids,[4] apigenin[6] and a soluble ß-fructofuranosidase).[7]

PHARMACOLOGY: Carrot seed oil exhibits both smooth-muscle relaxant and vasodilatory action in isolated animal organ studies. It depresses cardiac activity in both frog and dog hearts.[2]

The cultivated fleshy taproot of the edible carrot is widely eaten as a raw or cooked vegetable; even wine has been brewed from the plant. [1] A wide array of older references lists the uses of carrot seed oil as an aromatic, carminative, diuretic, emmenagogue, aphrodisiac, nerve tonic and as a treatment for dysentery, worms, uterine pain, cancer, diabetes, gout, heart disease, indigestion and various kidney ailments. [1] Of course, many of these areas have not yet been fully studied. The continued use of carrot seed oil is primarily as a fragrance in detergents, soaps, creams, lotions and perfumes (which contain 0.4%, the highest level) and as a flavoring in many food products (eg, liqueurs, nonalcoholic beverages, frozen dairy desserts, candy, baked goods, gelatins, puddings, meat products, condiments, relishes and soups), usually in levels below 0.003%. [2] The root oil is used in sunscreen preparations, as a yellow food color (because of its high carotene content) and as a good source of ß-carotene and vitamin A.[2]

Extracts of *D. carota* show only limited antifungal activity.[8] An ethanol extract (10 to 100 mg/kg dose) produced a dose-dependent decrease in systolic and diastolic blood pressure in anesthetized normotensive rats. Further experiments using beating guinea pig paired atria showed that the cardiovascular effects are independent of adrenergic or cholinergic receptors, and the extract induced a concentration-dependent (0.3 to 5 mg/ml) decrease in force and rate of atrial contractions. The same preparation applied to rabbit thoracic aorta produced inhibition of potassium-induced contractions. These results suggest that *D. carota*extract may exhibit calcium channel blocking-like direct relaxant action on cardiac and smooth muscle, and may explain its hypotensive action. [9] An extract of *D. carota* has also demonstrated hepatoprotective activity against carbon tetrachloride-induced intoxication in mouse liver. [10] Obviously, both these hypotensive and hepatoprotective properties need verification in humans.

TOXICOLOGY: Because myristicin (a known psychoactive agent) occurs in carrot seed, it has been proposed that ingestion of large amounts of *D. carota* may cause neurological effects. Some individuals have shown sensitivity (irritation, vesication) to carrot leaf when they handle it excessively, especially after exposure to sunlight.[1] Most data indicate that the vegetable and the seed oil are nontoxic.[2]

SUMMARY: The commonly cultivated edible carrot root is widely consumed as a vegetable because of its flavor and high vitamin A content. The seed and root oils of the wild and cultivated carrot are used pharmaceutically as a flavoring and fragrance, and the roots as sources of ß-carotene and vitamin A. More recent pharmacological studies indicate its potential usefulness as cardiovascular and hepatoprotective agents. These still need further verification and human clinical studies.

PATIENT INFORMATION— Carrot Oil

Uses: Lab studies show that carrot seed oil, which had a wide range of applications in folk medicine, acts as a muscle relaxant and vasodilator. It is now most commonly used as fragrance, flavoring and a source of food color, beta-carotene and vitamin A. Hypotensive and hepatoprotective properties have yet to be confirmed in humans.

Side Effects: Ingestion of large amounts may have neurological effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CARROT OIL

CASCARA

DATE OF ISSUE: MAY 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Rhamnus pushiana* DC. (Syn. *Frangula purshiana* (D.C.) A. Gray ex J.C. Cooper) Family: Rhamnaceae

COMMON NAME(S): Buckthorn, cascara sagrada, chittem bark, sacred bark

BOTANY: The official cascara sagrada is the dried bark of *Rhamnus pushiana* collected from small to medium-sized wild deciduous trees. They usually range from 20 to 40 feet high and possess thin, elliptic to ovate-oblong, acutely pointed leaves. The greenish flowers are arranged in umbellate cymes and the fruit is purplish-black and broadly obovoid (8 mm long). The commercial bark is flattened or transversely curved, longitudinally ridged with a brownish to red-brown color. It has gray or white lichen patches and occasional moss attachments. Cascara trees are found in North America in California, Oregon, Washington, Idaho, Montana and as far north as Southeast British Columbia.[1,2]

HISTORY: The American cascara is a folkloric medicine of relatively recent origin, having been introduced as a tree bark laxative by early Mexican and Spanish priests of California (probably *Rhamnus Californica*). *R. purshiana* itself was not described officially until 1805 and the bark was not brought into regular medicinal use until 1877. The European counterpart (European buckthorn, *Rhamnus frangula*) was described much earlier by the Anglo-Saxons. In fact, the berries were official in the 1650 London Pharmacopoeia.[3]

CHEMISTRY: The active laxative principles of cascara include at least 6% to 9% anthracene derivatives which exist as normal O-glycosides and C-glycosides. The four primary glycosides or cascaroside A, B, C and D, contain both O- and C-glycosidin linkages. Chemically these are designated as the C-10 isomers of the 8-O-ß-D-glucopyranosides of aloin and chrysophanol. The probable breakdown products of the C-glycosides are the two aloins: Barbaloin which is derived from aloe-emodin anthrone and chrysaloin which is derived from chrysophanol anthrone. Other glycosides isolated include a number of O-glycosides derived from emodin, emodin oxanthrone, aloe-emodin and chrysophanol. A number of dianthrones are also present including emodin, aloe-emodin, chrysophanol and the heterodianthrones, palmidin A, B and C. Compounds found in the free state include aloe-emodin, emodin and chrysophanol.

The free anthraquinones are likely formed in the leaves and stored in the bark largely as C-glycosides. The older bark contains the most C-glycosides. Although uneconomical for commercial exploitation, *R. purshiana* cell suspension cultures produce anthracene derivatives. [2,3]

Cascara juice also contains other non-laxative compounds eg, rhamnol (cinchol, cupreol, quebrachol); linoleic, myristic and syringic-acids; resins, fat, starch and glucose; malic and tannic acid. The dried seeds contain 6.7% to 25.4% protein, 13.4% to 56.9% oil and 1.3% to 2.3% ash. [4] The presence in the bark of bitter substance and methylhydrocotoin is disputed.[5]

A variety of extraction methods have been examined for cascara. Boiling water prevents the losses and changes to the compound that occur in cold water extraction. [6] Active fractions of anthraquinone glucosides have been isolated from *R. pushiana* and *R. frangula* by high pressure liquid chromatography.[7] Hydrophilic anthraquinone glycosides have been separated from lesser hydrophilic anthraquinone aglycones by XAD-2 column chromatography. [8] The quantitative analysis of anthraquinones and anthranol in 16 species of *Rhamnus* from South and East Anatolia have been examined.[9] Likewise, a new naphthalene compound, nakahalene and known anthraquinones, including physcion and frangulin B, have been isolated from *Rhamnus* species.[10]

PHARMACOLOGY: As in other laxatives (aloe, senna, etc), the anthraglycosides are responsible for the cathartic properties in cascara. Cascarosides A and B are the major active principles which act on the large intestine to induce peristalsis and evacuation. [2] More specifically, the anthraglycosides produce an active secretion of water and electrolytes within the lumen of the small intestine and inhibit the absorption of these from the large intestine. This causes an increase in the volume of the bowel contents and strengthens the dilatation pressure in the intestine to stimulate peristalsis. They exert this action with a minimum of side effects. [5] In general, the cascarosides are more active than their hydrolyzed by-products. [2] Furthermore, these cascarosides possess a sweet and more pleasant taste than the aloins and hence should be extracted separately, if possible. [3] Cascara is largely used in the form of a liquid extract or elixir or as tablets made from a standardized dry extract. [2]

The daily dose ranges from 20 to 160 mg of the cascara derivatives for the treatment of constipation. [5] The average dose range of total hydroxyanthracene derivatives is 20 to 70 mg daily.[11] The laxative action is seen within 6 to 8 hours after administration. Basically, cascara can be used in most conditions where easy defecation with a soft stool is desired (eg, constipation, hemorrhoids, anal fissures and post rectal-anal surgery). It is contraindicated in ileus of any origin and during pregnancy and lactation.[5]

No major side effects are known; however, chronic use or abuse (eg, for weight loss) can result in electrolyte loss, especially potassium. Chronic use can also lead to pigmentation of the intestinal mucosa (melanosis coli). No direct interactions are known with cascara except where chronic use leads to a potassium deficiency which can potentiate the effects of cardiotonic glycosides (eg, digitalis). The anthraquinone glycosides should not be used for long periods of time because they can cause the above problems or lead to laxative dependence.[5]

Because the freshly prepared cascara products contain anthrones, it can lead to severe vomiting and intestinal cramping. Therefore, the bark should be stored for at least a year before use or artificially changed by heating (in air) to preclude the presence of anthrones.

Recent studies have shown that aloe-emodin has antileukemic activity against the P-388 lymphocytic leukemia in mice, [2] that *Rhamnus* anthraquinones can act as sunscreens in cosmetics,[12] that cascarosides are not readily metabolized in animal model gut microflora,[13] that a Formosan *Rhamnus* species contains physcion and frangulin B which exhibited a high activity against human hepatoma PLC/PRF/5 and KB cell lines, [10] that *R. purshiana* extracts are capable of inactivating herpes simplex virus,[14] that anthranoids are transformed to their corresponding glucuronide and sulfate derivatives and appear in the urine and bile, [15] and that a mixture of *Curcuma amara* and *R. purshiana* roots have choleretic and serum cholesterol lowering effects in rats. [16]

TOXICOLOGY: Extended or habitual use of cascara is to be avoided because it can cause chronic diarrhea and weakness, due to excessive potassium loss. Chronic use can cause melanin pigmentation of the mucous membranes of the colon.[4,5] Emodin can produce dermatitis.[4]

SUMMARY: Cascara bark is an anthraquinone-containing stimulant laxative commonly used for managing simple constipation in doses ranging from about 20 to 70 mg daily of total hydroxyanthracene derivatives. A laxative effect occurs 6 to 8 hours after administration.

Some commercial products containing cascara are Concentrated Milk of Magnesia-Cascara, Herbal Laxative and *Kondremul* with Cascara or Veracolate.

PATIENT INFORMATION— Cascara

Uses: Cascara extracts are used in laxatives. BR>
Side Effects: Cascara should not be used during pregnancy and lactation, or in ileus of any origin. Extended use may cause chronic diarrhea and attendant ills.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CASCARA

CASTOR

DATE OF ISSUE: NOV 1992

REPLACES MONOGRAPH DATED: OCT 1986

SCIENTIFIC NAME(S): *Ricinus communis* L. and *R. sanguines* L. Family: Euphorbiaceae

COMMON NAME(S): Castor, Palma Christi, Tangantangan oil plant, African coffee tree, Mexico weed, wonder tree, Bofareira. [16]

BOTANY: A common annual ornamental whose native habitat is in the West Indies, the castor grows to heights of 40 feet, bearing broad, deeply lobed leaves on broad stalks. The flowers develop into spiny capsules each containing three seeds. As the capsules dry, they explode, scattering the beans. [1] The castor has been naturalized to temperate regions of the contiguous United States and Hawaii.

HISTORY: The name "ricinus" is derived from the Latin word meaning insect, because the seeds resemble some beetles in shape and markings. The plant has been used as an ornamental since antiquity. Castor beans are used as art objects and ornaments. [2] The Egyptians used castor oil as a lamp oil and unguent [1] and ingested the oil with beer as a purgative. The fast-drying, non-yellowing oil is used in industry to coat fabrics, in the manufacture of high-grade lubricants and in dyes and inks. The plant and oil have been used medicinally for an innumerable variety of diseases, rarely with any true clinical benefit. [3]

CHEMISTRY: Castor oil is obtained by cold expression of the kernels, which contain 45% to 50% oil. [17] The oil is a mixture of triglycerides, of which 75% to 90% is ricinoleic acid. [4] This mixture is hydrolyzed by duodenal lipases to release ricinoleic acid, which exerts a cathartic effect. [5] The cake left after the expression of the oil is the castor pomace. [17]

The phytotoxins ricin and ricinine are present in the seed cake and oil. Ricin is a glycoprotein of approximate molecular weight 65,000, consisting of a neutral A chain and an acidic B chain connected by S-S bonds. The A chain inhibits protein synthesis, which causes cell death, and the B chain serves as a carrier that binds the protein to the cell surface. [6] Other designations indicate that ricin can be separated into the highly toxic ricin D, acidic ricin and basic ricin. [7] The alkaloid ricinine is found in the seeds and leaves. Commercially, the oils and cakes are obtained by cold expression or are steam treated to denature the toxins.

In addition the seeds contain a lipase and an allergen designated CBA. [7]

PHARMACOLOGY: Ricin is a protoplasmic poison. It binds with normal cells and disrupts DNA synthesis and protein metabolism resulting in cell death. [8] In vitro studies have shown that 10 molecules of ricin bound to HeLa cells in culture are sufficient to cause cell death. Ricin is engulfed within 30 seconds, rapidly inhibiting peptide elongation. [8]

Ingestion, inhalation or intravenous (IV) administration of ricin results in rapid organismal death, and the toxin has been explored as a chemical warfare agent.

Ricin has been evaluated in the treatment of cancers [10] and was found to be active in mice inoculated with L1210 leukemia cells. When given intraperitoneally (IP), its effect was superior to that of 5-fluorouracil, but less than that of adriamycin. It was ineffective when given IV. [11] Ricin has been used with some clinical success as an analgesic. [12]

TOXICOLOGY: The castor is a commonly cultivated plant. Ornamental use of the seeds increases the likelihood of toxicities since the beans usually have been drilled, rupturing the seed coat and exposing the contents. If the seeds are swallowed without chewing, poisoning is unlikely because the impermeable seed coat remains intact.

The minimal lethal dose (given IP) in mice is 0.028 mcg crude ricin/g of body weight. As few as one or two chewed beans are lethal to humans. Although the seeds are most toxic, the leaves also may induce poisoning. Toxicity is characterized by burning of the mouth and throat, severe stomach pains, dull vision, renal failure, uremia and death. [13] Treatment is similar to that of other phytotoxin poisonings and generally consists of supportive therapy. Ricinine causes nausea, vomiting, hemorrhagic gastroenteritis, hepatic and renal damage, convulsions and death.

It should be noted that more recent analyses of clinical data from confirmed castor poisonings suggest that ingestion of castor seeds may not always result in severe toxicity. In one event, more than nine school children ingested the seeds without any signs of toxicity. In another more dramatic case, a 38-year-old woman ingested not less than 24 beans that had been cut and chopped to insure absorption. She was treated with induced emesis and remained completely asymptomatic. [14] Regardless of these more recent successful experiences, castor poisoning always should be treated as a serious medical emergency.

The castor has been implicated as an inhalant allergen. Burlap sacks used in the shipment of coffee beans may be contaminated with castor beans or residual castor pomace; this often occurs in the holds of ships or freight cars that have held castor beans. [15] Repeated exposure to castor dust is an occupational hazard to coffee industry workers who handle these sacks.

SUMMARY: Ricin is one of the most potent plant toxins. The widespread cultivation of castor plants represents a potential hazard to small children who ingest and chew the seeds. More recent clinical data suggest, however, that the ingestion of castor seeds by man may not always result in severe toxicity.

PATIENT INFORMATION — Castor

Uses: The oil has long been used for laxative effect.

Side Effects: Ingestion of leaves or seeds is often fatal. Inhalation of residual dust is a hazard to those who handle sacks of castor beans or who work in enclosures where these have been stored.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
      CASTOR

CATNIP

DATE OF ISSUE: APR 2000

REPLACES MONOGRAPH DATED: JAN 1991

SCIENTIFIC NAME(S): *Nepeta cataria* L. Family: Labiatae (Lamiaceae)

COMMON NAME(S): Catnip, catnep, catmint, catswort, field balm

BOTANY: Catnip is a native of Eurasia, now established throughout the northeastern US and Canada. It is an aromatic perennial with dark green, oval-toothed leaves growing as a branched bush to about 1 meter. The plant's dried leaves, along with its white flowering tops gathered in summer and autumn, are used medicinally.[1,2,3,4]

HISTORY: Catnip was documented in K'eogh's *Irish Herbal* in 1735. Historically, it had been promoted to induce urination, open lung and womb obstruction, and expel worms from the body.[2] However, catnip is widely recognized for its ability to elicit "euphoria" in some cats. In Appalachia, catnip tea is used by humans to treat colds, nervous conditions, stomach ailments, and hives. The dried leaves have been smoked to relieve respiratory ailments, and a poultice has been used externally to reduce swelling. In the early 1900s, the flowering tops and leaves were used to bring on delayed menses, a practice that continues today in Appalachia. During the 1960s, catnip was used by humans as an hallucinogen. A tea can be brewed from the leaves.[5]

CHEMISTRY: Catnip contains between 0.2% and 1% volatile oil, of which the major component is nepetalactone (alpha and betaforms) ranging from 80% to 95%.[2,3,6] Congeners of nepetalactone are also present and include epinepetalactone, dihydronepetalactone, neonepetalactone, and isodihydronepetalactone.[6] The minor isomer trans-cis-nepetalactone possesses the cat-attractant activity of the isomeric mixture.[7] Also contained in the volatile oil are citronellol and geraniol.[2,6] Beta-caryophyllene (14%), camphor, thymol, carvacrol, and nerol are also in the plant,[3] as are nepetalic acid,[8] nepetaside,[9] tannins,[2,6] and numerous other components.[10] Iridoids[2,11] in catnip include epideoxyloganic and 7-deoxyloganic acid.[6] One report discusses (1R,5R,8S,9S)-deoxyloganic acid from catnip.[12]

PHARMACOLOGY: Catnip is available in the wild or commercially in pet stores as the leaf or liquid extract. Best known for its appeal to felines, catnip transforms some cats into a "euphoric" state. Domestic cats and large cats, such as tigers and jaguars, respond to catnip by sniffing, licking, head shaking, rolling, and body rubbing.[6] This "catnip response" has been described in detail, consisting of 6 distinct phases, each lasting ~ 10 minutes and ranging from stretching and animation to euphoria and sexual stimulation.[13] The response is observed in essentially all species of cats, but not all individuals respond to the plant. Furthermore, the response does not appear to develop until 3 months of age. In Siamese cats, the response is inherited as an autosomal dominant gene. In a random sampling of 84 cats from the Boston area, one-third of the animals did not respond to catnip.[14]

Similar reactions to catnip in other animals have been reported. Amphetamine-like effects and other behavioral changes in mice due to catnip have been discussed.[15] Catnip oil and nepetalic acid increased (induced) sleeping time in mice. Other studies showed decreased performance in rats using the Sidman avoidance schedule, following intraperitoneal injections of both constituents.[16] In another report, high levels of catnip alcohol extract caused fewer chicks to sleep, while low-to-moderate dosing caused more chicks to sleep.[17]

Catnip also contains iridoids and has been used as an herbicide and insecticide.[6,11] Iridoids, which are named after a certain ant species, *Iridomirmex*, are involved in the insect's defense mechanisms.

In humans, catnip tea has been used as a calmative and sleep aid. The essential oil component, nepetalactone, is similar to the sedative compounds in valerian, another calming herb.[4] This calming effect makes catnip useful for migraine headaches, nervous disorders, and digestive complaints. It purportedly helps indigestion, colic, cramping, and flatulence.[2,3,4] Catnip has also increased gallbladder activity and been used for its diuretic effects.[3] Because catnip exhibits antipyretic and diaphoretic actions, it has been promoted for the treatment of flu, colds, and fever.[2,3]

Topically, catnip has been applied for arthritis treatment as a tincture and for hemorrhoids as an ointment.[2]

INTERACTIONS: Catnip may interact with other sedatives. Use with caution in patients taking standard sedative medications or alcohol.

TOXICOLOGY: Reports by human users describe a happy intoxication similar to the experience one might subjectively observe in an intoxicated cat. Four cases of catnip abuse have been reported,[18] with 2 modes of use being described. The first is similar to marijuana smoking in that the dried leaves are smoked as a "joint" or in a pipe, with catnip burning more rapidly than marijuana. An alternate method involves spraying or soaking tobacco in the volatile oil or extract and then smoking it. The latter method is purported to yield a stronger "high." These users consistently reported mood elevation and euphoria. Effects were of variable intensity ranging from "giddy" to a "feeling of unreality." The experiences were generally short-lived, lasting only a few hours, and could be reactivated for up to 3 days after smoking by some subjects. However, the validity of these case reports has been subjected to skepticism.[19,20]

The intraperitoneal LD_{50} for catnip oil is 1300 mg/kg.[10] Severe physical effects after catnip abuse are usually absent; however, users report some symptoms, generally consisting of headache and malaise. Large amounts of tea induce emesis. The ingestion of cupful quantities of catnip tea has not been associated with any important toxicity.[4] No health hazards or side effects have been associated with proper administration of catnip in designated dosages.[3] Catnip was once listed in the FDA's "Herbs of Undefined Safety" listing in the mid 1970s.[21]

Catnip is contraindicated during pregnancy because of its uterine stimulant activities. Because catnip may lead to excessive menstrual bleeding, it may be contraindicated in certain gynecological conditions.

SUMMARY: Catnip is mostly recognized for its euphoric effect in cats but may be useful in humans for certain minor ailments. It has been used as a sedative, and its calming effects are also useful for migraine, nervous disorders, or digestive problems. Catnip also reduces fever and may be beneficial for colds and flu. No major side effects have been associated with catnip ingestion when administered properly in the correct dosages.

PATIENT INFORMATION — Catnip

Uses: Catnip has been used as a sleep aid and calmative, in migraines, GI problems, colds, flu, fevers, and topically for arthritis and hemorrhoids.

Interactions: Catnip may interact with other sedatives. Use with caution in patients taking standard sedative medications or alcohol.

Side Effects: Excessive ingestion may result in headache and malaise. Catnip is contraindicated in pregnancy because of its uterine stimulant activities and may be contraindicated in certain other gynecological conditions because it could lead to excessive menstrual bleeding.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CATNIP

CAT'S CLAW (UNA DE GATO)

DATE OF ISSUE: APR 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Uncaria tomentosa* (Willd.) DC and *Uncaria guianensis* (Aubl.) (Gmel.) Family: Rubiaceae

COMMON NAME(S): Cat's claw, life-giving vine of Peru, samento, una de gato

BOTANY: Cat's claw, or una de gato (Spanish), is a tropical vine of the madder family (Rubiaceae). The name describes the small curved-back spines on the stem at the leaf juncture. The genus *Uncaria* is found throughout the tropics, mainly in Southeast Asia, the Asian continent and South America. The two species of current interest, *Uncaria tomentosa* (Willd.) DC and *Uncaria guianensis* (Aubl.) (Gmel.), are found in South America. These species are lianas or high climbing, twining woody vines.[1,2] Both species are known in Peru as una de gato.

There are 34 reported species of *Uncaria*. One Asian species, known as gambir or pole catechu (*Uncaria gambir*) (Hunter) Roxb., is a widely used tanning agent which also has long medicinal use as an astringent and anti-diarrheal. [3]

HISTORY: *U. guianensis* has long folkloric use in South America as a wound healer and for treating intestinal ailments. [2] Large amounts of *U. guianensis* are collected in South America for the European market, while American sources prefer *U. tomentosa*.[1]

The bark decoction of *U. guianensis*is used in Peru as an anti-inflammatory, antirheumatic and contraceptive, as well as in treating gastric ulcers and tumors, gonorrhea (by the Bora tribe), dysentery (by the Indian groups of Columbia and Guiana) and cancers of the urinary tract in women. [2]

The center of the *U. tomentosa* range is in Peru and its uses are similar to those of *U. guianensis*: Treatment of arthritis, gastric ulcers, intestinal disorders, and some skin problems and tumors.[2]

The Ashanica Indians believe that samento (also *U. tomentosa*) has "life-giving" properties and use a cup of the decoction each week or two to ward off disease, treat bone pains and cleanse the kidneys.[4] Recent interest in una de gato stems from a reference to the plant in a popular book: *Witch Doctor's Apprentice, Hunting for Medicinal Plants in the Amazonian* (3rd ed., New York: Citadel Press, 1990) by Nicole Maxwell.

Reviews and scientific studies by the National Cancer Institute in the last decade have led to verification of some of the anticancer and immunostimulant properties. [2] Some of the demand for the bark has been attributed to European reports on its clinical use with AZT in AIDS treatment. The demand for the bark in the US is based on the purported usefulness of its tea in treating diverticulitis, hemorrhoids, peptic ulcers, colitis, gastritis, parasites and leaky bowel syndrome. [4]

CHEMISTRY: Several studies on the chemistry of the genus *Uncaria* have been undertaken during the last 20 years. Research on Asian (Thai) species includes the isolation and identification of four pentacyclic oxindole alkaloids, isopteropodine, pteropodine, speciophylline and uncarine F from the leaves of *U. homomalla*,[5] as well as the alkaloids 3-isoajmalicine, 19-epi-3-isoajmalicine, mitraphylline and uncarine B from the leaves of *U. attenuata*.[6]

Of recent interest are the studies on Cat's claw (*U. guianensis*) oxindole alkaloids;[7] three indole alkaloidal glucosides (cadambine, 3-a-dihydrocadambine and 3-ß-isodihydrocadambine) from the Oriental crude drug chotoko (*Uncaria*hooks);[8] alkaloids of *U. ferrea*;[9] three new quinovic acid glycosides from *U. tomentosa*; [10] the isolation and structure of six quinovic acid glycosides from the bark of *U. tomentosa*;[11] alkaloids of *U. rhynchophylla*;[12] three new polyhydroxylated triterpenes from *U. tomentosa*;[13] and the alkaloid gambirine from *U. callphylla*.[14] The major alkaloids (rhynchophylline and isorhynchophyllin) occur in the roots, stem bark and leaves of una de gato, but show great seasonal variation in concentration. [4] Several of these constituents have verified some of the pharmacological activities reported for the crude extract of the bark used in folkloric preparations.

PHARMACOLOGY: Both species, *U. tomentosa* and *U. guianensis*, have been used folklorically in the form of a bark decoction for a wide range of disorders, including gastric ulcers, inflammation, rheumatism, tumors and as a contraceptive. Specifically, *U. guianensis* has been employed to treat dysentery, gonorrhea and cancer of the urinary tract in women.[1]

Recent reports have demonstrated *Uncaria's* role in improving immunity in cancer patients,[4] as well as its anti-mutagenic properties.[15] All the individual alkaloids of *U. tomentosa*, with the exception of hynchophylline and mitraphyllin, have immunostimulant properties [16] and the ability to enhance phagocytosis in vitro. Other researchers have shown pteropodine and isopteropodine to have immune-stimulating effects. [4]

The major alkaloid rhynchophylline has been shown to be anti-hypertensive, to relax the blood vessels of endothelial cells, dilate peripheral blood vessels, inhibit sympathetic nervous system activities, lower the heart rate and lower blood cholesterol.[4,17] The alkaloid mytraphylline has diuretic properties, [4] while the alkaloid hirsutine inhibits urinary bladder contractions and possesses local anesthetic properties. [4,18] At higher dosages, hirsutine showed a "curare-like" ability on neuromuscular transmission.[4,19] The Oriental crude drug "chotoko" (the dried climbing hooks of *Uncaria* species) has hypotensive properties.[8] Six quinovic acid glycosides in *U. tomentosa* have antiviral activity in vitro,[11,13] as well as anti-inflammatory activity in rats. The alkaloid gambirine isolated from *U. callophylla* has cardiovascular properties.[14] An intravenous injection of this alkaloid (dose range: 0.2 to 10.0 mg/kg) in normotensive rats produced a dose-related fall in both systolic and diastolic blood pressure. Plant extracts and fractions of *U. tomentosa* exhibit no mutagenic effects, but show a protective antimutagenic property in vitro and decreased the mutagenicity in a smoker who had ingested a decoction of the plant for 15 days. [15]

TOXICOLOGY: While there is little published data on the toxicology of una de gato, there is an international patent (1982) and a German dissertation (1984) which indicate low toxicity for this material.[4] The scattered pharmacological studies also seem to indicate little hazard in ingesting the plant decoction.

SUMMARY: Cat's claw, or una de gato, has folkloric use in Peru and elsewhere in South America for a variety of conditions, mostly gastrointestinal problems, tumors, cancers and as a contraceptive. No major toxicity problems appear in the world literature. Several chemical and pharmacological investigations have verified that the alkaloids have immune-stimulating effects (pteropodine and isopteropodine), anti-hypertensive properties (rhynchophylline), diuretic effects (mytraphylline) and smooth muscle relaxant and local anesthetic properties (hirsutine). Early reports indicate the clinical usefulness of una de gato and AZT in AIDS treatment. This, and other uses, have prompted sporadic demand for the crude botanical in the United States. At least one company advertises its availability through the Worldwide Web under the title, "Peruvian Cat's Claw: A Gift from Nature." [20] More research is needed to determine the true efficacy of the crude material and its numerous constituents.

PATIENT INFORMATION — Cat's Claw (Una De Gato)

Uses: Various species have been used as astringent, anti-inflammatory, GI and cancer treatment, contraceptive, general tonic, etc. Studies have verified some anticancer and immunostimulant properties. The major alkaloid is hypotensive.

Side Effects: Little known hazard ingesting the decoction.

Dosing: One gram of root bark given 2 to 3 times is a typical dose, while 20 to 30 mg of a root bark extract has been recommended. A standardized extract based on a particular chemotype of this species (C-Med-100, *Krallendorn*, Immodal Pharmaka GmbH) containing 8% to 10% carboxy alkyl esters, and < 0.5% oxindole alkaloids

has been used for clinical trials as an immunostimulant at doses from 250 to 300 mg. [21,22]

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "C" MONOGRAPHS
  CAT'S CLAW (UNA DE GATO)

CELERY

DATE OF ISSUE: JAN 1996

REPLACES MONOGRAPH DATED: MAY 1987

SCIENTIFIC NAME(S): *Apium graveolens* L. var *dulce* (Mill.) Pers. Family: Umbelliferae

COMMON NAME(S): Celery, celery seed, celery seed oil

BOTANY: This biennial plant is native to Europe,[1] yet grown and consumed worldwide. A number of varieties of celery exist, many developed to meet commercial demands for particular colors, tastes and stalk sizes. Celery generally grows between 1 to 2 feet tall. They have tough ribbed green stems and segmented dark green leaves containing toothed leaflets. During June and July, small white flowers bloom which later bear the smooth gray fruits of seeds. Wet and salty soils, swamps and marshes are the preferred environment for celery.[1] Celery is blanced to generate the edible white stem during cultivation. [1] Celery seeds have a spicy odor and a spicy, yet slightly bitter taste.[2]

The generic name pascal applies to any green celery. In Europe, the term celery is frequently used to refer to a related root vegetable, *Apium graveolens* L. var *rapaceum, DC.*Wild celery can refer to *Vallisneria spiralis*L., an aquatic perennial.

Celery seed oil is obtained by the steam distillation of the seed. According to the US Department of Agriculture, US growers in 1983 produced 914 tons of celery on 35,000 acres of farmland. The crop was valued at $235 million.

HISTORY: Celery originated as a wild plant growing in salt marshes around the Mediterranean Sea. About 450 B.C., the Greeks used it to make a type of wine called selinites. It served as an award at early athletic games, much as laurel leaves or olive branches. By the Middle Ages, Europeans were cultivating celery. Since that time, the plant has been used widely both as a food and as a medicine.

Late in the 19th century, various celery tonics and elixirs appeared commercially. These generally contained the juice of crushed celery seeds, often with a significant amount of alcohol. Celery seed is mainly used as a diuretic for bladder and kidney complaints and for arthritis and rheumatism. Sedative effects have been produced from the essential oil.[2]

Celery continues to be used as a food flavor, in soaps and in gum. One product that is still available is a celery-flavored soda, Dr. Brown's Cel-Ray. Celery has become increasingly popular with dieters. This particular attraction stems from celery's high fiber content and the (mistaken) belief that chewing and digesting the stalks uses more calories than celery contains.[3]

CHEMISTRY: Celery is high in minerals (including sodium and chlorine) and is a poor source of vitamins. [4] The major constituents of celery seed oil are d-limonene (60%), selinene (10%) and a number of related phthalides (3%) which include 3-n-butylphthalide, sedanenolide and sedanonic anhydride. Celery contains a pheromone steroid previously identified in boars and parsnips. [5]

The furocoumarin, bergapten, has been found in celery. [6] UV spectographic studies have indicated the presence of a compound similar or identical to 8-methoxypsoralen. Infrared spectography has confirmed yet another compound with a furocoumarin glucoside, isoquercitrin, and the coumarin glucoside apiumoside also have been identified.[8]

Other organic components include isovalerianic aldehyde, propionic aldehyde and acetaldehyde. [9] Oil of celery seed is sometimes adulterated with celery chaff oil or d-limonene from less expensive sources.

PHARMACOLOGY: Herbalists recommend celery for treatment of arthritis, nervousness and hysteria. Oriental medicine uses the seeds to treat headaches and as a diuretic, digestive aid and emmenagogue. Celery has also been prescribed as an antiflatulent, antilactogen and aphrodisiac.

The phthalides have been reported to have sedative[10] and anticonvulsive[2] activity in mice. An extract of celery (var dulce) has been reported to have hypotensive properties in rabbits and dogs when administered intravenously. In man, the juice has been shown to have effectively lowered blood pressure in 14 of 16 hypertensive patients.[11]

The essential oil has in vitro fungicidal effects. [12] The oil has hypoglycemic activity.[13] Essential oils from celery may also possess potential anticarcinogenic properties.[14] Two component of celery, 3-n-butylphthalide and sedanolide were experimentally found to reduce tumors in mice. [15]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Celery allergies in patients have led to urticaria and angioedema, respiratory complaints and anaphylaxis. [16] IgE antibodies have been experimentally associated with mediating celery allergies.[17] Since 1926, a number of sources have reported the occurrence of dermatitis in workers who cultivate or process celery. The dermatitis had been attributed to an allergic reaction to the volatile oil. [18]

Some celery workers, primarily Caucasian, develop phototoxic bullous lesions. Workers in greenhouses are less susceptible to lesions than those who work outside. Once healed, the lesions often leave areas of depigmentation or hyperpigmentation. Significantly, the bullae develop only after contact with celery affected by "pink-rot" a condition caused by the fungus *Sclerotinia sclerotiorum*. Skin reactions probably result from exposure to a furocoumarin followed by exposure to sunlight (UVA light). The pink-rot apparently increases the availability of the furocoumarin. Use of a sunscreen can prevent this reaction. [7] Furocoumarins may be carcinogenic, and their concentration increases 100-fold in celery that is injured or diseased. [19] Large doses of the oil may induce CNS depression, although the specific toxic syndrome has not been well characterized.

SUMMARY: Celery is a widely cultivated plant that remains popular, especially among dieters. It is a relatively poor source of vitamins and is relatively high in sodium. Contact with the plants by farmworkers or food processors may cause a phytophototoxic reaction that may be incapacitating. Ingestion of large amounts of celery oil may cause toxicity; however, the toxicity has not been well characterized in man. The medicinal uses for celery are beginning to be more thoroughly explored, particularly for potential anticancer properties.

PATIENT INFORMATION— Celery

Uses: The seed is used as a diuretic and as a treatment for arthritis and rheumatism. The seed oil has produced sedative effects. Celery has been used in herbal medicine to treat arthritis, nervousness, hysteria and various other conditions. The juice lowered blood pressure in several tested patients. Two components reduced tumors in mice.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Some patients have experienced allergic responses, including anaphylaxis. There are many reports of dermatitis among those cultivating and processing celery. Some develop phototoxic lesions, often followed by disturbed pigmentation in the same areas. Certain compounds in diseased or damaged plants may be carcinogenic. Large doses of the oil may produce CNS depression.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CELERY

CENTAURY

DATE OF ISSUE: OCT 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Centaurium erythraea* [(L.), Persoon, Rafin], *Erythraea centaurium*, *C. umbellatum* Gilbert, *C. minus*Moench. Family: Gentianaceae

COMMON NAME(S): Centaury, minor centaury, lesser centaury, centaury herb, centaurri herba, common centaury, feverwort, filwort, bitter herb, red centaury, Christ's ladder, centaury gentian

BOTANY: Centaurium consists of approximately 40 species (annuals or biennials) that can vary according to area, size, and other situations. Examples include C. spicatum (Australian species), E. latifolia (broad-leaved centaury), and the German species of C. pulchellum (dwarf centaury) and C. vulgare. The last 2 have similar effects to C. erythraea but are more scarce and, therefore, not used for medicinal purposes.

Centaury is a small, annual herb, native to Europe and naturalized in the US. It thrives in boggy meadows as well as in dry dunes. Its stiff, square stem is quite distinctive and ranges from approximately 7 to 30 cm in height. The root is fibrous and woody. The plant has pale green, oval leaves, a capsule fruit, and light pink to red flowers. The whole herb (Centaurii herba) is used in medicine. The dried preparation is easily identified by red particles (dried flower), among the pale green leaf matter.[1,2,3,4,5,6]

HISTORY: Genus Erythraea is derived from the Greek erythros, relating to the red color of the flowers. The genus was formerly called Chironia, from Centaur, Chiron. Hippocrates describes centaurium, under the Greek Kentareion and according to legend, Chiron (founder of medicine) used centaury to heal a wound inflicted by a poisoned arrow.[4,6]

Macer mentions centaury in the 10th century. Culpepper describes how the plant is safe but bitter. He mentions the plant's ability to kill worms and treat dropsy, snakebite, and other wounds. It was used by Saxon herbalists in a similar manner, along with treating fever, hence the name "feverwort." [4] Traditionally, centaury has been used for anorexia and dyspepsia.[7]

CHEMISTRY: C. erythraea contains several iridoid constituents, responsible for the bitter characteristics of the plant. The bitter taste can be detected in dilutions of 1 part centaury:3500 parts water.[3] Gentiopicroside, one of the major iridoids, is present in approximately 2% concentration. [7] Gentiopicroside has been determined by high-pressure liquid chromatography in plants in the Czech and Slovak Republics. [8] This constituent also has been studied by other methods. [9] Centapicrin[10] and centauroside[11] are other bitter secoiridoid glucosides present. Another bitter principle, erythrocentaurin, is found in the plant and reddens with sunlight. [4] Other bitter components include erytaurin,[3] swertiamarin, dihydrocornin,[12,13] amarogentin, amarogentrin, gentiopicrin, and gentioflavoside. [4,14,15,16] Centaury constituents are very similar to gentian, also containing gentiopicroside, amarogentin, swertiamarin, and others. [17]

Alkaloids present in centaury include gentianine, [18] gentioflavin,[19] gentianin,[16] and gentianidine.[7] Alkaloids from the family Gentianaceae have been reported. [20]

Xanthones also have been found in centaury, including tetraoxygenated xanthones, [21] eustomin, and demethyleustomin.[22,23] Other xanthones present include 1,6,8-trihydroxy-3,5,7-trimethoxyxanthone,[24] methylbellidifolin, methylswertianin,[25] and several others.[26,27,28,29,30] Xanthone biosynthesis studies report enzyme substances benzophenone synthase,[31] xanthone 6-hydroxylase,[32] and 3-hydroxybenzoate: coenzyme A ligase.[33,34]

Phenolic acids present in centaury include protocatechuic, hydroxybenzoic, vanillic, syringic, beta-coumaric, ferulic, sinapic, caffeic, and palmantinic acids. [7,16] Monohydroxy- and 2,5-dihydroxy terephthalic acids also have been identified in C. erythraea. [35]

Triterpenoids found in centaury are alpha- and beta-amyrin, crataegolic and oleanic acids, erythrodiol, and sitosterol. [7] Other sterols present include beta-sitosterol, stigmasterol, campesterol, and brassicasterol.[6]

Other components found in the plant include flavonoids, fatty acids, alkenes, waxes, resins, and essential oil. [7,16]

PHARMACOLOGY: Traditionally, centaury has been used as a remedy for snakebite, anorexia, and GI complaints such as bloating, dyspepsia, and flatulence.[2,3,4,7,17,36] It is reputed to be an aromatic bitter and tonic, and acts on the liver and kidneys to "purify the blood." [4] One report confirms diuretic activity in rats.[37] This bitter herb enhances production of gastric secretions, which stimulates appetite and improves digestion. [16] Long-term use of the herb is required for the tonic effects on the stomach to fully develop. [3]

Centaury is known to have anti-inflammatory effects in rats.[7] Anti-inflammatory and antipyretic, but not analgesic actions, of aqueous extracts of the plant have been shown in several animal models.[38]

Centaury has been used to treat fever.[3,7] This property was found to be due to phenolic acids present. [7,39]

Constituent gentiopicrin possesses antimalarial properties. [7] Certain xanthones demonstrated strong antimutagenic actions against several strains of Salmonella typhimurium.[22] Use of centaury as an anthelminthic and febrifuge has been reported.

Centaury also is used for the treatment of jaundice,[40] as a sedative,[7] and as a topical application for freckles and spots on the skin. [16]

TOXICOLOGY: The German Commission E lists contraindications or side effects of centaury as "none known." [36] Newall confirms "no reported side effects or toxicity data" relating to the plant as well. Because safety of centaury taken during pregnancy has not been established, its use during this time is best avoided. [7]

SUMMARY: Centaury is a small, annual herb, known best for its use as a bitter tonic. It plays a role in helping to treat GI complaints, such as bloating, dyspepsia, and flatulence. It helps to improve appetite and stimulate digestion. Other effects include anti-inflammatory and antipyretic actions, as well as antimutagenic effects. There are no reported side effects or toxicity data.

PATIENT INFORMATION — Centaury

Uses: Centaury has been used to treat snakebite, fever, anorexia, jaundice, and GI complaints such as bloating, dyspepsia, and flatulence. It also has been used as a sedative and topically for freckles and spots. It is reputed as an aromatic bitter and tonic and acts on the liver and kidneys to "purify the blood."

Side Effects: There are no known side effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CENTAURY

CHAMOMILE

DATE OF ISSUE: MAY 2000

REPLACES MONOGRAPH DATED: MAR 1991

SCIENTIFIC NAME(S): *Matricaria chamomilla*L. and *Anthemis nobilis* L. Sometimes referred to as *Chamaemelum nobile* (L.) All. L. Family: Compositae (Asteraceae).

COMMON NAME(S): *M. chamomilla*, is known as German, Hungarian, wild, or genuine chamomile and *A. nobilis* is called English, Roman, Scotch, garden, lawn, sweet, and true chamomile (common chamomile).[1]

BOTANY: *M. chamomilla* grows as an erect annual and *A. nobilis* is a slow-growing perennial. The fragrant flowering heads of both plants are collected and dried for use as teas and extracts.

HISTORY: Known since Roman times for their medicinal properties, the plants have been used as antispasmodics and sedatives in the folk treatment of digestive and rheumatic disorders. Teas have been used to treat parasitic worm infections and as hair tints and conditioners. The volatile oil has been used to flavor cigarette tobacco.

Chamomile has been utilized as a skin wash to cleanse wounds and ulcers, and has been used to increase the sloughing of necrotic tissue and promote granulation and epithelialization. It has also been reported to have anti-inflammatory, antibacterial, astringent, and deodorant properties. Various formulations of chamomile have been used to treat vomiting, colic, fever, flatulence, and cystitis. [1]

CHEMISTRY: Both plants contain related chemical constituents. The anti-inflammatory and antispasmodic effects of *M. chamomilla*are due to compounds contained in the light-blue essential oil, which constitutes about 0.5% of the flower head. [2] Chamazulene, an artifact formed during heating while preparing teas and extracts, comprises about 5% of the essential oil. Up to 50% of the essential oil consists of alpha-bisabolol, an unsaturated monocyclic sesquiterpene alcohol, [3] whose concentration can vary according to geographic origin and chemotype. Other minor components include apigenin and angelic acid. [4]

PHARMACOLOGY: Bisabolol exerts numerous pharmacologic effects, which may account for the many traditional uses of chamomile. The compound effectively reduces inflammation of carageenan-induced rat paw swelling and adjuvant-induced arthritis in rats, as well as inflammation induced by the cotton pellet granuloma test.[5] Bisabolol is antipyretic in yeast-induced fever in rats. It significantly shortens the healing time of cutaneous burns in guinea pigs. [3] In rats, the compound also inhibits the development of gastric ulcers induced by indomethacin, stress, and ethanol, and shortens the healing time of acetic acid-induced ulcers. [6]

Chamomile infusions have been used traditionally as GI antispasmodics. Alcohol extracts of *M. chamomilla* showed significant antispasmodic effects in vitro.[7] Bisabolol and the lipophilic compounds bisabolol oxides A and B, as well as the essential oil, have a papaverine-like antispasmodic effect. Bisabolol is about as potent as papaverine and twice as potent as the oxides.[8] The cis-en-in-ether and the flavones apigenin, luteolin, patuletin, and quercetin also have marked antispasmodic effects as do the coumarins umbelliferone and herniarin.

Chamazulene exerts anti-inflammatory and antiallergic activity in animal models. [9] The hydrophilic components of chamomile, principally the flavonoids, also contribute to the anti-inflammatory process. The most active flavonoids are apigenin and luteolin, with potencies comparable to those of indomethacin. [10] Because of the low water solubility of the essential oil, teas prepared from chamomile flowers contain only about 10% to 15% of the oil present in the plant. Despite the relatively low concentration of lipophilic components in water infusions, chamomile teas are generally used over long periods of time, during which a cumulative therapeutic effect may result.[11]

German chamomile flower is approved by the German Commission E for use as an inhalation in skin and mucous membrane inflammations, bacterial skin diseases (including those of the oral cavity and gums), and respiratory tract inflammations and irritations; for use in baths and irrigation for anogenital inflammation; and internally for GI spasms and inflammatory diseases.

Sedation and mood: A blinded, crossover, placebo-controlled study evaluating the effect of chamomile on both sedation and mood was conducted in 22 patients. Aromatized chamomile oil proved to have a sedative effect, as well as a positive effect on mood. Negative mood rating was also less pronounced when patients were using chamomile oil.[12]

Mucositis: The theory that chamomile could decrease 5-fluorouracil-induced mucositis was evaluated in 164 patients receiving chemotherapy. In this double-blind, placebo-controlled trial, 82 patients were randomized to receive chamomile mouthwash 3 times daily for 14 days starting on the first day of chemotherapy. An equal number of patients were randomized to a matching placebo regimen. At the end of the study, stomatitis scores between the 2 treatment groups did not differ. A limitation of this study may be the short, 2-week study period. [13]

Another study evaluating the efficacy of chamomile for both the prophylaxis and treatment of mucositis was conducted in 98 patients. Twenty patients were scheduled to receive a chamomile-derived oral rinse 3 times daily for the prophylaxis of radiation-induced mucositis. Additionally, 78 patients treated with chemotherapy were enrolled. In the group receiving chemotherapy, 46 patients received the rinse for prophylaxis and 32 patients received the rinse for treatment. Prophylactic use of the rinse prevented the occurrence of mucositis in 78% of the patients receiving chemotherapy, and delayed the onset and reduced the intensity of radiation-induced mucositis.[14]

Wound healing: Chamomile cream was tested against almond ointment to determine if it could decrease adverse skin reactions induced by radiation. Forty-eight women were included in this study for breast cancer surgery. Chamomile cream or almond ointment was randomly assigned to the area above and below the scar; therefore, each patient served as her own control. This study failed to show a difference in adverse skin reactions between the 2 groups. [15]

Diarrhea: A prospective, double-blinded, randomized trial assessed the efficacy of a chamomile preparation (n = 39) to that of placebo (n = 40) in children with acute, noncomplicated diarrhea. The patients ranged in age from 6 months to 5.5 years of age and all 79 subjects received rehydration and a realimentation diet. At the end of 3 days, more patients in the chamomile group had resolution of diarrhea. The treatment group also had a significant reduction in the duration of diarrhea. [16]

INTERACTIONS: Based on the actions of chamomile, potential drug interactions involving increased sedation, delayed gastric absorption, and altered anticoagulant activity have been proposed. Because chamomile is reported to have sedative effects, this action may be additive with other sedatives (eg, benzodiazepines) a patient is taking. Because chamomile has antispasmotic activity in the GI tract, the absorption of concomitantly administered drugs may be delayed. Chamomile contains coumarin derivatives. Thus, if patients take anticoagulants (especially warfarin), it would be prudent to closely monitor anticoagulant parameters. The clinical importance of these parameters has not been established.

TOXICOLOGY: The toxicity of bisabolol is low following oral administration in animals. The acute LD_{50} is ˜ 15 ml/kg in rats and mice. In a 4-week subacute toxicity study, the administration of bisabolol (1 to 2 mI/kg body weight) to rats did not cause significant toxicity. No teratogenic or developmental abnormalities were noted in rats and rabbits after chronic administration of 1 ml/kg bisabolol. [17]

The pollen in the *Matricaria chamomilla* flowers may cause hypersensitivity leading to sneezing, runny nose, anaphylaxis, dermatitis, and GI upset. The dried flowering heads can be emetogenic if ingested in large amounts. English chamomile is reported to be an abortifacient and to affect the menstrual cycle.

The use of chamomile is not without potential adverse effects. The tea prepared from the pollen-laden flower heads has resulted in contact dermatitis, [18] anaphylaxis,[19] and other severe hypersensitivity reactions in people allergic to ragweed, asters, chrysanthemums, and other members of the family Compositae. [20]

People with allergies to ragweed pollens should refrain from ingesting chamomile. A previously healthy female in labor developed an anaphylactic reaction after receiving a chamomile enema. After an emergency cesarean section, the newborn died shortly, thereafter due to inutero asphyxiation. [21] The dried flowering heads are emetic when ingested in large quantities.[22]

SUMMARY: The chamomiles are used widely. They exert significant antispasmodic activity in the GI tract and the potential for delaying concomitant drug absorption from the gut should be considered. Chamomile should not be used by people taking anticoagulants. There is evidence from animal models that some components of chamomile exert anti-inflammatory activity, but the extent to which this is observed in humans has not been established. The toxicity and teratogenicity potential appear to be low, but hypersensitivity has been reported.

PATIENT INFORMATION — Chamomile

Uses: Chamomile has been used as an antispasmodic and sedative. Teas have been used to treat parasitic worm infections and as hair tints and conditioners. It has been used as a skin wash to increase the sloughing of necrotic tissue, promote granulation and epithelialization, as an anti-inflammatory, antibacterial, astringent, and for its deodorant properties. Various formulations have been used to treat vomiting, colic, fever, flatulence, and cystitis.

Interactions: The sedative effects of chamomile may be enhanced with other sedatives (eg, benzodiazepines). Because of the antispasmotic activity in the GI tract, the absorption of coadministered drugs may be delayed. Closely monitor anticoagulant parameters in patients taking anticoagulants (especially warfarin), as chamomile contains coumarin derivatives.

Side Effects: The tea has resulted in contact dermatitis, anaphylaxis, and other severe hypersensitivity reactions in people allergic to ragweed, asters, chrysanthemums, and other members of the family Compositae. Do not use if currently taking anticoagulants or are allergic to ragweed pollens.

Dosing: Chamomile has been used to make a tea for diarrhea and as a sleep aid. Typical doses have been 9 to 15 g/day. An extract of chamomile with apple pectin, *Diarrhoesan* (Dr. Loges) standardized to 3.5 mg chamazulene/100 g extract and 50 mg bisabolol/100 g extract has been studied for treatment for diarrhea.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHAMOMILE

CHAPARRAL

DATE OF ISSUE: AUG 1993

REPLACES MONOGRAPH DATED: JUN 1987

SCIENTIFIC NAME(S): *Larrea divaricata* Cav. [synon. with L. *tridentata* (DC) Coville], also referred to as *L. glutinosa* Engelm. Family: Zygophyllacea.

COMMON NAME(S): Chaparral, creosote bush, greasewood, hediondilla[1]

BOTANY: The chaparrals are a group of closely related wild shrubs found in the arid regions of the Southwestern United States and Mexico. Chaparral found in health food stores usually consists of leaflets and twigs. This branched bush grows to 9 feet. Its leaves are bilobed and have a resinous feel and strong smell.

HISTORY: Chaparral tea was used as a remedy by Native Americans and has been suggested for the treatment of bronchitis and the common cold, to alleviate rheumatic pain, stomach pain, chicken pox and snake bite pain. A strong tea from the leaves has been mixed with oil as a burn salve.[2] It is an ingredient in some over-the-counter weight loss teas.

In 1959, the National Cancer Institute (NCI) was informed through lay correspondence that several cancer patients claimed beneficial effects on their cancers from drinking chaparral tea. Years later, a similar treatment was brought to the attention of physicians at the University of Utah, when an 85-year-old man with a proven malignant melanoma of the right cheek with a large cervical metastasis refused surgery and treated himself with chaparral tea. Eight months later he returned with marked regression of the tumor.[3] Additional cases observed by the physicians at the University of Utah included four patients who responded to some degree to treatment with the tea, including two with melanoma, one with metastatic choriocarcinoma, and one with widespread lymphosarcoma. After two days of treatment, the patient with lymphosarcoma discontinued chaparral treatment, despite the disappearance of 75% of his disease. The choriocarcinoma patient, who had not responded well to other therapies, responded well to chaparral tea for two months after which the disease became progressive. Of the melanoma patients, one experienced a 95% regression and the remaining disease was excised; the other, after remaining in remission for four months, subsequently developed a new lesion.[4]

Reports subsequently appeared in the lay literature describing the virtues of chaparral tea as an antineoplastic treatment.

CHEMISTRY: Phytochemical investigations of *L. divaricata* resulted in the isolation of nor-dihydroguaiaretic acid (NDGA) and the related lignans nor-isoguaiasin, dihydroguaiaretic acid, partially demethylated dihydroguaiartic acid, and 3'-demethoxyisoguaiasin. The total phenolics together with the small amounts of lipids produced by the plant range from 16% in older plants to 21% in younger growing plants.[4]

PHARMACOLOGY: NDGA is believed to be responsible for the biological activity of chaparral. Up until 1967, when more effective antioxidants were introduced, NDGA was used in the food industry as a food additive to prevent fermentation and decomposition. It is theorized that any anticancer effect of chaparral tea is due to the ability of NDGA to block cellular respiration. NDGA and its related compounds inhibit the beef heart mitochondrial NADH oxidase system and succinoxidase system, and therefore, exert some antioxidant activity at the cellular level.[5] NDGA inhibits the induction of the lipogenase inhibitor ornithine decarboxylase in mice.[6,7] DGA also inhibits collagen- and ADP-induced platelet aggregation and platelet adhesiveness in aspirin-treated patients.[8]

Studies conducted by the NCI found that in vitro, NDGA was an effective anticancer agent, being described as "the penicillin of the hydroquinones and the most potent antimetabolite in vitro."[9] This activity, however, is almost completely abolished in vivo. Chaparral failed to show any significant anticancer activity in two separate NCI chemotherapy screening tests in mice.[4] There is some evidence that when combined with ascorbic acid, NDGA shows some inhibitory effect against small Ehrlich ascites tumors in mice.

Other disconcerting data from 34 cancer patients treated for varying periods of time with chaparral suggest that a majority of malignancies are stimulated by NDGA, while some go on to regress.[4]

TOXICOLOGY: The creosote bush can induce contact dermatitis.[10] NDGA has been found to induce mesenteric lymph node and renal lesions in rats;[11] because of these problems, it was removed from the Generally Recognized as Safe (GRAS) list in 1970.[12]

Several recent reports have linked the ingestion of chaparral tea with the development of liver damage.[11,13] In all three cases, the patients took chaparral tablets or capsules for 6 weeks to 3 months. They developed signs of hepatic damage as evidenced by liver enzyme abnormalities; these resolved following discontinuation of the plant material. These reports indicate that chronic ingestion of chaparral may be associated with liver damage.

SUMMARY: Miracle cancer cures have an enormous public appeal. Like laetrile and taheebo, chaparral tea has gained attention as a natural cancer treatment, albeit with only inconclusive evidence to justify its safety or effectiveness. The results of in vivo and in vitro tests indicate that chaparral contains potent antioxidants that exert some biologic activity; however, the antineoplastic activity of chaparral is weak and inconsistent in vivo.

The numerous anecdotal reports of its efficacy suggest that further in vivo testing may be warranted. Because its use may stimulate the growth of certain tumors, however, chaparral cannot be recommended as an antineoplastic agent at this time.

PATIENT INFORMATION — Chaparral

Uses: Chaparral tea has been widely used in folk medicine to treat conditions ranging from the common cold to snake bite pain. A derivative was formerly used as a food preservative. Anecdotal and in vitro evidence suggests antineoplastic effects.

Side Effects: No longer classified safe. Chaparral may cause liver damage, stimulate most malignancies and cause contact dermatitis.

Dosing: Chaparral has been documented to be hepatotoxic at doses of crude herb from 1.5 to 3.5 g/day. Therefore, discourage its use.[11,14,15]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHAPARRAL

CHARCOAL

DATE OF ISSUE: APR 1996

REPLACES MONOGRAPH DATED: AUG 1987

COMMON NAME(S): Activated charcoal, animal charcoal, charcoal, gas black, lamp black

SOURCE: Charcoal is produced by pyrolysis and high temperature oxidation of organic materials. Animal charcoal is obtained from charred bones, meat, blood, etc. "Activated" charcoal is obtained from charred wood or vegetable matter and treated with various substances to increase its adsorptive power. Amorphous carbons (or charcoals) are obtained from the incomplete combustion of natural gas, fats, oils or resins.

CHEMISTRY: The chemistry of charcoals is complex. Although the purest forms of charcoal are essentially all carbon, the small amounts of impurities that remain following combustion of the source material have been difficult to characterize. Medicinal charcoals have been developed with a high surface area-to-weight ratio in order to maximize the adsorption capacity.

The adsorptive properties of charcoal may be significantly increased by treating it with such substance as carbon dioxide, oxygen, air, steam, sulfuric acid, zinc chloride or phosphoric acid (or combinations of these) at high temperatures (500°-900°C). These matreials help remove impurities and reduce the particle size of carbon, allowing charcoal to be more adsorptive due to an increased surface area. One ml of finely subdivided and activated medicinal charcoal has a total surface area of about 1000 m^2 . Medicinal or activated charcoal is a fluffy, fine, black, odorless and tasteless powder without any gritty material. It is insoluble in water or other common solvents, but may be suspended for a short time after vigorous shaking.[1]

PHARMACOLOGY: Activated charcoal has been used in the management of acute toxicity for almost a century. Its large surface area permits the absorption of a variety of complex chemicals, thereby rendering the toxic material unavailable for systemic absorption. In addition, charcoal may interrupt the enterohepatic circulation of compounds that are excreted into the bile. It is usually coadministered with a laxative and the combination may hasten the elimination of toxins from the gastrointestinal tract due to the resultant diarrhea and more rapid gastrointestinal transit time. [2]

Activated charcoal is used for the acute management of a wide variety of poisons, but is particularly used as an emergency antidote. It is commonly accepted by medical personnel as the antidote of choice for almost all drugs and chemicals (except mineral acids, alkalines and substances insoluble in aqueous acid solution, eg, tolbutamide).[1] Capsules of powdered medicinal charcoal are also used to relieve the discomfort of abdominal gas and flatulence. The capsules should be taken 2 hours before or 1 hour after any oral medication.

Charcoal is often underutilized or given in insufficient dosages. On average, it should be administered at least in a 10:1 proportion (charcoal-to-estimated poison dose). Caution should be used with the simultaneous administration of charcoal and the emetic ipecac, since charcoal may adsorb the ipecac and render it ineffective. The dosage range for medicinal charcoal (as an antidote) is 5 - 50 g. The usual adult dose is 50 g; children, 25 g. It is administered as an aqueous slurry and may be flavored, though the flavoring may reduce its effectiveness. As an antiflatulent, the dose range is 520-975 mg, taken after meals or at the first sign of discomfort. This may be repeated as needed, up to 4.16 g daily.[1]

It has long been known that uremic patients treated with charcoal hemoperfusion often have significant reductions in blood lipid levels. Repeated oral doses of activated charcoal have also been found to be effective in reducing blood lipid concentrations in uremic [3] and diabetic patients.[4] In a study of hypercholesterolemic patients given 8 g of activated charcoal three times a day for 4 weeks, the total cholesterol and low density lipoproteincholesterol (LDL) levels decreased by a mean of 25% and 41%, respectively. The high density lipoproteincholesterol (HDL) and the ratio of HDL:LDL increased. [5] Mention of this study in lay literature has resulted in an increased interest in the use of oral charcoal for the reduction of blood lipid levels. At present, however, there is insufficient evidence to confirm the effect of charcoal on lipid parameters or to determine an appropriate dose.

Numerous articles continue to appear in the medical literature on the usefulness of activated charcoal as an antidote in all kinds of poisoning and as a gastrointestinal decontaminant. Researchers discuss the controversy of whether activated charcoal should be used alone or if gastric lavage or ipecac syrup should be given before activated charcoal in treating poisonings. [6] Multiple studies indicate that a relatively small amount of gastric content is removed by ipecac syrup or gastric lavage.They argue that there are still no universal standards for the lavage method, the diameter of the orogastric tube or the size of the aliquot fluid. Furthermore, there is still a need for studies of lavage fluid temperatures, abdominal massage and even the positioning of patients during these procedures. Some studies, however, caution against the use of activated charcoal alone, since it does not adsorb all materials.

A later study comments on the gastric decontamination controversy and focuses on acute poisoning emergencies. [7] The researchers promote good supportive care in acute poisoning: Aggressive support of the cardiovascular, respiratory and central nervous systems and appropriate gastric decontamination. They contend that ipecac should be reserved for home use following ingestion of certain toxins and that activated charcoal should replace ipecac for the treatment of mild to moderate poisonings in the emergency room setting. Both gastric lavage and the proper dosage of activated charcoal (adults, 50-100 g; children, 25-50 g; infants 1 g/kg) should be considered in life-threatening cases. A cathartic should be considered after the administration of activated charcoal.

TOXICOLOGY: Activated charcoal is used in hemoperfusion for the removal of toxins from the blood following acute overdose. In general, there is little toxicity associated with the charcoal component of hemoperfusion.

The oral use of charcoal has been associated with unwanted side effects. Gastrointestinal obstruction, in the form of "briquettes," has been observed in patients who have received repeated doses of charcoal.[2,8,9] Other problems following the ingestion of charcoal preparations (in the form of a charcoal-sorbitol suspension) include hypernatremic dehydration[10] and aspiration pneumonia.[11] One drawback to the emergency use of oral charcoal is that adsorbed toxins may have the opportunity to dissociate from the charcoal and re-enter the systemic circulation before the charcoal is excreted. Although charcoal given alone may slow gastric transit time, it is often coadministered with a laxative to hasten its evacuation. It is not clear what effect the long-term ingestion of charcoal preparations may have on vitamin levels. At least one pediatric report has focused on the pulmonary aspiration of activated charcoal as a complication of its misuse in overdose management. [12]

SUMMARY: Charcoal has been used in the treatment of toxic events for almost 100 years with a remarkable record of safety. It adsorbs a wide variety of toxic compounds and facilitates their gastrointestinal removal. Charcoal is also used in hemoperfusion to remove toxic material from the systemic circulation. Recent reports indicating that blood lipid levels may be beneficially altered following the use of charcoal cannot be extrapolated to clinically useful therapeutic regimens until more is known about these effects.

PATIENT INFORMATION— Charcoal

Uses: Activated charcoal is used as an antidote to poisoning, as an antiflatulent and potentially as a treatment for reducing blood lipid concentrations in uremic and diabetic patients.

Side Effects: GI obstruction can develop in those receiving repeated doses.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHARCOAL

CHASTE TREE

DATE OF ISSUE: MAR 2004

REPLACES MONOGRAPH DATED: FEB 1998

SCIENTIFIC NAME(S): *Vitex agnus-castus* L. Family: Verbenaceae

COMMON NAME(S): Chaste tree, chasteberry, vitex, Monk's pepper, agnus castus, Indian spice, sage tree hemp, and tree wild pepper [1]

BOTANY: The chaste tree is a small tree or shrub that grows in moist river banks in southern Europe and in the Mediterranean region. [2] The plant is cultivated in the Jiangsu Province and Shanghai City of China. [3] It can grow up to 6 to 7 m in height. The plant blooms in summer, developing light purple flowers and palm-shaped leaves. The dark brown to black fruits are the size of a peppercorn; these fruits have a pepperish aroma and flavor and can be collected in autumn. [4,5]

HISTORY: The dried, ripe fruit is used in traditional medicine. The plant has been recognized since antiquity and has been described in works by Hippocrates, Dioscorides, and Theophrastus. [4] In Homer's epic, *The Iliad*, the plant was featured as a "symbol of chastity, capable of warding off evil." [5] Early physicians recognized its effect on the female reproductive system, suggesting its use in controlling hemorrhages and expelling the placenta after birth.

Monks have chewed its parts to decrease sexual desire. [4,5] At least one report discusses the chaste tree's use in ancient medicine to the present. [6]

The German Commission E has approved the plant for treatment of mastodynia (pain in breast) and menstrual irregularities. Chaste tree is primarily used in reproductive medicine for the following: Mastalgia, menopausal symptoms, depression, low libido, vaginal dryness, premenstrual syndrome (PMS), hyperprolactinemia, and inadequate luteal phase. [1]

CHEMISTRY: *V. agnus-castus* contains iridoids, flavonoids, diterpenoids, progestins, essential oils, and ketosteroids. [7,8]

Iridoid glycosides have been isolated from the leaves and fruit of the plant and include the following: Agnuside, aucubin, eurostoside, mussaenosidic acid, 6'-O-p-hydroxybenzoylmussaenosidic acid, and agnucastoside A, B, and C. [8,9,10,11]

Flavonoid content has been determined in chaste tree leaves (0.99% to 2.7%), flowers (1.01% to 1.47%), and fruits (0.45% to 0.97%). [12] Components of flavonoids include the flavonol derivatives of kaempferol and quercetagetin, the major constituent being casticin. [10] An earlier report identifies additional flavonols from the fruits, including 6-hydroxykaempferol-3,6,7,4'-tetramethyl ether (penduletin 4'-methyl ether), penduletin, and chrysosoplenol. [13] Other flavonoids present in the plant include orientin and isovitexin. [4] Four new flavonoids were isolated from the root bark and include the following: Luteoloin 6-C-(4'-methyl-6'-O-trans-caffeoylglucoside), luteolin 6-C-6(6'O-trans-caffeoylglucoside), luteolin 6-C-(2'-O-trans-caffeoylglucoside), luteolin 7-O-(6'-p-benzoylglucoside). [14]

Essential oils present in chaste tree mainly include the following: Monoterpenoids, cineol, and pinene (alpha and beta), along with limonene, sabinene, castine, eucalyptol, myrcene, linalool, citronellol, cymene, and camphene. Sesquiterpenoids such as caryophyllene, farnesene, cardinene, and ledol also are present. [7,10,15]

Total polyphenol content for the leaves (7.36% to 20%), flowers (9% to 10.64%), and fruits (6.92% to 24%) has been determined. The highest tannin content was found in the leaves (0.68% to 3%); tannin content was similar in the flowers (0.24% to 2%) and fruits (0.24% to 1.60%). [16]

The alkaloid vitricine also is present in the plant. [10] Vitexlactam A, a labdane diterpene, has been isolated from the fruit of *V. agnus-castus*; recent evidence has shown that labdane diterpenes have dopamine receptor affinity. [3,17] An overview of chaste tree is available, including chemical composition, pharmacology, and side effects. [18]

PHARMACOLOGY: *V. agnus-castus* contains hormone-like substances that competitively bind receptors making the plant useful in disorders in which progesterone deficiency might be suspected (eg, female infertility, menopause, PMS). [1,19]

After ingestion in females, the berries exert progesterogenic effects, balancing progesterone and estrogen production from the ovaries and regulating menstrual cycles. [4] A randomized, placebo-controlled trial used an agnus-castus-containing homeopathic preparation to treat infertility in 67 women, oligomenorrhea in 37 women, and amenorrhea in 30 women. All groups were treated with the preparation or placebo 3 times/day for 3 months (or 3 menstrual cycles). The researchers reported 38 of 67 women achieved spontaneous menstruation and improved progesterone concentration in the luteal phase, and experienced a shortening of the cycle, earlier ovulation, and pregnancy. [1]

A preparation of chaste tree (0.2% w/w) has been available in Germany since the 1950s and is used in treatment of breast pain, ovarian insufficiency (some cases resulting in pregnancy), and uterine bleeding. [10] Crude herb or alcoholic or aqueous extracts of pulverized fruit are used in commercial preparations. [20]

Agnus fruit (*V. agnus-castus* L. extract *Ze 440*) was compared with placebo over 3 menstrual cycles in a prospective, randomized, placebo-controlled study of 170 women (mean, 36 years of age) with PMS. Primary variables included change from baseline to endpoint in women's self-assessment of irritability, mood, alternation, anger, headache, breast fullness, and other menstrual symptoms including bloating. The authors concluded from the results of the primary ($P < 0.0001$) as well as secondary ($P < 0.0001$) variables that the extract was effective and well tolerated in relieving symptoms of PMS. [21,22,23] The extract is standardized to casticin.

Chaste tree preparations inhibit basal and thyrotropin-releasing hormone (TRH)-stimulated prolactin secretion from rat pituitary cells in vitro, suggesting its possible use in the treatment of hyperprolactinemia. [24] In addition, animal studies have found an increase in lactation and mammary enlargement, indicating an effect on prolactin release. [4]

Interestingly, studies on the essentials of the leaves and fruits of this plant also claimed to show usefulness in menstrual symptoms in limited human clinical trials. When studied in 52 women with luteal phase defects caused by latent hyperprolactinemia, a chaste tree preparation reduced prolactin release, normalized luteal phases, and eliminated deficits in luteal progesterone without side effects. Chaste tree extract contains an active principle that binds to dopamine receptor sites, inhibiting prolactin release. The prolactin-inhibiting action of the preparation was equivalent to high doses of synthetic dopamine agonists. This suggests therapeutic usefulness of the plant for treatment of premenstrual breast pain associated with prolactin hypersecretion. [25,26,27]

Twenty healthy male subjects received oral daily doses of 120, 240, and 480 mg *V. agnus-castus* extract (BP1095E1) vs placebo for 2 weeks. Dose-dependent effects on prolactin release were noted as compared with follicle-stimulating hormone, luteinizing hormone (LH), and testosterone serum concentrations. Prolactin secretion, stimulated by the thyrotropin-releasing hormone, increased with the 120 mg dose and decreased with the 480 mg dose. [1]

A case report documents mild ovarian hyperstimulation in the luteal phase in a woman 32 years of age undergoing in vitro fertilization. The patient was taking an herbal medicine containing *V. agnus-castus*. The authors concluded that a possible drug-herb interaction may have occurred and warned of similar interactions with bromocriptine, dopamine, and dopaminergic drugs. Women should be cautioned that *V. agnus-castus* may increase the risk of a multiple pregnancy and high LH levels may increase the risk of miscarriage. [1,27,28]

Chaste tree is reportedly effective in treating endocrine abnormalities such as menstrual neuroses and dermatoses. It also has been used to treat acne. [10]

In lactating women, extracts of the plant also have been used to increase milk production. [4] When analyzed chemically, the breast milk revealed no compositional changes after chaste tree use.[10]

TOXICOLOGY: Chaste tree administration has not been associated with important adverse events. In one large, German market surveillance study, 17 of 1542 women discontinued treatment because of an adverse event.[4] Minor side effects include GI reactions, allergic reactions (eg, itching, rash), headaches, fatigue, alopecia, acne, and menstrual flow increase.[4,10,21,29] The safety of the plant has not been determined in children. Chaste tree is not recommended for use during pregnancy because of its potential to inhibit secretion of prolactin.

SUMMARY: The chaste tree is a popular European plant that is used in traditional medicine for the management of disorders of the female reproductive tract. Chemical analysis indicates the presence of components that can affect the function of these systems, and the results of preliminary human investigations indicate that extracts of the plant have measurable pharmacologic activity.

PATIENT INFORMATION — Chaste Tree

Uses: Chaste tree has been used in females to balance progesterone and estrogen production and to regulate menstruation. It has also been used for the relief of breast pain, ovarian insufficiency, and uterine bleeding, and to increase breast milk production. However, there is limited clinical trial information to support these uses.

Side Effects: Minor side effects include GI reactions, itching, rash, headaches, fatigue, alopecia, acne, and increased menstrual flow.

Drug Interactions: Chaste tree has dopamine agonist activity and, thus, may increase activity of other dopamine agonists (eg, bromocriptine, levodopa). It also may reduce the effectiveness of birth control.

Pregnancy/Lactation: Chaste tree is not recommended for use during pregnancy because of its potential to inhibit secretion of prolactin.

Dosing: Daily doses of chaste tree are typically 30 to 40 mg of crushed fruit or 1.6 to 4.2 mg of dried extract. Chaste tree fruit is available in several different standardized extracts, with casticin content used for standardization. *Agncaston* is standardized to 1% casticin, while *PreMens* contains 0.6% casticin. Other products include *Agnolyt* (3.5 to 4.2 mg extract/pill), *Femicur* (1.6 to 3 mg extract corresponding to 20 mg drug), *Strotan*, *Mastodynan*, and *Ze 440*. Fluid extracts and tinctures are among the most common dosage forms for this product.[21,30,31]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHASTE TREE

CHICKEN SOUP

DATE OF ISSUE: MAY 1998

REPLACES MONOGRAPH DATED: APR 1987

SOURCE: Chicken soup is obtained from a hot water infusion of selected parts of the common chicken *Gallus domesticus*.

HISTORY: Chicken soup has long been recognized as an important part of the physician's armamentarium. Therapeutic observations were recorded as far back as 60 A.D. by Pedacius Dioscorides, an army surgeon under the emperor Nero. He was responsible for the book "De Materia Medica," which, among other natural science knowledge, discusses chicken soup. Aretaeus the Cappadocian (2nd to 3rd century), an author of causes, symptoms and treatments of diseases, is credited with describing how boiled chicken can treat respiratory tract disorders. [1]

As early as the 12th century, the theologian and physician Moses Maimonides wrote "Chicken soup...is recommended as an excellent food as well as medication." [2] He further specified that "One should not use the too large, that is of more than 2 years of age; nor the too small, that is those in whom the mucus still prevails; neither too lean, nor those who through feeding becomes obese; but those that are fat by nature without being stuffed." [3]

Chicken soup was used in Europe for centuries, but disappeared from commercial production after the inquisition. It remained popular in European tradition, and its use has grown steadily over the last 300 years.

CHEMISTRY: While details of the chemistry of chicken soup are poorly understood, it is recognized that the composition of this material can vary considerably, generally being related to the production technique. Some investigators have expressed concern about the cholesterol content of chicken soup, but there appears to be little evidence of a hypercholesterolemic effect when ingested in moderation.

Circa 1990, Dr. Irwin Zimet (University of California, Los Angeles) found that chicken, a protein, contains the amino acid cysteine. This is chemically similar to the drug acetylcysteine, which is prescribed for respiratory infections because it thins the mucus in the lungs. [4]

A study has been performed proving increased calcium content with duration of cooking soup with bones. Chicken soup prepared this way may be of use in patients who require calcium, but cannot tolerate dairy products. [5]

PHARMACOLOGY: In 1975, the editor of the journal *Chest* published the scientific spoof on uncontrolled studies entitled "Chicken Soup Rebound and Relapse of Pneumonia: Report of a Case." The patients suffered severe pneumonia requiring a thoracotomy and treatment with penicillin after he discontinued a course of self-treatment with chicken soup.[2]

The result of this report was a flood of correspondence over the next 5 years expounding the virtues of chicken soup. Readers reported the isolation of the "active ingredient"[6] that was claimed to have antibacterial activity[7] and could be useful in the treatment of impotence,[8] frustration, anxiety and backache.[9] It was also suggested that appropriate blends of chicken soup could be used as substitutes for aircraft fuel. [10]

Despite these barbs, a serious investigation was conducted comparing the effects of drinking hot water, cold water and chicken soup on nasal mucus velocity and airflow resistance. Drinking 200 ml of hot water, by sipping, increased nasal mucus velocity, but not when the cup was covered and a straw used for drinking. The latter procedure prevented hot water vapor from penetrating the nares. Drinking chicken soup by sipping and by straw caused a response similar to that of drinking hot water. It is believed that the additional effect seen when drinking chicken soup by straw may be related to an aromatic compound acting on the nasal pharynx or through a mechanism related to taste. The authors recommend hot rather than cold liquids for fluid intake in patients with upper respiratory tract infections. [11]

While the aroma of this agent precludes double-blind investigations, it is encouraging to know that one of the properties of chicken soup is to hasten the removal of pathogens from the nose.[12] Chicken soup has also been reported as therapy for facial pain [13] and for asthma.[14]

A detailed letter discussed the therapeutic efficacy of chicken and other fowl. Conditions in areas such as neurological, respiratory, urinary tract, antibacterial and gastrointestinal are relieved by chicken parts, soup or other fowl (eg, leprosy, sexual potential, snake bite antidote and memory enhancement). [15] The use of prednisone vs chicken soup for treatment of lymphocytic thyroiditis with spontaneously resolving hyperthyroidism has also been reported. [16]

The ability of chicken soup to inhibit neutrophil chemotaxis (and therefore reduce inflammation) has been presented at the 1993 International Conference of the American Lung Association and the American Thoracic Society. It was proven that chemotaxis was markedly reduced, even when the soup was diluted 200 times. The soup included onions, sweet potatoes, carrots, turnips and parsnips, all of which may have contributed to the beneficial effects. [4]

A Japanese trial demonstrated chicken cartilage soup to have therapeutic efficacy in 38 rheumatoid arthritis patients. [17]

TOXICOLOGY: The ingestion of chicken soup is not without danger. One case of pneumonia secondary to the aspiration of a bone from a dose of chicken soup has been reported. The authors concluded that "only bone-free chicken soup" should be used. [18] Another report describes severe respiratory distress in a 6-month-old infant from a hollow chicken bone in the left main bronchus after the child was spoon-fed chicken soup. [19] Information on the dangers of chicken soup in pediatrics is available.[20]

Hypernatremia was reported in a 75-year-old Chinese woman who ingested one or two bowls of three different kinds of high-salt soups to correct hydrochlorothiazide-induced hyponatremia. She became delirious but was treated uneventfully with hypotonic solutions. [21] Similarly, a 17-month-old child, who was given six packets of HERB-OX chicken broth (prepared as directed in 6 oz of water), was hospitalized due to hypernatremic dehydration. She recovered uneventfully with rehydration.[20] Hypernatremia following high-salt supplements is a complication sometimes seen in children, in particular those with acute diarrheal disease. Large amounts of hypertonic solutions, such as chicken soup, should not be given to young children. In addition, commercial soup bouillons may contain trace amounts of mutagens.[22]

There is at least one case report of anaphylaxis to chicken soup. [23] Also of concern may be migration of mineral hydrocarbons from polystyrene containers from which hot beverages, including chicken soup, are served. [24]

SUMMARY: Chicken soup has a historical legacy that spans hundreds of generations. It appears to be an effective adjunct in the treatment of mild upper respiratory tract infections. Toxicity involves mainly hypernatremia and physical obstruction by bone fragments present in the soup.

PATIENT INFORMATION— Chicken Soup

Uses: Chicken soup has been used to treat respiratory tract disorders, asthma and facial pain among other ailments.

Side effects: Adverse events include severe respiratory distress from aspirating chicken bone fragments.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHICKEN SOUP

CHICKWEED

DATE OF ISSUE: MAY 2003

REPLACES MONOGRAPH DATED: FEB 1992

SCIENTIFIC NAME(S): *Stellaria media* (L.) Villars. Family: Caryophyllaceae

COMMON NAME(S): Chickweed, mouse-ear, satinflower, starweed, starwort, tongue grass, white bird's-eye, winterweed, chickenwort[1]

BOTANY: Chickweed is a common plant, particularly throughout Europe and North America. This low-growing annual has a thin hairy stem with pointed oval leaves. It produces small, white, star-shaped flowers throughout much of the year.[2,3,4]

HISTORY: The whole dried plant has been used in the preparation of infusions. Chickweed extract has been used internally as a demulcent, but is more typically used externally for the treatment of rashes and sores. The young shoots are edible and have been used as salad greens. [5] In homeopathy, the plant is used to relieve rheumatic pains and psoriasis.[2] Chickweed is cited as a folk remedy for many conditions, including asthma, blood disorders, conjunctivitis, constipation, inflammation, dyspepsia, skin ailments, and obesity.[6] The Chinese use a sugar infusion for the treatment of epistaxis.[6]

CHEMISTRY: Nitrate salts and vitamin C (375 mg/100 g) have been identified in the plant.[5,6] Chickweed contains rutin and several other flavonoids.[7] Carotenoid content is about 4.2 mg/100 g.[8] Chickweed also contains alkaloids, octadecatetraenic acid, linolenic acid, and the esters hentriacontanol and cerylcerotate.

PHARMACOLOGY: Although there is an extensive base of scientific literature describing chickweed, this literature focuses largely on its control as an unwanted weed. There is no indication that any of the plant's constituents possess therapeutic activity, and its vitamin content is too low to be of therapeutic value. [9] A review of clinical research from PubMed and ChemAbstracts suggests that the plant is not actively under investigation, as there are no new pharmacological data to report.

TOXICOLOGY: Grazing animals have experienced nitrate poisoning secondary to chickweed.[6] Although poorly documented, human cases of paralysis have been reported from large amounts of the infusion. However, there is no overwhelming evidence to suggest that chickweed is toxic. [5]

SUMMARY: Although chickweed is ubiquitous and has been used in traditional medicine for centuries, there is no evidence that it offers any therapeutic activity. It is generally well tolerated, although the ingestion of large amounts of the plant may be associated with nitrate toxicity.

PATIENT INFORMATION — Chickweed

Uses: Chickweed infusions and extracts have been used internally as demulcents and topically as treatment for rashes and sores. Young offshoots are edible. There is no information to support chickweed use for any indication.

Side Effects: Ingestion of large amounts may be toxic.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHICKWEED

CHICORY

DATE OF ISSUE: MAR 2000

REPLACES MONOGRAPH DATED: MAR 1996

SCIENTIFIC NAME(S): *Chicorium intybus* L. Family: Compositae or Asteraceae

COMMON NAME(S): Blue sailor's succory, chicory, wild succory

BOTANY: Chicory is a perennial plant indigenous to Europe, India, and Egypt. It was introduced to the US in the late 19th century. It grows as a weed in temperate climates and is widely cultivated in northern Europe. There are 2 principal types: The Brunswick variety has deeply cut leaves and generally spreads horizontally; the Magdeburg variety has undivided leaves and grows erect. Chicory has bright blue flowers that bloom from July to September. The dried root is the primary part of the plant used.

HISTORY: In cultivation, chicory roots are "forced" during the fall and winter to produce 2 types of leaves used as greens: Barbe de capucin and witloof (or French endive). The leaves of young plants are used as potherbs, in which case they are cooked like spinach. Leaves of older plants, when blanched, are used like celery. Chicory roots are boiled and eaten with butter. They are also roasted and used to add a bitter, mellow taste to coffee and tea or used as a substitute for coffee. Chicory is on the FDA Generally Recognized as Safe (GRAS) list.

CHEMISTRY: Chicory flowers contain cichoriin, which is 6,7-glucohydroxycoumarin. The roots contain up to 8% inulin (a polysaccharide), a bitter principle consisting of 1 part protocatechuic aldehyde to 3 parts inulin, as well as lactucin and lactucopicrin. [1] Constituents of the greens include chicoric acid (dicaffeoyl tartaric acid), flavonoids, catechol tannins, glycosides, carbohydrates, unsaturated sterols and triterpenoids, sesquiterpene lactones, and tartaric acid. [2,3] Leaf proteins from chicory greens have also been reported. [4]

The root contains a large number of steam-distillable aromatic compounds. Acetophenone provides the characteristic chicory aroma. Upon roasting, inulin is converted to oxymethylfurfural, a compound with a coffee-like smell. [3] Fructan:fructan 6G-fructosyltransferase (6G-FFT) was found to be an important enzyme in the formation of inulin. According to 1 report, introduction of 6G-FFT from 1 plant into chicory resulted in inulin synthesis. [5] Chicory is the source of the taste-modifier maltol, which is known to intensify the flavor of sugar.

The caffeine content of beverages containing chicory was determined using high pressure liquid chromatography (HPLC). A coffee/chicory mixture substitute contains 3.18 mg/fl oz of caffeine, whereas instant coffee contains 12.61 mg/fl oz of caffeine. [6]

In identifying closely related chicory varieties, the use of polyacrylamide gel electrophoresis followed by leucine aminopeptidase and esterase staining of bulked seed sample extracts has been developed. [7]

PHARMACOLOGY: The water-soluble fraction of chicory has a sedative effect and antagonizes the stimulating effects of coffee and tea via a CNS mechanism. Lactucin and related compounds may be in part responsible for the plant's sedative effects.

The naturally occurring oligosaccharides in chicory are considered "probiotics" entering the large intestine and are substrates for intestinal fermentation. This maintenance of microbial composition in the colon is important for GI tract health. Because of certain bond configurations, these oligosaccharides resist hydrolysis by salivary and intestinal enzymes. In the colon they are fermented by anaerobic bacteria. The most well-known effects of nondigestible oligosaccharides is the selective stimulation of bifidobacteria, reducing the growth of other pathogenic bacteria. [8,9,10,11,12]

Studies conducted on rats show that inulin from chicory seems very effective in promoting proprionic fermentation and enhances the calcium content of the large intestines. [13] A reduction in intestinal absorption of glucose was observed in another report in rats administered chicory extract. [14] Improved lipid metabolism was demonstrated in rats fed inulin-containing chicory extract, as well. This effect possibly was due to changes in absorption or synthesis of cholesterol. [15] Chicory's inulin type fructans may have potential to benefit many conditions or disease states including constipation, infectious diarrhea, cancer, cardiovascular disease, and non-insulin-dependent diabetes. [16,17] Long- vs short-chain fructans from chicory have also been compared in the intestine. Absorption, transit time, fermentation factors, and abdominal symptoms have been studied in a 10-patient, single-blind trial. [18] More human trials are needed.

Chicory fructans oligofructose and inulin have also been found to inhibit colon carcinogenesis in rats. [19,20] Another study reports weak-to-moderate comutagenic effects using an extract of chicory greens against induced mutagenicity in vitro. [21] Other fruits and vegetables have been studied with respect to induced mutagenic activities. Chicory was shown to have strong-to-moderate antimutagenic activities that remained heat stable. [22] Root callus extract of chicory demonstrated liver protectant effects against carbon tetrachloride-induced hepatocellular damage. [23] Alcoholic extracts of the root also have anti-inflammatory activity. [24]

Experiments with the isolated toad heart show that chicory extracts reduce cardiac rate in a manner similar to quinidine. Although variable from one preparation to another, this effect is evident before and after ganglionic blockade and atropinization. Its potency is increased by heating the extract. These findings suggest chicory constituents may be effective in treatment of disorders involving tachycardia, arrhythmias, and fibrillation. [1]

Contraceptive activity was observed in female rats orally administered (days 1 to 10 postcoitum) seed extracts of chicory, as well as certain other plant fractions. [25] Chicory has also been noted as an appetite stimulant and for dyspepsia. [26]

TOXICOLOGY: Handling of chicory has been reported to cause occupational contact dermatitis. This effect may be caused by the presence of sesquiterpene lactones. [27,28] Other allergies to chicory include case reports or letters of occupational asthma in a chicory grower, [29] occupational and ingestive allergy to the plant, [30] food allergy, [31] and other allergies. [32,33] A recent report investigates chicory extract on mast cell-mediated immediate type allergic reactions. It was demonstrated that the extract inhibits this type of reaction in vivo and in vitro. [34]

A study of contamination showed that chicory absorbs the fungicide quintozene through the roots, which may present a toxic hazard. [35] In a study of 64 vegetable samples, 92.5% of the 654 bacterial lines isolated were *Enterobacteriaceae*, with the more contaminated being celery, fennel, onion, and chicory. These vegetables are a source of contamination and colonization of *Enterobacteriaceae*, especially in hospitals. [36]

Chicory sold commercially has, in some instances, been contaminated with crushed cashew shells that can cause an allergic toxicity similar to that observed with poison ivy. [37] High levels of inulin (greater than 10%) from chicory in the diet may affect growth in rats and lead to acidic (pH 5.65) cecal fermentation. [13]

In case of gallstones, consult with a physician before taking chicory. [26]

SUMMARY: Chicory is common to Europe, India, Egypt, and North America and is widely cultivated. The leaves are used as salad greens in cooked form; the roots are boiled and eaten or roasted for use as an additive or replacement for coffee or tea. Chicory's oligosaccharides are probiotic and are beneficial in maintaining healthy GI flora. Inulin type fractions of the plant may help certain conditions including constipation, diarrhea, cancer, and cardiovascular disease. Chicory has also been noted as an appetite stimulant and for dyspepsia. The principal toxicity related to chicory is contact dermatitis. In case of gallstones, consult with a physician before taking chicory.

PATIENT INFORMATION— Chicory

Uses: Chicory leaves and roots are used as a vegetable. Roasted roots are ground and brewed. Chicory is a sedative with potential cardioactive properties. Chicory's oligosaccharides are probiotic and are beneficial in maintaining healthy GI flora. Inulin type fractions of the plant may help certain conditions including constipation, diarrhea, cancer, and cardiovascular disease. Chicory has also been noted as an appetite stimulant and for dyspepsia.

Side Effects: Known toxicity includes contact dermatitis, contamination with foreign substances or bacteria, and various allergies. Significant contraceptive activity was observed in female rats orally administered seed extracts and other fractions of chicory. In case of gallstones, consult with a physician before taking chicory.

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "C" MONOGRAPHS
  CHICORY

CHINESE CUCUMBER

DATE OF ISSUE: MAR 1998

REPLACES MONOGRAPH DATED: APR 1990

SCIENTIFIC NAME(S): *Trichosanthes kirilowii* Maxim. Family: Cucurbitaceae

COMMON NAME(S): Chinese cucumber, Chinese snake gourd, gua-lou, tian-hua-fen, compound Q

BOTANY: The chinese cucumber is one of more than 40 recognized species of *Trichosanthes*. It is a member of the gourd family, and the root, fruit, seeds, stems and peel are used medicinally. While *T. kirilowii* is the plant most often referred to in Chinese materia medica, a number of related species are often used as adulterants.

HISTORY: *T. kirilowii* has a long history in traditional Chinese medicine where it is used to reduce fevers, swelling and coughing. A starch extracted from the root is used for abscesses, amenorrhea, jaundice and polyuria. Modern Chinese medicinal uses include the management of diabetes and use as an abortifacient. [1] The plant has been used for centuries in the treatment of tumors.

CHEMISTRY: The most studied component of *T. kirilowii* is the protein trichosanthin. [2,3] Two trichosanthins have been identified: Alpha from *T. kirilowii* and beta from *T. cucumeroides*. Alpha-trichosanthin is synonymous with Chinese cucumber. A highly purified form of trichosanthin has been investigated under the name GLQ-223. A second protein, trichokirin, was isolated and found to possess ribosome-inactivating activity. [4] A later study reports that a peptide trypsin inhibitor isolated from *T. kirilowii* roots may be the smallest naturally occurring protein inhibitor. [5]

An abortifacient protein, karasurin, has been isolated from fresh root tubers of the plant. It was found to express protein polymorphism separated by ion-exchange chromatography. [6,7] Three Japanese studies report structure and anti-inflammatory effects of five hydroxylated sterols from Chinese cucumber seeds. [8,9,10]

PHARMACOLOGY: The Chinese cucumber has gained enormous popularity because trichosanthin may be effective in the management of acquired immunodeficiency syndrome (AIDS) infections. A report by McGrath, et al described the ability of GLQ-223 to block HIV replication in infected T-cells and to kill HIV-infected macrophages. In vitro, this compound appears to selectively kill infected cells without damaging uninfected cells. Trichosanthin also appears to prevent the HIV virus from replicating in T-4 cells (immune cells that are killed by the virus). When freshly drawn blood samples from HIV-infected patients were treated with a single 3-hour exposure to GLQ-223, HIV replication was blocked for at least 5 days in subsequently cultured monocytes and macrophages. [11] Human clinical trials have been initiated in the United States to determine the drug's potential in man.

A report studied anti-HIV activity in trichosanthin purified from *T. kirilowii* root tubers. [12] A protein ("TAP 29"), distinct from trichosanthin, may offer a broader safe dose range compared with trichosanthin in AIDS treatment. The two proteins exhibit similar anti-HIV activity. [13]

Extracts of the plant have been known for centuries to be potent abortifacients. Trichosanthin inhibits ribosome activity and cellular replication. [14] One report says that trichosanthin inactivates ribosomes by cleaving the N-C glycosidic bond of adenylic acid at (position) 4324 of 28S rRNA in a hydrolytic fashion. [15] Another report discusses the importance of lysine and arginine to trichosanthin's activity. [16] Another ribosome-inactivating protein, beta-kirilowin, has recently been isolated from *T. kirilowii* seeds and exhibits strong abortifacient activity. [17] Studies on another abortifacient and antitumor protein, karasurin, report induction of mid-term abortion in pregnant mice. [6,7] Other proteins present in the plant have been reported to express similar abortive effects. [18]

Chinese cucumber juice, applied to a sponge inserted vaginally, can induce abortions. Trichosanthin has been used to abort ectopic pregnancies in place of management via salpingectomy. [19] The drug is also effective in inducing first-trimester abortion when administered intramuscularly or extra-amniotically. [19]

Trichosanthin possesses antitumor activity and has been used to treat invasive moles. [1,20] Selective killing of choriocarcinoma cells has occurred. [21] It also shows specificity as an antihepatoma agent. [22] Trichosanthin is a reported potent immunosuppressive protein, which could affect immunity and various cell-mediated processes. [23] The plant's other components, karounidiol and bryonolic acid, have been evaluated for their cytotoxic activity. [24,25,26]

Other immunological effects of trichosanthin include: Initiation of the alternative complement activation pathway in mice; [27] viability of human immunocytes, lymphocyte proliferation and cytotoxicity to lymphoma and leukemia cell lines; [28] and inhibitory effects on "IL-8 induction in lipopolysaccharide-activated rat macrophages." [29] Other effects of Chinese cucumber in animals include: Anti-inflammation, [8] anti-ulceration [30] and hypoglycemia. [31]

TOXICOLOGY: Extracts of the Chinese cucumber are extremely toxic, particularly if administered parenterally. Subacute LD-50 studies in mice resulted in deaths in 10 days. The LD-50 of intravenously administered freeze-dried root extract was 2.26 mg/mouse. Crystalline trichosanthin had an LD-50 of 0.236 mg/mouse.

Patients who receive injections of trichosanthin for abortion often develop strong sensitization to the compound. The risk of anaphylactic reaction secondary to a single exposure to trichosanthin may last longer than a decade. [1]

Other severe reactions produced by trichosanthin include pulmonary and cerebral edema, cerebral hemorrhage and myocardial damage. One report describes six patients with AIDS who purchased a cucumber root extract while in China. Following parenteral administration, the patients developed seizures and fever and were hospitalized. [20] The FDA has received a report of a patient who died following trichosanthin injections. [1] The crude mixture of plant proteins and lectins may have resulted in damage to blood cells. Clinical trials in the United States are confined to the use of highly purified trichosanthin.

Chinese cucumber use is contraindicated in pregnant women. Abortifacient effects have been well documented. [6,7,14,17] In vivo and in vitro teratogenic effects were evaluated in mice, resulting in aphysical abnormalities. [32] An additional study reported increased incidence of follicular atresia, ovulation changes and decreased hormone levels in mice given trichosanthin injections. [33]

SUMMARY: The Chinese cucumber has been recognized in oriental medicine for several thousand years. Extracts of the plant have been used to induce abortions. The primary component of the plant, trichosanthin, inhibits replication of the HIV virus in vitro. The plant also exhibits antitumor properties and other immunological effects. Extracts of the plant are extremely toxic and should never be ingested without supervision by a physician. The plant and its compounds are contraindicated in pregnant women or those of childbearing potential.

PATIENT INFORMATION — Chinese Cucumber

Uses: Chinese cucumber has been used to induce abortion. It possesses antitumor activity and has been used to treat invasive moles. Chinese cucumber is being studied as a treatment for the management of AIDS infections.

Side Effects: Side effects include allergic reaction, fluid in the lungs or brain, bleeding in the brain, heart damage, seizures, fever and death.

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Document Bibliographic Information:

- **Location In Book:**
  THE REVIEW OF NATURAL PRODUCTS (2004)
  "C" MONOGRAPHS
  CHINESE CUCUMBER

CHITOSAN

DATE OF ISSUE: MAR 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Chitosan

COMMON NAME(S): Chitosan

SOURCE: Chitin is a cellulose-like biopolymer found mainly in exoskeletons of marine invertebrates and arthropods, such as shrimp, crabs or lobsters. Chitin can also be found in fungi and yeasts. Deacylated chitin is called chitosan. [1] Chitosan is unique in that, unlike plant cellulose that is negatively charged, it possesses positively charged amino groups. These bind to the negatively charged lipid and bile components, preventing absorption by the body. [2] "Squid pens" (waste by-product of New Zealand squid processing) are a renewable and inexpensive source of chitosan. [3]

HISTORY: Chitosan has been used in the past 30 years in water purification plants to absorb greases, oils, metals and toxic substances. It can absorb four to six times its weight, and ascorbic acid can potentiate this action even further. [4]

CHEMISTRY: Chitin consists mainly of unbranched chains of beta-(1 ? 4)-2-acetamido-2-deoxy-D-glucose (=N-acetyl-d-glucosamine). It is similar to cellulose, where the C-2 hydroxyl groups are replaced by acetamido residue. Chitin is practically insoluble in water, dilute acids and alcohol. However, this varies depending on product origin.[1]

Chitosan, the partially deacetylated polymer of N-acetyl-D-glucosamine, is water-soluble. [3]

Rheology, flocculation and film formation testing have been performed with chitosan, demonstrating its usefulness in medical and analytical applications. [3] Biodegradable and biocompatible properties of chitosan films have been studied with good outcomes. [5] In vitro and in vivo degradation tests of chitin and chitosan have been evaluated, [6] as well as chitosan film chemistry on electrically charged metal plates. [7]

N-carboxymethylchitosan solubility and structure have been reported, [8] along with its ability to chelate metal ions and to enhance binding of dyes. [9]

Other chemical aspects involving chitin or chitosan include: Optical isomer separation, [10] mass-spectrometric analysis,[11] polyelectrolyte and sulfation studies,[12] adherence to liposomes[13] and properties of chitosan microspheres.[14]

PHARMACOLOGY: Chitosan is used in many areas, including the cosmetic and pharmaceutical industries, for medical use as a hyperlipidemic and in hypercholesterolemia therapy and for biomaterials. It is also used for antimicrobial and other effects.

Application of chitosan in the pharmaceutical industry is documented. Its ability to mask bitter tastes in oral pharmaceuticals has been reported. [15] There are reports employing chitosan in drug delivery systems of many types. Some of these reports include the following:

1.) ***Peptide/Diabetic use:*** Peptide drug delivery enhancement using chitosan,[16] colon-specific drug delivery of insulin using chitosan capsules, [17] mucoadhesion of chitosan-coated liposomes affecting insulin absorption in rats, [18] chitosan microcapsules to control insulin release, [19] and diabetic drugs in chitosan matrix tablets; [20]

2.) *Nasal route studies:* For insulin,[21,22] effects of chitosan on intranasal mucociliary clearance [23] and transport rates.[24] Pharmacokinetics on nasal administration on morphine-6-glucuronide in sheep;[25]

3.) *Transdermal delivery* using chitosan composite membranes;[26]

4.) *Various drug release evaluations on:* Chitosan hydrogels for organ specific antibiotic delivery in the stomach, [27] sustained release deoxytetracycline from chitosan microspheres,[28] biophosphonate-containing chitosan microspheres, [29] chitosan-indomethacin conjugates,[30] aspirin and heparin embedded in a chitosan matrix, [31] preparation and drug-release properties of chitosan-drug microspheres, [32] suitability of chitosan as a carrier, using indomethacin papaverine [33] and lidocaine,[34,35] cancer drug delivery,[36] buccal and vaginal tablets containing mycotic drugs and chitosan, [37] nifedipine release with chitosan microspheres, [38] chitosan beads to deliver salmon calcitonin;[39]

5.) *Chitosan to enhance absorption:* For poorly absorbable drugs [40] and across mucosal surfaces.[41]

Chitosan's role in the cosmetic industry has been reported. [42,43,44] Chitosan use as a natural product may substitute for the synthetic polymer elements in film-forming resins.[45]

Chitosan's characteristic as a film-forming and protective polysaccharide suggests its potential use as a biomaterial. Its applications in this area have been reported. [46] Safety and hemostatic potential have been evaluated, concluding low toxicity and tensile strength retention in many circumstances. [47] N,O-carboxymethyl chitosan gel and solution delivered postoperatively were effective in preventing peritoneal adhesions in rats. [48] A Russian article discusses chitosan's role in reparative skin regeneration.[49] Heparin-chitosan gel application has stimulated wound healing in human skin, hypothesized to possibly be caused by stabilization and activation of growth factors that bind to heparin.[50] In burn patients, where standard of care involves application of silver sulfadiazine cream, silver toxicity is a concern (because of reduced skin barriers). Membranes, including chitosan, reduce this toxicity caused by the entrapment of silver ions in the matrix. [51] Adsorption of lead ions on chitosan has also been evaluated.[52] Chitin's involvement with human enzymatic activity seems to be activation of macrophages and stimulation of fibroblasts, promoting normal tissue production.[53]

Fiber products such as bran, resins, pectins, etc. have been used in the past for cholesterol and weight reduction. Cross-linked O-carboxymethyl chitosan beads are capable of absorbing LDL-cholesterol in vitro. [54] Extensive animal studies have been reported on these topics. Chitosan decreases lipid concentrations in affected rats, decreasing VLDL and increasing HDL levels. [55] Chitosan also has hypocholesterolemic actions in rats, [56,57,58] and has shown to lower cholesterol triglycerides.[59,60] Chitosan alters metabolism of bile in the intestines, affecting lipid and cholesterol levels. [61] One report relates many enzyme-involvements to oral administration of chitosan but proposes physical chitosan-lipid aggregate adsorption to be the mechanism of lipid adsorption. [53] Hypocholesterolemic effect in humans has been reported.[62,63]

Chitosan has been reported to exert some antimicrobial actions, exhibiting bactericidal actions against several pathogens in the field of dentistry, [64] inhibiting adhesion of *Candida albicans*to human vaginal epithelial cells[65] and inhibiting chlamydial infection by interfering with adsorption. [66]

One report suggests chitosan to be effective treatment for renal failure patients. [67]

Chitosan's use includes photographic emulsions and improving dyeability of synthetic fibers in the fabric industry. [1]

TOXICOLOGY: Chitosan's toxicity profile is relatively low. Dietary chitosan reportedly affects calcium metabolism in animals. [68] Toxic effects of chitosans are dependent mainly on their chemical composition.[40]

SUMMARY: Chitosan is deacylated chitin, which is a polymer found mainly in shellfish exoskeletons. It has been used in water treatment to soak up grease and other undesirable substances. Chitosan is used in many areas, including the pharmaceutical and cosmetic industries, in medicine as treatment of hyperlipidemias and as biomaterials. It has antimicrobial effects and other actions. Most studies report low toxicity profiles, but individuals with shellfish allergy or pregnant women should consult with their doctors before use. Chitosan may affect mineral metabolism. The chemical composition of chitosans may affect its toxicity.

PATIENT INFORMATION— Chitosan

Uses: Chitosan has been used in various drug delivery systems. It has antimicrobial and other effects and can be used for kidney failure and to lower cholesterol.

Side Effects: Consult your physician if you are allergic to shellfish or if you are pregnant or breastfeeding.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHITOSAN

CHONDROITIN

DATE OF ISSUE: APR 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Chondroitin sulfate, chondroitin sulfuric acid, chonsurid, structum

COMMON NAME(S): Chondroitin

SOURCE: Chondroitin is a biological polymer that acts as the flexible connecting matrix between the protein filaments in cartilage. [1] Chondroitin can come from natural sources, such as shark or bovine cartilage or can be manufactured in the lab, using different methods. [2] Danaparoid sodium, a mixture of heparan sulfate, dermatan sulfate and chondroitin sulfate (21:3:1), is derived from porcine intestinal mucosa. [3]

HISTORY: Chondroitin sulfates were first extracted and purified in 1960. Studies suggested that if enough chondroitin sulfate was available to cells manufacturing proteoglycan (one of the substances that forms the cartilage matrix), stimulation of matrix synthesis could occur, leading to an accelerated healing process. [4] This idea of natural regeneration of cartilage has been popularized with the publication of the J. Theodosakis Book, "The Arthritis Cure." [5]

CHEMISTRY: Chondroitin sulfate is a high-viscosity mucopolysaccharide (glycosaminoglycan) with N-acetylchondrosine as a repeating unit and one sulfate group per disaccharide unit. Its molecular weight is about 50,000, depending on product source or preparation. [1] Danaparoid sodium (a mixture containing chondroitin) has a low molecular weight (5500 to 6000).[3] Analytical determination including HPLC, spectrophotometric analysis, chemical methods, ultraviolet spectrometry, and IR spectroscopy has been performed on chondroitin and its related structures. [6,7,8,9,10] A method for potentiometric titration of chondroitin sulfate has also been reported.[11]

PHARMACOLOGY: The pharmacokinetics of chondroitin sulfate have been determined in rats and dogs. [12] Another pharmacokinetic study, involving eight healthy volunteers, reports similar results in metabolism to those in animals. Other parameters evaluated included half-lives of distribution and elimination, volumes of distribution, excretion values, urine and blood levels and bioavailablity. [13] Another report concludes oral chondroitin sulfate B (dermatan sulfate) to reach significant plasma levels, with 7% bioavailability.[14] In 22 patients with renal failure, chondroitin sulfate half-life was prolonged, but it could be administered for clot prevention during hemodialysis in this population. [15]

Chondroitin's role in treating arthritis has gained popularity. Ongoing research continues with some controversial outcomes.

Articular cartilage is found between joints (eg, finger, knee, hip) allowing for easy, painless movement. It contains 65% to 80% water, collagen and proteoglycans. Chondrocytes are also found within this matrix, to produce new collagen and proteoglycans from building blocks, including chondroitin sulfate, a glycosaminoglycan (GAG). Chondroitin helps attract essential fluid into the proteoglycan molecules, "water magnet," which not only acts as a shock absorber but "sweeps" nutrients into the cartilage as well.[4] Chondrocytes must derive nutrition from this synovial fluid as there is no vasculature to nourish them. [16] Glucosamine, another of the beneficial substances in this area, stimulates chondrocyte activity. It is also the critical building block of proteoglycans and other matrix components. [4] Both chondroitin and glucosamine play vital roles in joint maintenance, which is the reason the combination of the two are found in many arthritic nutritional supplements (eg, "chondroitin complex" by Nature's Bounty, Bohemia, NY; 11716).

In inflammation and repeated wear of the joint, chondrocyte function is disturbed, altering the matrix and causing breakdown. [16] Proper supplementation with glycosaminoglycans (eg, chondroitin sulfate) may enable chondrocytes to replace proteoglycans, offering "chondroprotection." [17] Cartilage contains the biological resources to enhance repair of degenerative injuries and inflammation. It has been proposed that a certain chondroitin sulfate sequence, released from cartilage proteoglycans, can inhibit elastase, regulating the matrix. [18]

Results of a multicenter study of chondroitin sulfate in finger, knee and hip joint therapy are comparable with other international, double-blind, placebo controlled studies, all indicating beneficial results in osteoarthritis treatment. [19] An overview of chondroitin sulfate in another report, however, concluded the product has no clear value in osteoarthritis treatment.[20]

There is considerable controversy regarding absorption of chondroitin. Absorption of glucosamine is 90% to 98%, but chondroitin absorption is only 0% to 13% because of molecule size. Chondroitin is 50 to 300 times larger than glucosamine. (Note in chemistry section "MW") Chondroitin may be too large to be delivered to cartilage cells. In addition, there also may be purification and identification problems with some chondroitin products, some of which have tested subpotent. [4]

The American College of Rheumatology has stated that although chondroitin sulfate is readily available in health food stores, the supplements are not regulated by the Food and Drug Administration. Longer-term clinical trials, with larger groups of people are warranted to determine whether or not it is safe and effective. They also warn against discontinuaton of conventional therapy without consulting a physician and stress the importance of maintaining proper body weight and exercising. [21]

Chondroitin sulfate has been used as a drug delivery system for diclofenac and flurbiprofen. [22] Additionally, the polymer has been used as a stabilization agent for iron injection hyperalimentation.[23]

Chondroitin sulfate B (dermatan sulfate) has potential as an antithrombolytic agent, as it inhibits venous thrombi, with less effect upon bleeding than heparin. It is an effective anticoagulant in hemodialysis.[24] Another study found dermatan sulfate to have no direct, observable relation to heparin aggregation. [25] Dermatan sulfate's efficacy, compared with heparin, has been determined in acute leukemia patients. [26]

Chondroitin sulfate has been used to treat extravasation after ifosfamide therapy, decreasing pain and inflammation. [27] It has also been used to treat extravasation from vindesine,[28] doxorubicin and vincristine[29] and an etoposide needlestick injury in a healthcare worker. [30]

Levels of chondroitin sulfate increase 10 to 100 times in tumors compared with normal tissue. In one report, all 44 cancer patients analyzed showed the structural anomaly of the urinary chondroitin sulfate. This may provide a potential new marker for diagnosis and follow-up of cancer therapy. [31]

General reviews are available on chondroitin sulfate and chondroitin sulfate B. [32,33]

TOXICOLOGY: Little information about long-term toxic effects of chondroitin sulfate is available. Most reports conclude that it is not harmful compared with other arthritis therapies, such as NSAIDs. Because the drug is concentrated in cartilage, the theory is that it produces no toxic or teratogenic effects. [19] Long-term clinical trials with larger populations are needed to fully determine toxicity. [21]

SUMMARY: Chondroitin sulfate is a biological polymer important in the formation of cartilage. Its role in treatment for arthritis has gained in popularity but is controversial. It seems to help arthritis sufferers in some clinical trials. Chondroitin sulfate has also been studied in drug delivery, antithrombotic therapy and extravasation treatment.

PATIENT INFORMATION — Chondroitin

Uses: Chondroitin has been used to treat arthritis. It has also been studied for use in drug delivery, antithrombotic and extravasation therapy.

Side Effects: There is little information on chondroitin's long-term effects. Most reports conclude that it is not harmful.

Dosing: Chondroitin sulfate has been administered orally for treatment of arthritis at a dose of 800 to 1200 mg/day. Positive results often require several months to manifest, and a posttreatment effect has been observed.[34,35,36,37,38,39,40,41]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHONDROITIN

CHROMIUM

DATE OF ISSUE: JUN 1992

REPLACES MONOGRAPH DATED: N/A

SOURCE: Chromium is abundant in the earth's crust and is found in concentrations ranging from 100 to 300 ppm.[1] Commercially, it is obtained from chrome ore among other sources. The organic form of chromium exists in a dinicotino-glutathionine complex in natural foods, and appears to be absorbed better than the inorganic form. Good dietary sources of chromium include brewer's yeast, liver, potatoes with skin, beef, fresh vegetables and cheese.[2]

HISTORY: Chromium is important as an additive in the manufacture of steel alloys (chrome-steel, chrome-nickel-steel, stainless steel) and greatly increases the durability and resistance of these metals. Synthetically-produced $_{51}Cr$ is used as a tracer in various hematologic disorders and in the determination of blood volume.[3] Because chromium is a recognized element required for the normal glucose metabolism, a number of over-the-counter products promote the use of chromium, alone or in combination with "glucose tolerance factor" (GTF), to improve carbohydrate utilization. The effectiveness of these products has not been established although they represent nutritionally sound sources of chromium.

CHEMISTRY: Chromium (Cr) has an atomic weight of 51.996. The element has four valences. A number of naturally-occurring isotopes have been identified, the most common of which is $_{52}Cr$ (approximately 84% of the isotopes). $_{51}Cr$ has a half-life of approximately 28 days. Chromium is a steel-gray lustrous metal. Many of the salts of chromium (ie, chromic acid) are industrial hazards.

PHARMACOLOGY: The recommended daily allowance for chromium in healthy adults is 50 to 200 mcg.[4]

Trivalent chromium plays a role in a cofactor complex for insulin, and is involved in normal glucose utilization.[5] Chromium forms part of the glucose tolerance factor (GTF) which may facilitate binding of insulin to insulin receptors, thereby amplifying its effects on lipid and carbohydrate metabolism.[6]

Chromium deficiency is rare in the general population but may play a role in the development of adult diabetes mellitus and atherosclerosis.[6] Persons who have a high intake of highly refined foods may be at risk for developing chromium deficiency, as are patients receiving total parenteral nutrition. Trace metal solution for intravenous administration are available containing chromium alone or in combination with other metals.[7] These patients may experience peripheral neuropathy or encephalopathy that could be alleviated by administration of chromium. Marginal levels of chromium have been associated with decreased glucose utilization during pregnancy and in the elderly. Administration of chromium has improved glucose tolerance in these patients. It should be noted that supplemental amounts of dietary chromium do not have a hypoglycemic effect in normal individuals.[5] Most absorbed chromium is eliminated through the kidneys (3 to 50 mcg/day).[6,7]

TOXICOLOGY: Acute oral ingestion of chromate salts may lead to irritation of the gastrointestinal tract (nausea, vomiting, ulcers), circulatory shock or hepatitis.[7] Renal damage (including acute tubular necrosis) has been observed following occupational exposure to chromium.[8] Trivalent chromium compounds (the kind found in foods) show little or no toxicity.

Exposure to occupational dust contaminated with hexavalent chromium and CrO_3 or CrF_2 (which are used as corrosion inhibitor pigments, and in metallurgy and electroplating) has been associated with the development of mucous hypersecretion and respiratory (lung) cancers.[9] The incidence of lung cancer is increased up to 15 times normal in workers exposed to chromite, chromic oxide or chromium ores.[10] The hexavalent species of chromium appears to be most highly associated with the development of cancers.[11]

Topical effects following exposure to chromium and chromates may lead to incapacitating eczematous dermatitis and ulceration. Ulceration and perforation of the nasal septum have also occurred.[10] About 1% to 4% of a topically applied dose of hexavalent and trivalent chromium penetrate guinea pig skin in 24 hours. Only 2 mcg of hexavalent chromium are required to induce a topical reaction in sensitive individuals.[12] Chromium may be chelated by the systemic administration of dimercaprol.[10]

SUMMARY: Chromium is a trace element that is required for normal metabolic function. Although dietary requirements may generally be met by a balanced diet, supplements are available. Certain forms of chromium are associated with the development of topical skin irritation and the induction of renal disease and cancers.

PATIENT INFORMATION — Chromium

Uses: Chromium is a necessary nutrient. Deficiencies, though rare, may contribute to adult diabetes and atherosclerosis and may complicate aging and pregnancy.

Side Effects: Ingestion or exposure to certain forms of chromium may cause or contribute to GI irritation and ulcers, cancer, dermatitis, circulatory shock, and hepatitis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CHROMIUM

CIGUATERA

DATE OF ISSUE: JUL 1994

REPLACES MONOGRAPH DATED: MAR 1988

HISTORY: Ciguatera (from "cigua," a poisonous tuban snail of the Spanish Antilles) is primarily a tropical disease but is also seen in the southern coastal United States. It is caused by the ingestion of a wide variety of normally safe, bottom-feeding coral-reef fish that contain toxins accumulated via the marine food chain. Ciguatera outbreaks are usually localized and often follow major disturbances of reefs, as in construction of wharves. [3] Over 400 species of fish and several invertebrates are known to contain ciguatera toxin (ciguatoxin). Ciguatoxic fish are restricted to species feeding on organisms around tropical reefs and include the sturgeon fish, reef sharks, moray eels, parrotfish, jacks, snappers, sea bass and barracuda. [4] The red snapper and barracuda are the most frequently implicated species, although, in Miami, grouper has been implicated in 60% of cases. The sale of barracuda is now prohibited there. [2]

CHEMISTRY: Ciguatera poisoning is caused by ciguatoxin, which fish are believed to acquire through the food chain. Other compounds that may also be involved include maitotoxin, lysophosphatidylcholine, scaritoxin and ciguatoxin-associated ATPase inhibitor. [5] The marine reef dinoflagellate *Gambierdiscus toxicus* (formerly misidentified as *Diplopsalis* spp.) is the most likely source of the toxin.[6] Reef disruptions release unusually large numbers of the organisms into surrounding waters. These organisms are eaten by reef herbivores, which are then eaten by successively larger carnivores, which store the toxin in their organs (muscle, liver, brain, intestines, gonads). For this reason, large fish are more likely to be toxic and have a higher concentration of toxin. In a study of Pacific red snapper, 69% of the fish weighing more than 2.8 kg were toxic, compared with 18% of smaller fish.[7]

Ciguatoxin has been difficult to characterize because it is present only in minute quantities. About 1000 kg of toxic eel liver yields approximately 1 mg of purified toxin. Ciguatoxin is a crystalline, colorless, heat-stable solid with a molecular weight of about 1100 (because it is heat-stable, it cannot be deactivated by freezing or cooking).[2] Only general functional groups (quaternary nitrogen, hydroxyl) have been identified. Certain features of ciguatera are thought to be caused by polycyclic ethers.[5]

PHARMACOLOGY: Ciguatoxin is one of the most potent marine toxins known, with an LD-50 of 0.45 mcg/kg (mouse IP). In an outbreak involving 14 members of an Italian freighter crew who ate portions of a 25-pound barracuda caught near Freeport, Bahamas, the CDC determined from remaining fish parts that the fish had an LD-50 (mouse IP) equivalent to 2 g to 5 g of original fish flesh. [8]

All people known to have eaten at least one bite of fish associated with a documented outbreak developed symptoms of ciguatera. [9]

The main pharmacologic action of ciguatoxin is an increase in cell permeability to sodium, causing sustained depolarization. This change can be antagonized by large doses of calcium. The toxin has been shown to inhibit red cell cholinesterase in vitro. [10] Its mechanism of action in man is not only dependent on anticholinesterase activity, but also in part to a transmitter-like cholinomimetic action. [11]

Ciguatera poisoning is endemic in islands of the Pacific where a 43% annual incidence was found during one household study. [12] Florida and Hawaii are the states with the highest incidence. In an analysis of 129 cases reported to the Dade County (Miami) Department of Public Health from 1974 to 1976, [9] the estimated incidence of the disease was 5 cases per 10,000 residents. Ciguatera poisoning accounts for more than half of all foodborne outbreaks related to fish in the United States. [13] More than 600 people in the Hawaiian islands have reported contracting ciguatera during the years 1900 to 1980. [14] Although mortality rates as high as 20% have been reported,[15] no deaths occurred in the 184 cases reported to the Centers for Disease Control between 1970 and 1974 [16] or among 129 cases reported in Dade County, Florida between 1974 and 1976. Isolated outbreaks in non-endemic areas, such as Maryland, North Carolina and Vermont, have been reported. These are usually attributed to importation of fish, recent travel to endemic areas or by migration of fish from endemic areas. [17]

The symptoms of ciguatera are various and complex, with over 175 manifestations.[5] Diagnosis is based largely on the clinical manifestations. Poisoning is usually characterized by gastrointestinal symptoms (abdominal cramps, nausea, vomiting, diarrhea) appearing within one to 6 hours after ingestion. Numbness of the lips, tongue and throat, paresthesias, blurred vision, hypotension, bradycardia and itching have been reported; reversal of hot and cold sensations (the feeling of heat when in contact with cold, or vice versa) is often diagnostic. Coma is unusual, but has been reported, which suggests possible confounding factors such as co-ingestion of alcohol or non-seafood related toxins, or genetic susceptibility to a more severe response to ciguatera toxin. [17] In severe cases shock, muscular paralysis and death may occur. Recovery is often prolonged. The gastrointestinal symptoms usually subside within 24 hours, but muscular weakness and numbness may persist for weeks to months. Repeated episodes may be more severe.[2]

Several case reports of ciguatera poisoning during pregnancy have been published reporting fetal symptoms beginning simultaneously with the mother's symptoms. These consisted of tumultuous fetal movements and an intermittent, peculiar fetal shivering. None of the liveborn infants appeared to have lasting effects from exposure ot the toxin (one fetus was aborted during the acute phase of the poisoning), although, this could not be ruled out in one infant exposed shortly before birth. Ciguatera is also, apparently, excreted in breast milk, and gastrointestinal problems and pruritic symptoms have been reported in infants whose mothers continue to nurse during their illness. Cessation of breastfeeding appears to resolve the problem. [18]

There is no antidote for ciguatera poisoning, and therapy is symptomatic. Although emesis and gastric lavage have been recommended if vomiting has not occurred, 16 up to 30 hours may have elapsed before the first signs of intoxication appear, and these maneuvers may be fruitless. A cathartic may be used to remove toxin from the lower gastrointestinal tract. Since calcium is a competitive inhibitor of ciguatoxin, infusions of calcium salts have been reported to be beneficial. [19] Other therapeutic agents have included atropine, neostigmine (*Prostigmin*), steroids, *Protopam* (pralidoxime Cl), vitamins B_{12} and C, antihistamines, amitriptyline (eg, *Elavil*), morphine and mannitol (*Osmitrol*).[20,21,22]

Immune sensitization is a major feature of ciguatera and can lead to substantial hypotension; sensitization can make responses to subsequent ingestions more serious. Hypotension can be a particular problem for patients who have been treated with opiates, which are cyclic ether histamine releasers. A "ciguatera diet" has been proposed that is high in protein, carbohydrates and vitamins and allows no fish or fish products, shellfish or shellfish products, seeds, nuts, mayonnaise or alcohol. The diet also specifies avoidance of marijuana, opiates, barbiturates, solvents, herbicides, cosmetics and other substances, as a means of reducing the potential effects of sensitization.[5]

DETECTION: Ciguatoxic fish appear normal in all ways including the smell and taste of the flesh. The detection of ciguatoxic fish has been based largely on unsubstantiated and erroneous rules of thumb such as: A lone fish separated from the rest of the school should not be touched; if ants are repelled by a fish, or a turtle refuses to eat it, it is probably unsafe for humans; if a thin slice of the fish does not show a "rainbow effect" when held up to the sunlight, it is inedible; a silver spoon will tarnish if placed in the cooking pot with a toxic fish. [23] There are no distinguishing routine laboratory features of ciguatera toxin, however, testing of the toxin source is available in some endemic areas. The stick enzyme immunoassay provides promise as a simple widespread test for clinical laboratories and the fishing industry. Other tests include the mouse intraperitoneal injection and radioimmunoassay (RIA) and guinea pig atrium assay. [17,24] RIA has been used to screen amberjack in Hawaii,[25] but this method is time consuming. An electrophoretic technique to evaluate potentially toxic fish has been described but requires further evaluation.[26]

TOXICOLOGY

CIGUATERA POISONING: Vertebrate fish containing toxins capable of causing human illness can be divided into three major groups based on the location of the toxin. Ichthyosarcotoxic fish (hagfish, lamprey, puffer, snapper, barracuda) contain toxin in their musculature, viscera, skin or mucus, and are responsible for most fish poisonings. Ichthyo-ootoxic fish contain toxins in their gonads, and ichthyohemotoxic species contain toxins in their blood. The most frequently implicated ichthyosarcotoxism is ciguatera.[1] Ciguatera poisoning is on the increase because of a recurrence of it in normally edible fish, the sporadic and unpredictable nature of

the toxicity and the increased demand for seafood worldwide.[2]

SUMMARY: Although a common source of fish-induced poisoning, ciguatera is little known by the general public and poorly understood by health practitioners. The ingestion of large reef fish, especially snappers, jacks, parrotfish and barracuda, is associated with this illness, and consumption of these fish by natives and tourists in areas of recent reef disturbances should be avoided.

PATIENT INFORMATION — Ciguatera

Uses: None.

Side Effects: Ciguatera is a toxin which sometimes contaminates reef fish. Symptoms may be delayed up to 30 hours. Sensitization can render subsequent ingestion far more dangerous.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CIGUATERA

CINNAMON

DATE OF ISSUE: DEC 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Cinnamomum* spp.

COMMON NAME(S): Cinnamon, cinnamomon, ceylon

BOTANY: The plant form of cinnamon consists of short, oval-lanceolate, rough-textured leaves up to 20 cm in length. The food additive form is a brown bark that forms quills and longitudinal striations. Cinnamon bark is also found in ground form as a spice. [1] The plant is native to Sri Lanka, southeastern India, Indonesia, South America and the West Indies.[2]

HISTORY: Cinnamon is primarily used as a spice, taste enhancer or aromatic. Historically, its drop-like oil ("Cinnamon drops") has been used to treat gastrointestinal upset and dysmenorrhea. The essential oil derived from the plant has also been used for its antagonist activities against various microorganisms and fungi.[1]

CHEMISTRY: The primary constituents of the essential oil are 65-80% cinnamaldehyde and lesser percentages of various other phenols and terpenes, [2] including eugenol, *trans* -cinnamic acid, hydroxycinnamaldehyde, *o*-methoxycinnamaldehyde, cinnamyl alcohol and its acetate, limonene, a-terpineol, tannins, mucilage, oligomeric procyanidins and trace amounts of coumarin.[1]

PHARMACOLOGY: Water and ether extract of *Cinnamomum cassia*have shown antidiarrheic effects in laboratory mice. Choleretic and analgesic effects have been seen in anesthetized laboratory rats. These effects are possibly due to the "warming" and analgesic effects of the stomach and spleen. [3] *Cinnamomum cassia* has also been shown to increase the levels of atrial natriuretic factor (ANF) in the plasma of mice during an experiment studying the action of pharmaceutically (with Wu Lin powder, WLP) increased urination. [4]

The essential oils of cinnamon were shown to halt mycelial growth and aflatoxin synthesis in Aspergillus parasiticus at a concentration of only 0.1%. The essential oils also displayed high activity against aflatoxino-genesis.

TOXICOLOGY: Human consumption of large quantities of cinnamon bark or moderate quantities of cinnamon oil has been shown to increase heart rate, intestinal movement, breathing and perspiration via a chemical stimulation of the vasomotor center. This state of accelerated body function is followed by a period of centralized sedation which includes sleepiness or depression. [1]

Skin irritation and pruritus have been found after repeated contact with cinnamon powder. (Most of these outbreaks being observed at spice factoreis where contact is exceptionally high.) Further skin cell irritation has been observed in oral leukoplakic lesions caused by allergic reactions to the cinnamon component of chewing gum.

SUMMARY: Cinnamon has been in use for centuries, with references in ancient Greek and Latin writings, both as a spice and as a "folk medicine" for gastrointestinal disorders. The essential oil has displayed antidiarrheic, analgesic and germicidal properties. High contact with cinnamon powder has caused dermatitis.

PATIENT INFORMATION — Cinnamon

Uses: Cinnamon is used as a spice and aromatic. The bark or oil has been used to combat microorganisms, diarrhea and other GI disorders, dysmennorhea, etc.

Side Effects: Heavy exposure may cause skin irritation and allergic reactions. Ingestion of larger than usual amounts may accelerate and then depress body function.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
      CINNAMON

CITRONELLA OIL

DATE OF ISSUE: FEB 2003

REPLACES MONOGRAPH DATED: OCT 1991

SCIENTIFIC NAME(S): *Cymbopogon nardus* L. *Rendle* and *C. winterianus Jowitt*. Sometimes referred to as *Andropogon nardus* L. Family: Gramineae

COMMON NAME(S): Citronella oil, Ceylon oil, citronella

BOTANY: *C. nardus* (Ceylon citronella) and *C. winterianus* (Java citronella) are both perennial grasses. These 2 species are distinguished from each other by different leaf morphologies and chemical composition.[1] This plant should not be confused with the citrosa plant, *Pelargonium citrosa*, introduced into North America as a biological repellent against mosquitoes.[2] Citronella's essential oils are obtained by steam distillation of the fresh or dried grass. The Java-type oil generally is considered to be of superior quality to the Ceylon oil.[3]

HISTORY: Citronella oil has been used as a flavoring for foods and beverages in very low quantities (approximately 45 ppm).[3] In traditional medicine, the oil has been used as an aromatic tea, vermifuge, diuretic, and antispasmodic.[3] Perhaps the most widely recognized use for the oil is as an insect repellent. It is sometimes incorporated into perfumes and soaps.[4]

CHEMISTRY: Citronella oil contains a number of fragrant fractions of which citronellal, geraniol, and citronellol are the major components.[3,5] Gas chromatographic analysis of the Ceylon variety indicates that the oil contains large amounts of monoterpenes (approximately 27%), as opposed to the Java variety, which contains only 1% to 3%, mostly in the form of limonene.[1] Both types contain comparable amounts of geraniol (18% to 21%). The Java oil is superior to the Ceylon type; the Java variety contains 15.9% citronellol and 32.7% citronellal, whereas the Ceylon type contains only 8.4% and 5.2%, respectively.[1] The chemical composition of essential oil can vary tremendously. Other compounds predominant in citronella oil include citronellyl acetate, ß bourbonene, geranyl acetate, elemol, L-borneol, and nerol.[1,6,7] A geraniol-rich mutant of citronella has been developed; it is reported to have a geraniol content as high as 60%.[8] The wild Ceylon variety (commonly called mana grass) has a chemical profile very different from the 2 cultivated types.[1]

Fractional distillation of Ceylon citronella yielded 13 fractions that were tested against mosquito larvae. Monoterpene fractions containing mycrene were very lethal to late third instar *Culex quinquefasciatus* larvae.[9] Elemol and methyl iso-eugenol were responsible for larvacidal activity in other fractions.[9]

PHARMACOLOGY: Citronella oil has been found to have in vitro antibacterial activity against gram-positive organisms.[3] The essential oil also displays antifungal activity.[10]

TOXICOLOGY: Animal toxicity studies have shown that citronella oil has an LD_{50} in mice of 4600 mg/kg and in rats of 7200 mg/kg. A dose of 1 to 4 mL/kg given by stomach tube in rabbits caused paralysis, coma, and death. At least 1 case of death has been reported in a child who ingested an unknown quantity of citronella oil. A review of 5 cases of childhood citronella oil poisoning suggests that dilution of the oil following ingestion may be sufficient to treat most cases of ingestion and that emesis may be induced with a relatively low risk of major pulmonary complications. If spontaneous vomiting has occurred, observation for respiratory symptoms is required.[10]

Citronella oil has been reported to cause contact dermatitis in humans.[3]

SUMMARY: Citronella oil commonly is used as an insect repellent and also has been used in foods, cosmetics, and toiletries. As with any volatile oil, ingestion of the product poses a toxicologic problem that in rare cases may lead to severe toxicity and death.

PATIENT INFORMATION — Citronella Oil

Uses: Citronella oil is used in small amounts to flavor foods, scent cosmetics, and repel insects. It has been used in aromatic tea as a vermifuge, diuretic, and antispasmodic although no clinical trials have been performed.

Side Effects: Citronella oil may cause contact dermatitis. Ingestion may be fatal in some cases.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CITRONELLA OIL

CLEMATIS

DATE OF ISSUE: OCT 1996

REPLACES MONOGRAPH DATED: MAR 1996

SCIENTIFIC NAME(S): *Clematis virginiana* L. Family: Ranunculaceae

COMMON NAME(S): Clematis, devil's-darning-needle, old-man's beard, traveler's-joy, vine bower, virgin's bower, woodbine

BOTANY: Clematis is a genus of mostly climbing perennial shrubs in the buttercup family and has over 200 species worldwide, mainly in North America and Asia. Several species are cultivated in North America for their beautiful flowers. The common species include: Woodbine (*C. virginiana*), virgin's bower (*C. cirrhosa*), old-man's beard (*C. vitalba*) and vine bower (*C. viticella*).

C. virginiana is a trailing vine which can grow up to 50 feet higher than other botanicals, often resulting in a bower or shaded shelter. The long, feathery, beard-like tail on the fruit led to the synonym, old-man's beard. This species is a North American native plant which was once in the continental pharmacopeia as a medicine.

Its habitat is in thickets, roadsides, woods and stream banks. It may be found from Manitoba to Quebec, as far south as Alabama and Louisiana, and west all the way to Kansas. The vine has leaves which are divided into three oval and toothed leaflets, each of which are on a long stalk. These stalks are like tendrils which aid in its climbing habit. From July to September, it displays creamy white flowers which bloom into large clusters; these become fruit heads with long plume-like tails. [1,2]

Other related species in the genus include: *C. dioica* from tropical America,[3] *C. recta* (*C. erecta*) of Southern Europe,[4] *C. vitalba*of Eurasian and North African origin,[4] *C. chinensis* (Wei Ling Xian) of Chinese origin[5] and *C. thunbergii* from Senegal.[3]

HISTORY: The popular use of *C. virginiana*in pioneer medicine was probably learned from the Native Americans. It was a common remedy for skin disorders (sores, cuts), itching and venereal eruptions.[1] Throughout history, the leaf of the plant was used in folk remedies for treating cancers and tumors, as well as for itching, fever, renosis, nephrosis, ulcers and scrofula.[2] Past uses also report diuretic, poisonous, rubefacient, sudorific, purgative and vesicant properties. Clematis has long been cultivated as a woody climbing or trailing vine for growing over a fence or wherever dense foliage is desired. Others have mentioned using the fuzzy seed mass for smoking and utilizing the young shoots of a Eurasian variety (*C. taurica*) in cooking.

CHEMISTRY: Early literature reports extraction of alkaloidal, glycosidal and saponic fractions from certain species. [6] Members of Ranunculaceae contain protoanemonin, an irritant compound found mostly in the fresh leaves and sap; this is derived from a precursor glycoside known as ranunculin. [7] Some report the same principles for *C. vialba*, as well as: Anemonin; caulosaponin; caulosapogenin; stigmasterol glycoside; ceryl alcohol; myricylalcohol; beta-siterosterol; trimethylamine; beheinc-, caffeic-, choregenic- and melissic-acid; n-triacontane; n-nonacosane; ginnone; ginnol; and campesterol. [2] The dried seeds contain about 15% protein and 14% fat.

More recent reports identified anemonin (the dilactone of cyclobutane-1,2-diol-1,2 diacrylic acid derived from the cyclodimerization of protoanemonin) in *C. hirsutissima*,[8] a new oleanic saponin named clemontanoside B from *C. montana* leaves,[9] two saponins named hushangoside and hederagenin glycoside from the stems of *C. montana*,[10] other saponins from *Clematis*species,[11] clemontanoside F from the roots of *C. montana*,[12] and two triterpenoid saponins named clematichineno-side A and B from the roots of *C. chinensis*.[13] The major components of the essential oil of *C. hexapetala* are palmitic acid and 3-hydroxy-4-methoxyl benzaldehyde.[14]

PHARMACOLOGY: Modern herbalists cite the older uses of *C. virginiana* as a treatment for skin disorders, but caution that the juice is a powerful irritant. [1] Generally, all of the historic uses stated above have not been verified in modern studies. Among the more recent verified pharmacological effects are: the CNS stimulant properties of anemonin in horses;[8] the CNS activity of clemontanoside B from C. montana in mice;[9] the androgenic effects (in mice) of *C. fusca* Turcz. preparations;[15] the anti-inflammatory activity of the Chinese medicine "Wei Ling Xian" (*C. chinensis* and related species);[16] and the cardiovascular and hypotensive action,[17] the hepatic protective[18] and the biliary tract effects of *C. chinensis.*[19]

TOXICOLOGY: A recent poisonous plant reference focused on those buttercup species which contained protoanemonin in the fresh leaves and sap (including Clematis). When the plants were handled or eaten, protoanemonin irritated and blistered the skin. Intense inflammation and burning around the mouth and digestive tract followed oral ingestion. Other side effects associated with oral intake included: Profuse salivation, blistering, inflamed eyes, abdominal cramping, vomiting of blood, weakness and bloody diarrhea.[7] Kidneys may also be irritated, resulting in painful and excessive urination and bloody urine, ultimately leading to diminished urinary output. Poisoning symptoms also include: Dizziness, confusion, possible fainting and convulsions.

Fatalities are not common, probably due to the rapid and intense acrid taste and irritation resulting from oral contact. If a large amount has been ingested accidentally, gastric lavage is recommended, followed by demulcents to soothe irritated membranes. Fortunately, the protoanemonin is present mainly in fresh plant material and cooking or drying should result in its decomposition.

SUMMARY: While there is considerable older literature on the use of Clematis for a wide variety of skin and other disorders, the human and animal toxicological experiences preclude recommending it for any of these purposes. Recent Asian studies hint at the presence of numerous active principles possessing CNS activity, anti-inflammatory effects, cardiovascular and hypotensive properties; however, none of these have been developed to the point where they have proven clinical value. Currently, the Chinese are clinically evaluating *Clematis chinensis* as one of their traditional medicines.

PATIENT INFORMATION — Clematis

Uses: Primarily used for skin disorders. In animals, it has caused CNS stimulant, androgenic, anti-inflammatory, cardiovascular, hypotensive and hepatic effects.

Side Effects:
Topical: Can cause skin irritation.

Oral: Notify physician if painful or bloody urine occurs. Profuse salivation, blistering, inflamed eyes, abdominal cramping, vomiting of blood, weakness, bloody diarrhea, and painful, excessive or bloody urine.

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "C" MONOGRAPHS
  CLEMATIS

CLOVE

DATE OF ISSUE: SEP 1997

REPLACES MONOGRAPH DATED: JUN 1996

SCIENTIFIC NAME(S): *Eugenia caryophyllata* Thunb. also described as *Caryophyllus aromaticus* L. and *Syzygium aromaticum* L. Merr. and Perry. Family: Myrtaceae

COMMON NAME(S): Clove, caryophyllus

BOTANY: The clove plant grows in warm climates and is cultivated commercially in Tanzania, Sumatra, the Molucca Islands and South America. The plant, a tall evergreen, grows up to 20 meters tall and has leathery leaves. The clove spice is the dried flower bud. Essential oils are obtained from the buds, stems and leaves. The dark brown buds are 12 to 22 mm in length with four projecting calyx lobes. The four petals above the lobes fold over to form a hood, which hides numerous stamens. The cloves are strongly aromatic.[1]

HISTORY: Cloves have a long history of culinary and medicinal use. The oil was used as an expectorant and antiemetic with inconsistent clinical results. Clove tea was used to relieve nausea. The use of the oil in dentistry as an analgesic and local antiseptic continues today. The oil has been used topically as a counterirritant.

CHEMISTRY: Clove buds yield approximately 15% to 20% of a volatile oil that is responsible for the characteristic smell and flavor. The stems yield about 5% of the oil and the leaves about 2%. In addition, the bud contains a tannin complex, a gum and resin and a number of glucosides of sterols. The principal constituent of distilled clove bud oil (60% to 90%) is eugenol (4-allyl-2-methoxyphenol). The oil also contains about 10% acetyleugenol and small quantities of gallic acid, [2] sesquiterpenes,[3] furfural, vanillin and methyl-n-amyl ketone.[4] Other constituents include flavonoids,[1] carbohydrates, lipids, oleanolic acid, rhamnetin and vitamins.[5]

PHARMACOLOGY: Clove oil has antihistaminic and spasmolytic properties, most likely because of the presence of eugenyl acetate.[6] Cloves have a positive effect on healing stomach ulcers.[1] A 15% tincture of cloves has been shown to be effective in treating topical ringworm infections. As with many other volatile oils, clove oil has been found to inhibit gram-positive and gram-negative bacteria. Its fungistatic action has been documented, suggesting use as an antidermatophytic drug.[7] Clove oil also has anthelmintic and larvicidal properties. Another report suggests clove oil suppresses aflatoxin production.[8] Sesquiterpenes from cloves show potential as anticarcinogenic agents.[9] Similarly, eugenol present in clove oil may ameliorate effects of environmental food mutagens.[10] Whole cloves were chemoprotective against liver and bone marrow toxicity in mice.[11] Eugenol in high concentrations can inhibit reactive oxygen species generated by macrophages during inflammation.[12] Eugenol has also been found to possess marked antipyretic activity in animals, similar to the activity of acetaminophen.[13]

Aqueous extracts of clove increase trypsin activity. Eugenol inhibits prostaglandin biosynthesis, the formation of thromboxane B2, and arachidonic acid-induced platelet aggregation in vitro. This effect has been postulated to contribute to the antidiarrheal effect of other oils that contain eugenol (such as nutmeg oil).[14] Other reports also confirm inhibition of platelet aggregation and antithrombotic activity of clove oil.[15,16]

Clove oil is applied for the symptomatic treatment of toothaches and is used for the treatment of dry socket (post-extraction alveolitis). Recent studies indicate that newer techniques, such as the application of collagen paste, may be more effective than clove oil/zinc oxide preparations in the management of alveolitis.[17]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Cloves and clove oils are used safely in foods, beverages and toothpastes. In general, the level of clove used in foods does not exceed 0.236%; the oil is not used in amounts greater than 0.06%. Toxicity has been observed following ingestion of the oil, but this type of poisoning is rare and poorly documented. In rats, the oral LD-50 of eugenol is 2680 mg/kg; however, the toxicity of the compound increases almost 200-fold when administered by the intratracheal route (LD-50 11 mg/kg).[18] This increase in toxicity by the pulmonary route has become more important in light of the toxicity reported among persons who have smoked clove cigarettes. Clove cigarettes, called "kreteks," generally contain about 60% tobacco and 40% ground cloves. More than a dozen brands of kreteks exist, and they enjoy some popularity in Asian countries. This popularity is growing in the US and Europe.

More than a dozen cases of pulmonary toxicity have been reported in people who have smoked clove cigarettes.[19,20] There is evidence that clove cigarettes may anesthetize the throat, leading to deeper and more prolonged inhalation of the smoke. Blood-tinged sputum and hemoptysis have been noted in smokers and may be related to eugenol's antiplatelet effects.[14] The American Lung Association has issued a warning against clove cigarette use, noting that they can have a higher tar content than ordinary cigarettes. One study, however, found no carcinogenic effect of hot aqueous clove extracts in the *Drosophila* mutagenicity assay, although metabolites and pyrolysis products of eugenol are carcinogenic.[21]

Clove oil can be a skin and mucous membrane irritant and sensitizer.[5] A case of a 24-year-old woman reports permanent local anesthesia and anhidrosis following clove oil spillage into the facial area.[22] Other case reports exist, including treatment of a 2-year-old child suffering from disseminated intravascular coagulation and liver failure following clove oil ingestion,[23] and development of depression and electrolyte imbalance in a 7-month-old child after accidental oral ingestion of clove oil.[24]

There has been no documentation of toxicity in the bud, leaf or stem of the plant.[5]

SUMMARY: Cloves are used as a common condiment and have found favor in most regional cuisines. Clove extracts and oil have been used medicinally for their antiseptic and analgesic effects. Cloves have also been studied for use in platelet aggregation inhibition, anti-thrombotic activity and chemoprotective and antipyretic effects. Toxicity from clove oil can occur by inhalation of smoke from clove cigarettes or by ingestion of large amounts of the oil.

PATIENT INFORMATION — Clove

Uses: Cloves have been used for their antiseptic and analgesic effects and have been studied for use in platelet aggregation inhibition, antithrombotic activity and chemoprotective and antipyretic effects.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Blood-tinged sputum and hemoptysis have been noted in clove cigarette smokers. Clove oil can irritate skin and mucous membranes.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CLOVE

COCOA

DATE OF ISSUE: MAY 2002

REPLACES MONOGRAPH DATED: JAN 1992

SCIENTIFIC NAME(S): *Theobroma cacao* L. subspecies *cacao*. Family: Sterculiaceae or Byttneriaceae

COMMON NAME(S): Theobroma, cacao. Compounds derived from this product include cocoa, chocolate, and cocoa butter.

BOTANY: The cocoa tree grows to heights exceeding 8 meters. The fruits are berry-like and are borne on the trunk and branches with the seeds imbedded in a sticky pulp. The fruits are large and football shaped, and the seeds are the size of a quarter. The seeds are referred to as cocoa beans. Cacao is often used to describe the crude material, while cocoa is used to describe the processed products. Although several varieties of cacao exist, the forastero variety from West Africa accounts for more than 90% of world production.[1]

HISTORY: Cortez described the preparation and use of a beverage called chocalatl, based on the seeds of *T. cacao*, among the members of the Aztec court. The Mayan word cacaoentered scientific nomenclature in 1753 and the words theo broma are Latinized Greek; theo is "god" and broma is "nectar" or "food." In the 1600s it was argued that chocolate should be called a medicine because it changed a patient's health. At that time, physicians also stated that all that was necessary for breakfast was chocolate as it yielded good nourishment for the body.[2]

Cacahuatl (cacao) beans, resembling the almond, have been used for commerce. Chacah (medicinal chocolate) mixed with 2 peppers, honey, and tobacco juice has been ingested to treat a variety of illnesses, such as skin eruptions, fever, and seizures.[2]

The 3 main commercial products obtained from cacao seeds are cocoa powder, cocoa butter, and cocoa extracts. Following curing and fermentation, the beans are dried and roasted to yield the desired flavor, color, and aroma.

CHEMISTRY: The nib, which contains about 55% cocoa butter, is ground into a liquid mass called chocolate liquor, from which the butter is removed by hydraulic pressing. The remaining cocoa cake is dried and ground to a fine powder to yield cocoa powder with a fat content of 22% or more. Specially treated cocoa powder, called alkalinized cocoa, is considered to have improved color, flavor, and dispersability over unalkalinized powder. Cocoa butter (also known as theobroma oil) may have a faint chocolate odor that may be removed following further purification. Cocoa contains more than 300 volatile compounds. The important flavor components are aliphatic esters, polyphenols, aromatic carbonyls, and theobromine.[1] These phenolics also prevent the rancidity of the fat in chocolate.[3]

Cocoa contains the alkaloids theobromine (0.5% to 2.7%), caffeine (approximately 0.25% in cocoa), trigonelline, and others.[1,4] A standard chocolate bar (40 to 50 g) contains theobromine (86 to 240 mg) and caffeine (9 to 31 mg).[5] The characteristic bitter taste of cocoa is because of the reaction of diketopiperazines with theobromine during roasting. Theobromine is produced commercially from cocoa husks.[1]

Cocoa butter contains triglycerides consisting mainly of oleic, stearic, and palmitic acids. About 75% of the fats are present as monounsaturates.[1] Cocoa butter has a high digestibility, similar to that of corn oil, with a digestible energy value of approximately 37 kJ/g in humans; therefore, it cannot be considered low-calorie.[6] However, one randomized trial demonstrated that supplementation of chocolate with 0.9% calcium (0.9 g/day) reduced the absorption of cocoa butter, thus reducing the digestible energy value.[7]

A substantial amount of polyphenols are in the form of procyanidin (ie, epicatechin and catechin) oligomers.[8,9,10,11,12] Epicatechin has been shown to scavenge free radicals and to inhibit lipid peroxidation.[13,14]

PHARMACOLOGY

Theobromine: Theobromine, the primary alkaloid in cocoa, has activity similar to that of caffeine (ie, increases in energy, motivation to work, and alertness).[5] It is a weak CNS stimulant, with only one-tenth the cardiac effects of other methylxanthines (eg, caffeine, theophylline).[15,16]

Theobromine, when ingested in the form of a large chocolate bar, did not cause any acute hemodynamic or electrophysiologic changes in the hearts of young, healthy adults when results from echocardiographic data were obtained.[16] Theobromine pharmacokinetics were found to be similar after administration in healthy males when measured after 14 days of abstention from all methylxanthines and then after 1 week ingestion of high levels of theobromine (6 mg/kg/day) in the form of dark chocolate.[17] However, the results of these studies cannot be extrapolated to patients with any condition(s) or disease(s), nor to the effects of chronic chocolate consumption.

Magnesium: The magnesium contained in cocoa has been shown, in rats, to prevent and correct chronic magnesium deficiency.[18,19] Low intakes of magnesium may be responsible for some cardiovascular alterations and renal, GI, neurological, and muscular disorders.[18,19] The use of cocoa to treat or prevent magnesium deficiency in humans has yet to be explored.

Cocoa products: Cocoa products are used extensively in the food and pharmaceutical industries. Cocoa powder and syrup are used as flavorings. Cocoa powder and butter are important components of chocolate, where they are mixed with chocolate liquor (ground cacao nibs), sugar, milk, and other flavors.

Cocoa butter: Cocoa butter is used as a suppository and ointment base, as an emollient, and as an ingredient in various topical cosmetic preparations.[20] Cocoa butter suppositories have been used since the early 1900s to relieve hemorrhoids, and as an ointment applied to the breasts of nursing women.[2]

Cocoa butter has a higher content of stearic acid than any other fat, and has been useful for studying the effects of this saturated fatty acid on cholesterol. Substitution of a milk chocolate bar for a high-carbohydrate snack in healthy young men on a blood cholesterol-lowering diet (eg, National Cholesterol Education Program [NCEP]/American Heart Association [AHA] Step 1 Diet) did not adversely affect the low-density lipoproteins (LDL)-cholesterol and increased high-density lipoprotein (HDL)-cholesterol levels.[21,22]

Cocoa butter has been reported to be a source of natural antioxidants.[1] This antioxidant activity has been attributed to the oligomeric flavonoids known as procyanidins. It has been reported that the polyphenols in cocoa are similar to the phenol in red wine, which has been shown to inhibit the oxidation of LDL. Thus, it has been shown that dark chocolate and cocoa inhibit LDL oxidation and increase HDL-cholesterol concentrations, thereby potentially decreasing the risk of cardiovascular disease.[23,24,25] However, the relation between chocolate consumption and risk of coronary heart disease remains controversial.[26,27]

Procyanidins: The procyanidins contained in chocolate have shown platelet inhibition by suppressing epinephrine-induced platelet activation.[28] A study in rabbits also has shown that the procyanidins cause endothelium-dependent relaxation by activating endothelial nitric oxide synthase.[29]

Potential immune modulator effects of cocoa procyanidins by inhibiting cytokine transcription have been demonstrated. Therapeutic effects have not been studied.[30]

Other findings: An interesting use of chocolate as an inhaler has been studied. This edible inhaler, the *Chocuhaler*, was shown to produce a clinical effect when used to administer albuterol.[31]

A study in which a depressive mood was induced demonstrated a correlation with an increase in chocolate craving. It has been demonstrated that thoughts of chocolate are overpowering and prey on the mind. Questionnaires filled out by study subjects have shown that there is a weakness for chocolate in individuals who are under emotional stress, bored, upset, or feeling down.[32] A study that followed changes in brain activity related to eating chocolate demonstrated that one area of the brain is involved when there is motivation or craving to eat chocolate, while another area is involved when the desire to eat chocolate is decreased or becomes unpleasant. A similar result also has been shown with cocaine craving. Studies are needed to test the importance of this activity related to eating disorders and obesity.[33]

Researchers at the Neurosciences Institute in La Jolla, CA, have found 3 substances in dark chocolate and cocoa powder that could act as cannabinoid mimics either directly (by activating cannabinoid receptors) or indirectly (by increasing anandamide levels).[34,35,36]

TOXICOLOGY: Although cacao is not considered to be toxic in typical confectionery doses, at least 1 report of animal toxicity has been published. A dog that ate 1 kg of chocolate chips suffered hyperexcitability and convulsions, and collapsed and died, most likely because of acute circulatory failure secondary to theobromine/caffeine toxicity.[37]

Caffeine from the ingestion of large amounts of chocolate, along with 2 to 4 caffeinated beverages, was shown to be correlated with the appearance of tics in 2 children.[38]

Cocoa butter may be allergenic and have comedogenic properties in animals.

The plant has been reported to contain small amounts of safrole, a carcinogen banned by the FDA.[39]

Patients diagnosed with irritable bowel syndrome who experience reflux esophageal symptoms should eliminate from their diet foods that decrease lower esophageal sphincter pressure, such as chocolate and cocoa-containing products.[40]

Cocoa has caused occupational asthma in patients working in a confectionery factory.[41] A high prevalence of chronic respiratory symptoms has also been recorded in workers exposed to cocoa.[42]

Conflicting results were demonstrated when chocolate was tested as an initiator of migraine headaches. Phenolic flavonoids, which are present in red wine and chocolate, may have a role in precipitating a migraine headache.[43,44,45]

SUMMARY: Products derived from *T. cacao* are used in a variety of food and cosmetic applications, including flavorings and pharmaceutical bases. Potential use of cocoa or chocolate as antioxidants to decrease cholesterol lipoproteins and decrease risk of coronary heart disease needs to be clarified. Although toxicity has been reported, probably from the theobromine and caffeine components, cocoa is generally nontoxic. Conflicting results have been found when chocolate was tested as an initiator of migraine headaches.

PATIENT INFORMATION — Cocoa

Uses: Cocoa products are used in foods and cosmetics. The primary alkaloid has activity similar to caffeine. Ingestion of chocolate, when following a low-cholesterol diet, is being investigated to determine the effect on cholesterol levels.

Side Effects: Cocoa usually is nontoxic; however, children consuming large amounts of chocolate and caffeinated beverages may exhibit tics or restlessness. Patients with irritable bowel syndrome should omit cocoa products from their diet. Large amounts of cocoa products may be fatal to pets. Ingredients in chocolate may precipitate migraine headaches.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    COCOA

COLTSFOOT

DATE OF ISSUE: JAN 1999

REPLACES MONOGRAPH DATED: JUN 1996

SCIENTIFIC NAME(S): *Tussilago farfara* (L. Family: Compositae)

COMMON NAME(S): Coltsfoot, coughwort, feuilles de tussilage (Fr.), horse-hoof, huflattichblatter (Ger.), kuandong hua

BOTANY: Coltsfoot is a low-growing perennial (up to 30 cm high) with fleshy, woolly leaves. In early spring, the plant produces a stem with a single golden-yellow, narrow, ligulate flower head that blooms from April to June. As the stem dies, the hoof-shaped leaves appear. The plant is native to Europe, but also grows widely in sandy places throughout the United States and Canada.[1] Coltsfoot is collected widely from wild plants in the Balkans, Eastern Europe (Bulgaria, Czechoslovakia, Hungary, Poland, the former Yugoslavia), and Italy.[2] It has also been a part of Chinese folk medicine for centuries. The morphology and anatomy of coltsfoot have been described in detail, including the plant's underground parts.[3] A later report on leaf differentiation is also available.[4]

HISTORY: As part of its Latin name Tussilago implies, coltsfoot is reputed as an antitussive.[5] The buds, flowers, and leaves of coltsfoot have long been used in traditional medicine for dry cough and throat irritation. The plant has found particular use in Chinese herbal medicine for the treatment of respiratory diseases, including cough, asthma, and acute and chronic bronchitis. It is also a component of numerous European commercial herbal preparations for the treatment of respiratory disorders. A mixture containing coltsfoot has been smoked for the management of coughs and wheezes, but the smoke is potentially irritating. Its silky seeds were once used as a stuffing for mattresses and pillows.[6] Extracts of coltsfoot had once been used as flavorings for candies. All early references emphasize the usefulness of coltsfoot's mucilage for soothing throat and mouth irritation.[2]

CHEMISTRY: Coltsfoot contains a number of diverse components including tannins, a mucilage, terpene alcohols, carotenoids, and flavonoids.[7] The mucilage is present in a concentration of about 8%. It yields sugars following hydrolysis including arabinose, fructose, galactose, glucose, and others.[8] Water-soluble polysaccharides from coltsfoot leaves have been reported.[9,10] Mucilaginous polysacchrides have been investigated in another report.[11] Tussilagone, a sesquiterpene, has been isolated from ether extracts of the plant. It is a potent cardiovascular and respiratory stimulant.[12]
BR>Acids found in coltsfoot include caffeic, caffeoyltartaric, ferulic, gallic, p-hydroxybenzoic, tannic, malic, and tartaric.[8]

Farfaratin, a novel sesquiterpenoid compound, has been isolated from flower buds collected from the Shaanxi Province in China.[13] At least 7 pyrrolizidine alkaloids,[14] including tussilagin,[15] senkirkine,[16] and senecionine[6] have been identified in coltsfoot. Coltsfoot leaves contain 2.8 to 4.1 ppm and the flowers 2.4 ppm senkirkine.[17] Quantitative gas chromatographical analyses of pyrrolizidine alkaloids have been performed for various commercial coltsfoot preparations.[18]

Other constituents in coltsfoot include choline, paraffin, phytosterols, amyrin, and volatile oil.[6,8] A recent report reviews chemistry and other aspects of the plant.[19]

PHARMACOLOGY: Coltsfoot preparations have long been used to soothe sore throats. The mucilage is most likely responsible for the demulcent effect of the plant. The mucilage is destroyed by burning; smoking the plant or inhaling vapors of the leaves steeped in water would not be expected to provide any degree of symptomatic relief. Instead, the smoke may exacerbate existing respiratory conditions. However, one source mentions coltsfoot in the form of a medicinal cigarette to help relieve asthma.[20] Coltsfoot components have been found to increase the cilia activity in the frog esophagus, and this action may contribute to the plant's expectorant effect.[21] Related conditions for which coltsfoot has been used include bronchitis, laryngitis, pertussis, influenza, and lung congestion.[5,6,8] It is one of the most popular European remedies to treat chest ailments.[20] Coltsfoot, in a mixture of Chinese herbs, has been evaluated in 66 cases of convalescent asthmatics and found useful in decreasing airway obstruction.[22]

Coltsfoot polysaccharides and flavonoids have anti-inflammatory actions.[20] This effect was similar to that of indomethacin in one report.[23] Weak anti-inflammatory actions have also been observed when tested against induced rat paw edema.[8]

A compound designated L-652,469, was isolated from coltsfoot buds. This compound has been found to be a platelet-activating factor (PAF) inhibitor and a calcium channel blocker. PAF is known to be an integral component of the complex cascade mechanism involved in both acute and chronic asthma, and a number of naturally occurring PAF antagonists are being clinically evaluated for the treatment of this and other inflammatory diseases. The isolation of PAF antagonists from coltsfoot indicates that the traditional uses of the plant in the management of certain inflammatory respiratory diseases may be verifiable.[24]

L-652,469 is also a competitive inhibitor of the calcium channel in the rat aorta, but the clinical importance of this finding has not been explored.

Tussilagone is a potent cardiovascular stimulant. When administered intravenously (0.02 to 0.3 mg/kg), it produced a rapid and dose-dependent pressor effect in dogs. This increase in blood pressure was similar to that observed following the administration of the cardiac stimulant dopamine. The increase in blood pressure was short-lived, lasting about 5 minutes. Tussilagone also increased the rate of respiration. The cardiovascular effects appear to be peripherally mediated, while the site of respiratory stimulation is central.[12]

Aqueous leaf extracts and phenolic components have been found to have in vitro antibacterial activity generally limited to gram-negative bacteria.[25] Some of these organisms include *Staphylococcus aureus*, *Bordetella pertussis*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*.[8]

A report discusses coltsfoot's historical, traditional, and modern medical uses, along with the plant's pharmacology and toxicity.[26]

TOXICOLOGY: The use of teas prepared from coltsfoot has not generally been associated with acute toxicity. Several members of this family of plants (eg, chamomile, ragweed) cause common allergies, and some people may exhibit a cross-sensitivity to coltsfoot.[27] While coltsfoot is only a weak topical sensitizer in guinea pigs, other members of the family are strong sensitizers (blessed thistle, dwarf sunflower), and cross-sensitivity may exist.[28]

Several reports have noted the presence of hepatotoxic pyrrolizidine alkaloids in coltsfoot. Pre-blooming flowers have been reported to contain the highest concentration of these alkaloids, although considerable loss of both senkirkine and senecionine occurs upon prolonged storage of the plant.[8] In one long-term safety study, the alkaloid senkirkine (0.015% by weight in dried flowers) was incorporated into rat diets in concentrations of up to 8% of the diet for 2 years. Among the rats fed the 8% meal, two-thirds developed cancerous tumors of the liver characteristic of pyrrolizidine toxicity.[15] This alkaloid is also present in the leaves.[29] The acute intravenous LD-50 of tussilagone is 28.9 mg/kg.[12] These pyrrolizidine alkaloids have well documented toxicities in humans as well, presenting as anorexia, lethargy, abdominal pain and swelling, and liver changes. The alkaloids destroy the liver's hepatocytes and damage small branches of the hepatic vein. In Germany, consumption of > 1 mg of pyrrolizidine alkaloids per day is prohibited.[30]

Of interest is a case of reversible hepatic veno-occlusive disease in an infant after consumption of coltsfoot, later found to be *Adenostyles alliariae* (these two plants can be easily confused, especially after the time of flowering.) Seneciphylline and related hepatotoxins were identified via thin-layer chromatography, mass spectrometry, and NMR spectroscopy.[31]

Coltsfoot has been classified by the FDA as an herb of "undefined safety."[32] However, although the pyrrolizidine alkaloids of coltsfoot are hepatotoxic, mutagenic, and carcinogenic, there is little danger of acute poisoning when it is used as prescribed (as an occasional tea or cough preparation).[2] The German Commission E Monographs recommend a limit of 10 micrograms per day of pyrrolizidine alkaloids with the 1,2-unsaturated necine structure, including their N-oxides.[33]

Excessive consumption of coltsfoot may interfere with preexisting antihypertensive or cardiovascular therapy. Prolonged ingestion of the plant should be avoided. Duration of administration should not exceed 4 to 6 weeks per year.[33] Because the plant may be an abortifacient, it should not be taken during pregnancy or lactation.[8] The flowers of coltsfoot should not be used. The plant is subject to legal restrictions in some countries.[20]

SUMMARY: Coltsfoot has been used for centuries in the treatment of respiratory diseases. The plant contains a mucilage, which may provide some therapeutic effect in relieving sore throats, asthma and related conditions. It also has some anti-inflammatory and antibacterial activities. A PAF antagonist and cardiac and respiratory stimulant have been identified in the plant. The use of coltsfoot is not generally associated with acute toxicity, but users should be warned that the plant has the potential to cause allergic reactions, to increase blood pressure, and to pose a risk of carcinogenicity if used chronically. Its pyrrolizidine alkaloids are known hepatotoxins. Prolonged use of the plant should be avoided.

PATIENT INFORMATION— Coltsfoot

Uses: Coltsfoot has been used to treat sore throats, asthma, and some related conditions such as bronchitis, laryngitis, pertussis, influenza, and lung congestion.

Side Effects: Allergic reactions may occur. Coltsfoot has an "undefined safety" classification by the FDA. Avoid prolonged use of the plant; it may increase blood pressure and pose a risk of carcinogenicity, hepatotoxicity, or mutagenicity.

Dosing: Because of the content of hepatotoxic pyrrolizidine alkaloids, coltsfoot is not recommended for internal use. Historical use of 4.5 to 6 g/day of crude herb has been documented.[34]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    COLTSFOOT

COMFREY

DATE OF ISSUE: MAR 2004

REPLACES MONOGRAPH DATED: OCT 1995

SCIENTIFIC NAME(S): *Symphytum officinale* L., *S. asperum* Lepechin, *S. tuberosum*, *Symphytum* x *uplandicum*. Nyman (Russian comfrey) is a hybrid of *S. officinale* and *S. asperum*. Family: Boraginaceae

COMMON NAME(S): Comfrey, Russian comfrey, knitbone, bruisewort, blackwort, slippery root

BOTANY: Comfrey is a perennial plant found in moist grasslands, and it grows to about 0.9 m. It has lanceolate leaves and bell-shaped purple or yellow-white flowers. Comfrey is usually associated with temperate regions of the world, including western Asia, North America, and Australia.

HISTORY: Comfrey has been cultivated in Japan as a green vegetable and has been used as an herbal medicine for over 2000 years. [1,2]

Comfrey's original name, knitbone, derives from the external use of poultices of its leaves and roots to heal burns, sprains, swelling, and bruises. In western Europe, comfrey has been used topically for treating inflammatory disorders such as arthritis, thrombophlebitis, and gout, and internally for treating diarrhea. Comfrey has been claimed to heal gastric ulcers and hemorrhoids, and to suppress bronchial congestion and inflammation. [1,3]

Comfrey distribution is banned in Germany and Canada because of the substantial health hazard and toxicity of the plant. The sale of comfrey products for internal use is also banned in the United States. [3,4]

CHEMISTRY: Numerous pyrrolizidine alkaloids (PAs) have been identified in the plant; therefore, chronic ingestion may be potentially hepatotoxic. Not all PAs have similar toxicity. Studies confirm the following structure-toxicity relationships (from most to least toxic): macrocyclic diesters > retronecine and heliotridine diesters > heliotridine monoesters > retronecine monoesters. Comfrey PAs are retronecine mono and diesters. [5]

The PAs symphytine, echimidine, and lasiocarpine have been found in *S. officinale*. [6] Lasiocarpine and symphytine are carcinogenic in rats. [7,8] Liver analysis of rats given doses of 50 mg/kg of comfrey-derived alkaloids showed vascular congestion, as well as necrosis, and hepatocyte cellular membrane damage. [9] The liver damage was dose dependent. [10]

The healing action of the poultices of comfrey's roots and leaves may be related to the presence of allantoin, an agent that promotes cell proliferation. Large amounts of mucilage are found in both leaves and roots. The underground roots contain 0.6% to 0.7% allantoin and 4% to 6.5% tannin. The leaves contain a higher content of tannin vs. allantoin. The roots contain about 100 times the alkaloid content as compared with the aerial portions. [11,12]

Rosmarinic acid, lithospermic acid, and a pentacyclic triterpene glycoside of oleanolic acid have been identified in the root. [13,14] The alkaloid content of *S. asperum* ranges from 0.14% to 0.4%. [15]

PHARMACOLOGY: The therapeutic use of comfrey is limited, and review of the scientific literature reveals most studies associated with its toxicity. Ointments containing comfrey have been found to possess anti-inflammatory activity, which appears to be related to the presence of allantoin and rosmarinic acid [16] or to another hydrocolloid polysaccharide. [17] Lithospermic acid isolated from the root appears to have antigonadotropic activity. [13] Pain at rest and on movement was improved for patients in a prospective, open, multicenter, observational study. Patients applied comfrey topically 1 to 3 times/day over a 2-week period. The duration of morning joint stiffness decreased from 20 minutes initially to 3 minutes, and many of the patients eventually discontinued their use of nonsteroidal anti-inflammatory drug therapy. [18] The aqueous extracts from the leaves of comfrey have strong inhibitory activity, likely derived from the plant's phenolic compounds on the rate of germination of *Erysiphe graminis* conidia and *Puccinia graminis* ureidospores of pathogenic fungi. [19]

TOXICOLOGY: In the early 1990s, several cases of veno-occlusive disease (VOD) were reported in humans. VOD involves the destruction or obliteration of small hepatic veins leading to cirrhosis and eventually liver failure. Human poisoning with PAs are usually accidental and may be caused by ingestion of contaminated flour, milk, animals such as goats (resistant to the toxin), honey produced by bees that have fed on pyrrolizidine-containing weeds, and consumption of certain herbal or bush teas. It also may be caused by Russian comfrey used in salads. [4,5]

Several members of the comfrey family (*Senecio*, *Heliotropium*) contain related alkaloids reported to cause liver toxicity in animals and humans. Some of these compounds predispose to hepatic tumor development. The conclusion that comfrey is not safe for internal use is based primarily on toxicity studies in rodents administered high doses of purified PAs. [5]

The carcinogenic potential of *S. officinale* was tested in rats fed 0.5% to 8% comfrey root or leaves for 600 days. [20] Signs of liver toxicity were seen within 180 days and hepatocellular adenomas were induced in all groups. Urinary bladder tumors also were induced at the lowest comfrey levels. The incidence of liver tumors was higher in groups fed a diet of roots rather than leaves.

The alkaloids of Russian comfrey caused chronic liver damage and pancreatic islet cell tumors after 2 years of use in animal models. Eight alkaloids have been isolated from *Symphytum* x *uplandicum*. [21] Alkaloid levels range from 0.003% to 0.115%, with highest concentrations in small young leaves. [22]

Wheat contaminated with PAs from the *Heliotropium* genus, ingested by 7200 Afghanis, resulted in 23% of these individuals suffering liver impairment. An indirect estimate of alkaloid ingestion determined the consumption of toxic alkaloids to be 2 mg/700 g flour. Based on this value, a calculation of 8 to 26 mg of toxic alkaloids per 237 mL comfrey root tea suggests that comfrey ingestion poses a significant health risk. [23]

PAs in herbal teas and similar preparations of *Symphytum* have been shown to cause blockage of hepatic veins, leading to hepatonecrosis. [24] Veno-occlusive disease has been reported in a woman who ingested a comfrey-pepsin preparation for 4 months; [23] one woman died following the ingestion of large quantities of yerba mate tea (*Ilex paraguariensis*), which also contains PAs. [25] Four Chinese women who self-medicated with an herbal preparation that contained PAs from an unknown plant source also developed the disease. [26] One man presented with portal hypertension and hepatic veno-occlusive disease and later died of liver failure. It was discovered that he used comfrey in his vegetarian diet. [27]

Oral ingestion of pyrrolizidine-containing plants, such as comfrey, poses a great risk because the alkaloids are converted to toxic pyrrole-like derivatives following ingestion. [28] The alkaloids of comfrey applied to the skin of rats were detected in the urine, and lactating rats excrete PAs into breast milk. [29] If animals consume plants containing PAs, they could pass these alkaloids on to humans via milk. [30]

SUMMARY: Chronic ingestion of comfrey roots and leaves poses the potential for hepatic damage and hepatic tumor development. Based on a lack of scientific evidence of a therapeutic effect, the consumption or use of comfrey and its teas cannot be recommended because of numerous reports of liver toxicity. BR>

PATIENT INFORMATION — Comfrey

Uses: Comfrey has been used as a vegetable. It has been used topically for treating inflammatory disorders such as arthritis, thrombophlebitis, and gout, and internally to treat GI disorders (eg, diarrhea, gastric ulcers, hemorrhoids), bronchial congestion, and inflammation.

Side Effects: The internal or extensive topical use of comfrey cannot be recommended because of numerous reports of liver toxicity.

Pregnancy/Lactation: Comfrey is contraindicated during pregnancy and lactation because PAs are teratogenic and are excreted in the milk of animals. [28,29,30]

Dosing: Comfrey is not recommended for internal or even limited topical use today because of the content of hepatotoxic PAs. Older preparations may still be on the market in Europe and Asia. For informational purposes, typical older daily doses of the leaf ranged from 5 to 30 grams. [5]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    COMFREY

CORAL

DATE OF ISSUE: JAN 1994

REPLACES MONOGRAPH DATED: N/A

SOURCE: Coral is harvested from a wide region of the Pacific and other tropical oceans. A number of coral genera have been collected for medicinal use, including *Goniopora* and *Porites*.

HISTORY: While coral has been used by the inhabitants of Pacific regions for cutting tools and as the basis of jewelry and amulets, it was not until the mid 1980s that its value in surgery was fully recognized. The natural material derived from the matrix of sea coral has been found to serve as an effective substrate for the growth of new bone in areas damaged by trauma or requiring reconstruction. Coral may be more durable than bone and appears to eliminate some of the complications inherent in traditional bone graft surgery. [1]

Today, coral-based material is used to aesthetically enhance the facial skeleton in cosmetic surgery and is used as a surgical aid in maxillofacial reconstructive surgery.[7]

CHEMISTRY: Although the structural and mineral composition of coral is very similar to that of bone, coral is not implanted in its natural state. Following its harvest, the coral is treated chemically together with heat and high pressure to convert the calcium carbonate matrix to hydroxyapatite (calcium phosphate hydroxide). Hydroxyapatite is the normal mineral portion of bone.

The pores of the processed coral exoskeletal matrix range from 150 to 600 microns in diameter, with interconnecting pore sizes averaging approximately 260 microns in diameter.[2,3] These dimensions are in the range for normal bone and, therefore, make the coral an excellent base for the spread of new bone growth.

SURGICAL USES: During surgery, the processed coral is shaped to fit the patient's facial structure. Sea coral has several advantages over human bone. Unlike traditional procedures that require the surgical removal of bone matrix from elsewhere in the patient's body (ie, hip) for grafting, coral implant requires only facial incision; it retains its shape well, and it provides a long-lasting matrix that closely resembles natural bone. [1,4]

In baboon studies, surgically made bone defects that were grafted with coral demonstrated substantial bone growth ($p < 0.01$) compared to bone grafts as early as 3 months after surgery, culminating with complete penetration of bone into the tridimensional porous spaces of the coral. [2] Similar good results were observed when the material was implanted in the mandibles of rabbits.[3] In dogs, bone regrowth in experimentally created proximal tibia defects demonstrated that the stereological distribution of regenerated bone in the porous hydroxyapatite was the same as in normal tibial bone; after 12 months, 66% of the surface of the coral was covered with new bone ingrowth.[6]

Although experience is somewhat limited, published results suggest that in man, the use of coral in maxillofacial surgery results in good bone conduction into the surgical site.[3] Bone defects in man have been shown to heal rapidly following reconstruction with coral microgranules. Biopsies at 8 and 18 months showed good bone formation around the coral particles.[5]

TOXICOLOGY: Follow-up of patients for 6 to 24 months found no deleterious host responses and good tolerability to coral implants. [3] To date, insufficient experience has been gained with the use of coral products to confirm their benefit in assisting bone growth in severely damaged weight-bearing bones.

SUMMARY: Coral is now under investigation for its use in facial reconstructive surgery. The chemically modified coral exoskeleton provides a strong matrix for bone regeneration. The product does not appear to be associated with adverse effects or tissue rejection.

PATIENT INFORMATION— Coral

Uses: Coral is used in cosmetic and reconstructive surgery and as a substrate for new bone growth.

Side Effects: Coral does not appear to be rejected or produce adverse effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CORAL

CORDYCEPS

DATE OF ISSUE: FEB 2004

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Cordyceps sinensis* (Berk.) Sacc. Family: Clavicipitaceae

COMMON NAME(S): Cordyceps, Chinese caterpillar fungus, Cs-4, Dong Chong Xia Cao, [1,2] semitake

BOTANY: *C. sinensis* is a black, blade-shaped fungus found primarily in the high altitudes on the Tibetan plateau in China. Wild cordyceps is rare. This mushroom is parasitic and grows on and derives its nutrients from moth caterpillars. In the fall, the fungal mycelia infect the caterpillar. The fungal infestation kills the caterpillar by early summer of the following year, thus releasing the fruiting body. The wild form of *C. sinensis* is harvested, while the principal fungal mycelium (*Paecilomyces hepiali* Chen) is cultivated aseptically.[2]

HISTORY: The fruiting body and attached mycelium of cordyceps has been used in Chinese culture for centuries. In traditional Chinese medicine, it is valued for its activity in restoring energy, promoting longevity, and improving quality of life. *C. sinensis* affects numerous human body systems including the circulatory, respiratory, and immune systems, as well as the liver, kidneys, and sex organs. Cordyceps has been used as an adjuvant in cancer therapy.[2,3,4]

CHEMISTRY: Seven classes of natural chemical constituents are found in wild *C. sinensis* including proteins, peptides, all essential amino acids, and polyamines; saccharides and sugar derivatives; sterols; nucleosides (including adenine, uracil, uridine, guanosine, thymidine, and deoxyuridine); fatty acids and other organic acids; vitamins (including B_1, B_2, B_{12}, E, and K); and inorganic elements.[2,5] Cordycepin and other adenosine derivatives, mannitol, several unique sterols and their glycosides, polysaccharides, and cyclic peptides have been identified. [6]

PHARMACOLOGY: Over 2000 patients with various medical disorders have been involved in clinical trials using Cs-4 in China. Cs-4 is a strain of the wild *C. sinensis* and has been studied extensively in China. The chemical and pharmacological profiles are similar to natural *C. sinensis* and most of the research available was completed using Cs-4.

In traditional Chinese medicine, *C. sinensis* has been used to treat male impotence and other types of sexual dysfunction. Numerous animal studies and clinical trials have studied the effects of *C. sinensis* on sexual function. In several placebo-controlled, double-blind studies, patients with reduced sexual drive are typically treated with Cs-4 (3 g/day) for approximately 2 months. In elderly patients, clinical improvement of sexual drive and function for the Cs-4 group was statistically significant as compared with the control group. There was an increase in 24-hour urine 17-ketosteroids in the Cs-4-treated patients; thus Cs-4 may affect sexual drive through the sex hormone systems or through a direct action on the sexual center of the brain and sexual organs. [2,7,8]

Investigators studied the effect of a fraction of mycelia of *C. sinensis* (150 mg/kg/day) for its antifatigue and antistress effects against a stimulus (swimming endurance capacity) in vivo using rats and mice. The researchers concluded the fraction of mycelia of *C. sinensis* has antifatigue and antistress effects on the following stress indices: serum level measurements of total cholesterol, lactate dehydrogenase, alkaline phosphatase, aspartate transaminase, and alanine transaminase. [8,9] In a double-blind, placebo-controlled trial, elderly patients with senescence-related symptoms had significant improvements in tolerance to cold ($P < 0.001$), fatigue ($P < 0.001$), dizziness ($P < 0.001$), tinnitus ($P = 0.001$), frequent nocturia ($P = 0.004$), hyposexuality ($P = 0.05$), and amnesia ($P = 0.003$). Patients were randomly assigned and received either Cs-4 (3 g/day) or placebo for 3 months. There was a concurrent increase in red blood cell superoxide dismutase (SOD) activity ($P < 0.001$). Reduction in SOD is recognized as one of the factors related to aging and may lead to accumulation of excessive oxygen-free radicals and oxidative damage to cells.[2]

Cs-4 also has been used in the treatment of hyperlipidemia and may have a hypocholesterolemic effect. [2,10] In a double-blind, placebo-controlled clinical trial involving 273 patients, the Cs-4 group had a reduction in triglycerides after only 1 month of treatment. Overall, half of the patients on Cs-4 therapy (3 g/day) had reductions in total cholesterol and triglycerides, and a significant increase in high-density lipoprotein. [2]

Investigators have reported the following pharmacological activities of natural *C. sinensis* on the cardiovascular system in animal studies in vivo or with isolated organs: Dilation of arteries and improvement of nutritional blood supply to organs and extremities; reduction of heart rate; antiarrhythmic effects; effects against acute myocardial ischemia and stress-induced myocardial infarction; and effects of thrombosis and anti-aggregation of platelets. In a 3-month, open-label clinical trial, Cs-4 was used to treat 38 elderly patients with various arrhythmias. The investigators concluded that Cs-4 was effective in treating patients with tachyarrhythmia and bradyarrhythmia, and the longer the therapy duration, the better the clinical improvement. The majority of patients with supraventricular arrhythmias experienced partial to complete recovery in the electrocardiograms. [3,11]

A 26-month trial using Cs-4 (3 to 4 g/day) in combination with standard therapy (digoxin, hydrochlorothiazide, isosorbide dinitrate, furosemide, lanatoside, dopamine, and dobutamine) was studied in 64 chronic heart failure patients. Patients using Cs-4 as an adjuvant treatment reported improvement in general physical, emotional, and psychological well-being as compared with controls. There were no statistically significant differences in mortality between the two groups. Overall, patients taking Cs-4 had statistically significant improvements in the shortness of breath/fatigue index ($P < 0.01$), general physical condition ($P < 0.05$), emotional-psychological condition ($P < 0.05$), and sexual drive ($P < 0.001$) as compared with controls.[2]

In an open-label, clinical trial, patients with chronic obstructive pulmonary disease reported improvements in cough, phlegm, appetite, vitality, and pulmonary symptoms after treatment with Cs-4 (3 g/day for 3 weeks) compared with controls. There was a significant increase in SOD activity ($P< 0.001$) compared with baseline. In another open-label, clinical trial, patients with chronic renal dysfunction also had significant increases in SOD activity ($P < 0.001$) compared with pretreatment levels after treatment with Cs-4 (5 g/day for 4 weeks).[2]

More than 5 clinical studies (all approximately 4 weeks in duration) demonstrated significant clinical improvements ($P < 0.01$) in respiratory symptoms (including chronic bronchitis, bronchial asthma, and cor pulmonale) after administration of a cordyceps-containing medication. Dosages ranged from 3 to 4.5 g/day of Cs-4 for 2 to 12 weeks. When Cs-4 was used in combination with oxygen and other drugs in treating patients with cor pulmonale (right-sided heart failure), improvements were seen in respiratory and heart function as well as in sleep and emotional-spiritual state. The combined use of Cs-4 (3 g/day) with astemizole (10 mg/day) and ketotifen (2 mg/day) was effective in treatment of asthma as compared with the controls treated with Western medicine alone ($P < 0.05$). A potential mechanism may involve Cs-4 reducing the production of IgE (which will reduce the asthma attack) through T_{H1} and T_{H2} immune responses.[3,12]

C. sinensis may improve kidney function and have renal protective effects against nephrotoxic chemicals. Cs-4 (6 g/day for 30 days) was effective in improving renal function in 30 patients with chronic renal failure. Compared with pretreatment levels (not necessarily a valid reference point), investigators reported significant improvement in serum creatinine ($P < 0.02$), red blood cell count ($P < 0.05$), anemia ($P < 0.02$), creatinine clearance ($P < 0.001$), and blood urea nitrogen ($P < 0.01$). Another study found similar significant improvements as well as reduction in urinary protein ($P < 0.01$). Results from other studies suggest improvement of renal function by *C. sinensis* linked with involvement of T-cell-mediated immune functions. In both animal and human clinical studies, *C. sinensis* has shown renal protective effects against nephrotoxicity of aminoglycosides and cyclosporin A. In one study, elderly patients (53 to 73 years of age) with no history of renal disease were treated IM or IV with amikacin (0.4 g/day for 6 days) with either placebo or *C. sinensis* (6 g/day for 7 days) for the treatment of an acute infection. After the therapy, the accumulated 24-hour urinary N-acetyl-beta-D-glucosaminidase (NAG) level was increased by 4 times in controls compared with double in those patients receiving *C. sinensis* ($P< 0.05$). NAG is an index for aminoglycoside-induced renal damage.[3,13]

C. sinensis also has demonstrated hepatoprotective effects in an animal study [14] and in clinical trials. In a 3-month, open-label trial of 33 patients, a cultivated mycelial product of *C. sinensis* was effective in the treatment of chronic active hepatitis B. Investigators reported after the treatment that the thymol turbidity test (TTT) and serum glutamic-pyruvic transaminase (SGPT) either improved or returned to normal. In addition, serum albumin increased and gamma globulin decreased

significantly. No significant changes were seen in TTT or ALT in another study of 22 patients with hepatic cirrhosis; although significant improvements were seen in serum albumin ($P < 0.01$) and gamma globulin ($P < 0.05$). Other references referred to in this report have shown similar results. [3]

A hypoglycemic effect has been documented in animal studies.[15,16,17] In a randomized trial involving 42 patients with diabetes, Cs-4 (3 g/day for 30 days) was found to be an effective treatment in combination with traditional Chinese herbs compared with a control group given only the herbs. Patients in the treatment group previously had a positive urinary protein test; after treatment, half of these patients tested negative compared with no change in the controls. [3]

Investigators also have reported enhanced immune system activity in animal and in vitro studies with *C. sinensis*. One study demonstrated enhanced activity of natural killer (NK) cells in patients with leukemia and in immunocompetent individuals. It also prevented reductions in NK cell activity in immunosuppressed mice. [3]

Cordyceps has been used as an adjunct in cancer treatment and appears to improve tolerance to the adverse effects associated with radiation and chemotherapy. In 59 patients with terminal lung cancer, administration of Cs-4 (2 to 3 g/day) resulted in more patients completing radiation and/or chemotherapy compared with a control group ($P < 0.01$). Cs-4 also may minimize bone marrow impairment because patients in the Cs-4 treatment group had normal blood counts as compared with the control group ($P < 0.01$). One study concluded that the fruiting body of *C. sinensis* contains growth inhibitors against tumor cells.[3,6]

The anti-inflammatory properties of cordyceps also have been reviewed; however, the mechanism of action has yet to be elucidated. [3]

TOXICOLOGY: Cordyceps is considered to be very safe and an oral LD50 (median lethal dose) could not be defined. Doses in mice of 80 g/kg body weight did not cause death. One study indicated that Cordyceps is not mutagenic or teratogenic. There are reports from clinical studies of mild GI discomfort (including nausea, upset stomach, and dry mouth). In another report, some patients taking Cs-4 developed a systemic allergic reaction. [3]

SUMMARY: *C. sinensis* has been used in Chinese traditional medicine for centuries. *C. sinensis* affects numerous human body systems and its activity is supported by historical records and human clinical trials.

PATIENT INFORMATION— Cordyceps

Uses: Affects numerous human body systems, including the circulatory, respiratory, and immune systems, as well as the liver, kidneys, and sex organs. Cordyceps has been used as an adjuvant in cancer therapy.

Side Effects: Mild GI discomfort (including nausea, upset stomach, and dry mouth).

Dosing: Accurate dosing is not available. Many herbal supplements on the market contain varying undefined levels of this product.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CORDYCEPS

CORKWOOD TREE

DATE OF ISSUE: MAY 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Duboisia myoporoides* Family: Solanaceae

COMMON NAME(S): Corkwood tree, pituri

BOTANY: The plant is found throughout most of Australia[1,2] and has also been cited in botanical texts from South America.[3]

HISTORY: The leaves of the corkwood plant are cured and rolled into a quid. These are chewed by the natives to ward off hunger, pain and tiredness. [1] Because the leaves contain anticholinergic stimulants, it has been reported that Australian aborigines taint waterholes in order to stun and capture animals. The alkaloids derived from the plant are sometimes used as a therapeutic substitute for atropine and the plant had once been an import source of Australia's scopolamine. [1] The plant has been used in homeopathy to treat eye disorders. The corkwood is used for carving. [2]

CHEMISTRY: The plant is rich in alkaloids, yielding more than 2% alkaloids. These consist primarily of hyoscyamine and hyoscine. Also isolated are the alkaloids scopolamine, atropine, butropine and more than a dozen additional related compounds. Nicotine and nornicotine have been reported to exist in the leaves. [1]

PHARMACOLOGY: The tropane alkaloids (atropine, scopolamine, etc) are potent anticholinergic agents. Even therapeutic doses may cause central nervous system disturbances. The alkaloid tigloidine has been found to have an antiparkinson effect, which is not unexpected from an anticholinergic compound. [1]

TOXICOLOGY: Scopolamine and related alkaloids can be fatal in large doses. This plant demonstrates stimulant and hallucinogenic properties by virtue of the anticholinergic effects of its major constituents.

SUMMARY: The corkwood tree is used as a central nervous system stimulant and hallucinogen by native Australians. There is little medicinal use of the plant, and other sources of scopolamine and atropine have become more commercially viable.

PATIENT INFORMATION— Corkwood Tree

Uses: Corkwood tree leaves have been used as a CNS stimulant and hallucinogen.

Side Effects: Even small doses may cause CNS disturbances. Large doses may be fatal.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CORKWOOD TREE

CORN COCKLE

DATE OF ISSUE: AUG 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Agrostemma githago* L:, Family: Caryophyllaceae

COMMON NAME(S): Cockle, corn campion, corn cockle, corn rose, crown-of-the-field, purple cockle

BOTANY: *Agrostemma githago* is an annual herb showing a few erect branches which are heavily pubescent overall. The leaves are linear lanceolate and the flowers red growing up to 2 inches broad. It was originally native to Europe but has long been naturalized in the US to the extent that it is a troublesome weed in winter wheat fields.[1]

HISTORY: Though corn cockle has an attractive red flower, it is not usually cultivated horticulturally and is generally considered a weed. In fact, its seeds have long been considered poisonous; it causes problems when gathered together with cereal grains with which it grows as a weed. In European folklore, its seeds have been used for treating cancers, hard tumors, warts and apostemes (hard swellings in the uterus). Seeds have also been put into the conjunctival sac to induce keratoconjunctivitis. Its saponins are irritating and have been claimed to have local anesthetic effects. [2]

CHEMISTRY: At least two saponins, githagin and agrostemmic acid, are contained in corn cockle.[1] The saponin, sapotoxin A, with the prosapogenin githagin ($C_{35}H_{54}O_{11}$), the aglycone githagenin ($C_{30}H_{46}O_4$), and agrostemmic acid ($C_{35}H_{54}O_{10}$) have also been reported.[2] The ripe seeds contain a number of aromatic amino acids, including 2,4-dihydroxy-6-methylphenylalanine, L(+)-citrullin ($C_6H_{13}N_3O_3$), sugar, oil, fat and starch. The seedlings, like others, possess allantoin and allantoic acid. The roots are reported to contain up to 2.02% starch labeled "lactosin." The oil contains 41.4% unsaturated fatty acids and a high portion (3.42%) of unsaponifiable lipids.[3] These, in turn yield 8.3% mixed alkanes from C19 to C33. The unsaponifiable lipids were found to have 44.7% crystalline alpha-spinasterol as well as small quantities of a triterpene ester and a di- or tri-terpene-like unsaturated acyclic ketone.

PHARMACOLOGY: Corn cockle has been used historically as a diuretic, emmenagogue, expectorant, poison and vermifuge. It has been used to treat cancer, dropsy (edema) and jaundice. Corn cockle roots have been used for exanthemata and hemorrhoids. The seeds have been used homeopathically in treating gastritis and paralysis.[2]

TOXICOLOGY: The sapoinins githagin and agrostemmic acid are reported to be absorbable from the alimentary canal and may produce systemic poisoning, including gastrointestinal irritation, severe muscle pain and twitching, followed by depression and coma. In veterinary experiences, poultry and livestock have been poisoned by the seeds of corn cockle. As a seed, it commonly contaminates wheat seed. Hogs that have ingested the roots have died. Consumption of 0.2% to 0.5% of the body weight of seed is lethal to young birds. Cows have also died from this seed. The repeated ingestion and chronic poisoning by small doses of corn cockle is referred to as githagism. Acute poisoning by large doses is manifested by vertigo, respiratory depression, vomiting, diarrhea, salivation and paralysis. Gastric lavage or emesis are recommended for poison treatment.[2]

SUMMARY: Since there are few, if any, modern acceptable medical uses for corn cockle, its record of toxicity relegates it to the category of a poisonous plant. It cannot be recommended for any of the reported folklore uses. The seeds and roots of *A. githago* are the most toxic parts of the plant, probably due to the numerous saponins reported.

PATIENT INFORMATION— Corn Cockle

Uses: Corn cockle has been used in folk medicine to treat a range of ills, from parasites to cancer.

Side Effects: Corn cockle may produce chronic or acute, potentially fatal poisoning.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CORN COCKLE

CRAMP BARK

DATE OF ISSUE: MAY 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Viburnum opulus* L.; *V. opulus* var. *americanum*(Miller) Ait. Caprifoliaceae (honeysuckle family)

COMMON NAME(S): Cramp bark, guelder rose, snowball, squaw bush, cranberry tree, highbush cranberry, pimbina

BOTANY: *Viburnum opulus* is a large bush that is often grown ornamentally for its attractive white flowers. It is native to northern Asia and Europe. The American variety of *V. opulus* (also known as *V. trilobatum*) has edible red berries while the European variety bears bitter fruit. An extensive study of *Viburnum* botany and pharmacognosy was published in 1932.[1] The trunk and root bark are the commonly used drug products.

HISTORY: The American variety was used by the Iroquois for prolapsed uterus after childbirth, [2] and other tribes recognized its use as a diuretic. [1] The Eclectic medical movement in the 19th century adopted cramp bark for dysmenorrhea and to prevent miscarriage. It was believed to be a stronger antispasmodic than the related *Viburnum* species *V. prunifolium*(black haw).[2] The bark was made official in the *U.S. Pharmacopeia* in 1894 and was included in the *National Formulary* in 1916. Widespread adulteration by mountain maple (*Acer spicatum*) and other *Viburnum* species led to confusion about the correct source plant. A later review surveyed the botanical, chemical, and pharmacological differences between black haw and cramp bark. [3]

CHEMISTRY: The coumarin scopoletin has been isolated from cramp bark.[4] The sesquiterpenes viopudial[5] and viburtinal[6] also have been found. The former compound was isolated by preparative gas chromatography, and the latter compound resulted from hydrolysis of undetermined esters. These compounds may be degradation products of iridoids, which have been reported from the leaves of this species. [7] Common plant triterpenes, such as alpha- and beta-amyrin, also have been reported;[8] cramp bark also contains substantial quantities of catechin tannins. [3]

PHARMACOLOGY: Early pharmacologic studies of cramp bark and black haw did not demonstrate activity in uterine preparations (see Black Haw monograph for details). However, it has been shown that *V. opulus* and other species did indeed produce uterine relaxation in isolated rat tissues. [9] Both scopoletin[4] and viopudial[5] have been determined to be responsible for the uterine relaxant activity of *V. opulus*. However, viopudial has not been found in black haw bark, which may account for its reputation for weaker activity. No clinical studies examining efficacy in humans have been performed.

TOXICOLOGY: There are no studies of the toxicology of cramp bark.

SUMMARY: Cramp bark was official in the *U.S. Pharmacopeia*from 1894 to 1916 and in the *National Formulary* for a number of years thereafter. No current monographs have been produced. Cramp bark has uterine relaxant activity in experimental tissue preparations; however, little formal study has been made of its safety or efficacy for dysmenorrhea in humans. A typical dose of the bark is 3 to 4 g/day.

PATIENT INFORMATION— Cramp Bark

Uses: Cramp bark has been used for painful menstruation and to prevent miscarriage.

Side Effects: No studies have been performed.

Dosing: 3 to 4 g/day.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CRAMP BARK

CRANBERRY

DATE OF ISSUE: AUG 2001

REPLACES MONOGRAPH DATED: JUL 1994

SCIENTIFIC NAME(S): *Vaccinium macrocarpon*Ait. (cranberry, trailing swamp cranberry), *V. oxycoccos* L. (small cranberry), *V. erythrocarpum* Michx. (Southern mountain cranberry), *V. vitis* (lowbush cranberry), *V. edule* (highbush cranberry). Family: Ericaceae

BOTANY: A number of related cranberries are found in areas ranging from damp bogs to mountain forests. These plants grow from Alaska to Tennessee as small, trailing evergreen shrubs. Their flowers vary from pink to purple and bloom from May to August depending on the species. The *Vaccinium* genus also includes the blueberry (*V. angustifolium* Ait.), deerberry (*V. stamineum* L.), the bilberry (*V. myrtillus*), and the cowberry (*V. vitis-idaea* L.). They are not to be confused with another highbush cranberry, *Viburnum opulus* L. (family: Caprifoliaceae).[1]

HISTORY: During the mid-1800s, German physicians observed that the urinary excretion of hippuric acid increased after the ingestion of cranberries. It was believed that cranberries, prunes, and plums contained benzoic acid or another compound that the body metabolized and excreted as hippuric acid (a bacteriostatic agent in high concentrations). This hypothesis has always been disputed because the amounts of benzoic acid present in these fruits (˜ 0.1% by weight) could not account for the excretion of the larger amounts of hippuric acid.

Despite a general lack of scientific evidence to indicate that cranberries or their juice are effective urinary acidifiers, interest persists among the public in the medicinal use of cranberries. Cranberries are used in eastern European cultures because of their folkloric role in the treatment of cancers and to reduce fever. Cranberries make flavorful jams and preserves.

CHEMISTRY: Natural, unprocessed cranberry juice contains a variety of constituents, few of which have shown important pharmacologic activity. The berries contain about 88% water.[2] The juice contains anthocyanin dyes, catechin, triterpenoids, ˜ 10% carbohydrates, and small amounts of protein, fiber, and ascorbic acid (2 to 10 mg %).[3] The major organic acids are citric, malic,[4] and quinic acids, with small amounts of benzoic and glucuronic acids. The glycoside leptosine and several related compounds have been isolated[5] along with small amounts of alkaloids.[6] Anthocyanin pigments obtained from cranberry pulp are used in commercial coloring applications.[7]

PHARMACOLOGY: The discovery of cranberries' ability to acidify urine was based on an early experiment with two healthy subjects. [8] Following a basal diet, one subject was given 305 g of cooked cranberries and the other an unspecified amount of prunes. In the first subject, urinary pH decreased from 6.4 to 5.3 with a concomitant increase in the excretion of total acids. Hippuric acid excretion increased from 0.77 to 4.74 g. Presumably, urinary hippurate resulted from the slow biotransformation of quinic and benzoic acids or from a glucoside that hydrolyzed to quinic acid. Since mammalian tissues cannot convert quinic to hippuric acid, intestinal bacteria may play a role in this conversion. [9]

Despite these early observations, the value of cranberries in treating urinary tract infections continues to be controversial. In one study, three of four subjects given 1.5 to 4 L per day of cranberry cocktail (1/3 juice mixed with water and sugar) showed only transient changes in urinary pH. [10] The maximum tolerated amounts of cranberry juice (about 4 L per day) rarely result in enough hippuric acid excretion to achieve urinary concentrations that are bacteriostatic at the optimum activity level of pH 5. The antibiotic activity of hippuric acid decreases about five-fold at pH 5.6. [11] When five subjects were given 1.2 to 4 L per day of cranberry juice, urinary pH decreased only 0.2 to 0.5 units after 4 days of treatment; no urinary pH was ever lowered to pH 5. [11] A placebo-controlled study assessed the value of drinking 300 mL per day of cranberry juice on bacteria and white blood cell counts in the urine of 153 elderly women. [12] The odds of having bacteria or white blood cells in the urine were significantly lower in the group of women who ingested cranberry juice and their odds of remaining bacteria-free from one month to the next were only 27% of the controls (p = 0.006). This is one of the largest studies of its kind and suggests that there may be a microbiologic basis for cranberry's activity. Questions have been raised about the study design and specimens used.[13,14,15,16,17]

A study of elderly men and women (9 and 29, respectively) suggested that drinking cranberry juice reduces the frequency of bacteriuria in the elderly. [18]

Reduced symptomatic urinary tract infections were seen in women residing in a long-term care facility after ingestion of cranberry juice or concentrated cranberry capsules in another study (p = 0.01).[19] In a randomized, double-blind, crossover study of 10 young women with recurrent urinary tract infections, it was found that daily treatment with 400 mg of cranberry concentrate resulted in significantly fewer urinary tract infections than in the control group. [20]

In a case-control study of 86 sexually active college students, a 50% reduction in the odds of first-time urinary tract infections was related to regular ingestion of cranberry juice.[21]

Two studies in children with neurogenic bladder receiving intermittent catheterization, showed no significant difference in the acidification of urine or frequency of bacteriuria with ingestion of cranberry concentrate.[22,23]

Two reviews assessing the validity of using cranberries for the prevention and treatment of urinary tract infections concluded, on the basis of the available evidence, that cranberry juice cannot be recommended for the prevention nor treatment of urinary tract infections. [24,25] Because of questions that arose from the study, which included 153 elderly women, and these reviews, it was concluded that well-designed, placebo-controlled trials with significant outcomes are still needed. [26]

It is therefore likely that the juice does not exert a direct antibacterial effect via a compound such as hippuric acid, but that an alternate mechanism accounts for the anti-infective activity.[27] This is supported by the observation that cranberry and blueberry juices contain a high molecular weight compound (identified as condensed tannins or proanthocyanidins)[28] that inhibits the common urinary pathogen *Escherichia coli* from adhering to infection sites within the urinary tract, thereby limiting the ability of the bacteria to initiate and spread infections. [29,30] Preliminary data suggest that concentrated cranberry juice has some antibacterial activity, but whether sufficient urinary concentrations of the active ingredients can be achieved needs further investigation. [31]

One promising use for the juice is as a "urinary deodorant." The malodor of fermenting urine from incontinent patients is a persistent, demoralizing problem in hospitals and long-term care facilities. Cranberry juice appears to lower urinary pH sufficiently to retard the degradation of urine by *E. coli*, limiting the generation of the pungent ammoniacal odor.[32,33,34]

Using the juice in combination with antibiotics has been suggested for the long-term suppressive therapy of urinary tract infections. [35,36] Anecdotal reports have described the benefits of drinking 6 oz of juice twice daily to relieve symptoms of chronic pyelonephritis and to decrease the recurrence of urinary stones. [35] The juice shows slight antiviral activity in vitro.[37]

TOXICOLOGY: There have been no reports of toxicity with the use of cranberry juice. The ingestion of large amounts (> 3 to 4 L per day) of the juice often results in diarrhea and other GI symptoms. A case of nephrolithiasis in a 47-year-old man with a history of nephrolithiasis was attributed to his ingestion of cranberry concentrate tablets. As calcium oxalate is the most common type of urinary stone, the oxalate content of the cranberry concentrate tablets contributed to the formation of urinary tract stones.[38] One 450 mg tablet of cranberry concentrate is equivalent to 2880 mL of cranberry concentrate, and 500 mL of cranberry juice contains 22 mg of oxalate.[39]

SUMMARY: Based on more than 100 years of clinical experience, the data are still conflicting about whether cranberries and their juice can reliably decrease urinary pH to a bacteriostatic level. Hippuric acid excretion alone does not exert a reliable clinical effect and it is more likely that the effects of cranberries on urinary

tract infections are related to their ability to interfere with bacterial adhesion. The juice has been given to decrease the rate of urine degradation and odor formation in incontinent patients. Well-designed, placebo-controlled trials with significant outcomes are still needed to determine that cranberry products can prevent or treat urinary tract infections.

PATIENT INFORMATION— Cranberry

Uses: Cranberries and cranberry juice appear to combat urinary tract infections. The acids lower urine pH levels sufficiently to minimize the ammoniated odor in incontinent patients.

Side Effects: Extremely large doses can produce GI symptoms such as diarrhea. Contact your health care provider before taking cranberry products if you are prone to kidney stones.

Dosing: Cranberry juice, juice concentrate, and dried extract have been studied in urinary tract infections. Doses of juice studied have ranged from 120 to 4000 mL/day; 400 mg of cranberry extract daily has been given in an effort to avoid the large volumes that seem to be required for efficacy. [10,12,20,23,36,40,41,42,43,44]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CRANBERRY

CREATINE

DATE OF ISSUE: JUL 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Methylguanidine acetic acid, N-amidinosarcosine [1,2]

SOURCE: Creatine is a constituent of muscle tissue and occurs naturally in meat, fish, and other animal products, with trace amounts found in milk and some plants. Herring, for example, contains 6.5 to 10 g/kg, while salmon, tuna, beef, and pork all contain ~ 4 to 5 g/kg. [3] A typical American/Western diet provides 1 to 2 g/day; vegetarians consume much less and thus their daily creatine needs are met completely via de novo synthesis. [2,3,4,5] Endogenous creatine is synthesized from arginine, glycine, and methionine in the liver, pancreas, and kidney and is then transported via circulation to various tissues for utilization. [1,3,6]

The majority of studies evaluating the effects of oral creatine supplementation have been conducted using creatine monohydrate powder; the effects of other supplement formulations such as creatine citrate or creatine phosphate (CP) are yet to be determined. Creatine monohydrate is available in several doseforms, including powder, liquid, capsules, bar, gel, candy, and gum. [7] The efficacy of some of these doseforms remains to be demonstrated.

HISTORY: Creatine was first discovered by Michel Chevreul, a French chemist, in 1832 as an organic constituent of meat. [3] Muscle work was later associated with creatine in 1847 when Lieberg observed that the flesh of wild foxes killed in the chase contained 10 times more creatine than those living in captivity. [3] In 1911, Thunberg reported that creatine was involved in muscle metabolism; he showed that oxygen consumption could be stimulated by adding creatine to muscle mince. [6] In the early 1930s, it was suggested that CP might serve as the source of energy for muscle contraction when its large free energy of hydrolysis (12 kcal/mol) was identified.[6] By 1939, oxygen consumption was shown to be coupled to CP synthesis in muscle, which confirmed that oxidative phosphorylation was indeed a function of creatine.[6]

In the late 1960s, researchers began using needle biopsy techniques to study the breakdown and resynthesis of adenosine triphosphate (ATP) and creatine phosphate with exercise. But it was not until the early 1990s that creatine's influence on exercise performance in humans began to be studied. This followed the findings of Harris and coworkers in 1992 who reported a 20% increase in human muscle mass subsequent to creatine supplementation. [3,8] Over the last 10 years, researchers have conducted numerous studies in untrained or moderately trained subjects in the laboratory setting to determine the potential ergogenic value of creatine supplementation.[8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23] Benefit has extended beyond simple laboratory exercises, and enhanced sprint exercise performance has been reported in elite athletes. [19,20,21]

CHEMISTRY

Biochemistry: Arginine and glycine undergo reversible transamidination in the human liver, pancreas, and kidney to form guanidinoacetic acid and ornithine. [3,6] Guanidinoacetic acid is then irreversibly N-methylated by *S*-adenosylmethionine, in the presence of a methyltransferase, to form creatine. [3,6] Creatine enters the circulation and is carried to utilization sites (eg, muscle, heart, brain, testes), where it is moved against a concentration gradient by a saturable sodium- and chloride-dependent creatine transport protein. [24] At these utilization sites, creatine and CP react nonenzymatically to form creatinine, which is subsequently excreted by the kidney.[3,6,24]

Different sites of creatine synthesis and utilization allow for independent regulation of each process. [3] Intra- and extracellular creatine regulation is controlled by feedback inhibition on the arginine-glycine amidinotransferase, which is dependent on changes in the relatively small amounts of circulating creatine and its precursors.[3,24] Secondary regulators appear to involve factors affecting creatine tissue entry and retention, possibly via control of expression and activity of the creatine transporter protein.[3,24] Additionally, a series of hormones have been identified that influence net creatine uptake into muscle cells, including catecholamines (eg, norepinephrine, isoproterenol), insulin (at supraphysiological levels), and IGF-1. [24]

Approximately 95% of the total creatine pool (both free and phosphorylated forms) is found in human skeletal muscle. [2,3] Most of the remaining 5% is found in the heart, brain, retina, and spermatozoa.[3,5,25] The size of the total creatine pool is not under strict metabolic control and can be influenced by dietary creatine and the administration of precursor amino acids. Free creatine accounts for about 33% of the total body creatine pool, with phosphorylated creatine making up the remaining 67%.[3]

Creatinine output remains a constant fraction of the total creatine pool and can change independently of lean body mass. [3,26,27] About 1.5% to 2% of the creatine pool is converted to creatinine daily and is excreted in the urine; in a 70 kg man with a total creatine pool of 120 g, this is equal to ~ 2 g/day. [1,3,27]

Potential creatine uptake is reportedly higher when initial total creatine levels in muscle are low. [3] This is supported by several studies that have reported highest initial uptake on the first day of creatine supplementation relative to subsequent days and higher uptakes in vegetarian study subjects compared with omnivores. [3] Researchers also discovered that this initial high uptake was followed during subsequent days of supplementation by recovery of almost all of the administered supplemental creatine from the urine. This indicated a possible upper limit or threshold for creatine storage. [3]

The type of muscle fiber has been shown to have an effect on muscle creatine concentrations.[3] Fast-twitch muscle fibers (type ??) in human skeletal muscle have been shown to have higher levels of CP at rest than slow-twitch fibers (type ?).[3]

Gender was reported in one study to have an effect on total muscle creatine concentrations, but data are equivocal. [8] A few other studies with small sample sizes (n < 20) have been unable to duplicate this result and have shown no gender differences in body composition values, total body water, total creatine before supplementation, or magnitude of creatine loading.[16,18]

Aging per se does not appear to affect total muscle creatine concentrations, but rather a shift in the CP:creatine ratio occurs, which appears to be related to inactivity associated with increased age.[3,8] The percentage of CP has been found to be lower (with higher free creatine) in elderly subjects, but when placed on a training program, percentages of CP and free creatine have been observed to approach those of younger subjects. [3]

Results of the effect of training on creatine concentrations in skeletal muscle are, however, equivocal. [3] In general, short-term training studies in young adults have failed to show any definite changes in free or phosphorylated creatine between trained and untrained subjects. [3]

PHARMACOLOGY

Physiology: The role of creatine in facilitating energy distribution and responding to energy demand can be explained by the creatine phosphate shuttle; this concept arose from studies of insulin action. It was proposed that creatine from the contracting muscle provided the stimulus for oxygen uptake in much the same manner as insulin causes the phosphorylation of glucose by ATP yielding adenosine diphosphate (ADP) for respiratory control. [6]

Creatine, released from contracting myofibrils during exercise, moves to the mitochondria and in the presence of ATP produces CP and releases ADP. ADP then

stimulates oxygen uptake. CP, synthesized in the mitochondria under anaerobic conditions, returns to the myofibril, where the MM isozyme of creatine kinase (CK_{MM}) catalyzes the resynthesis of ATP as an energy source for subsequent contractions, mimicking the effect of insulin in attaching hexokinase to the mitochondrion during glucose phosphorylation.[6]

Three major cell functions have been shown to be terminals for the CP shuttle: Contraction (myofibrils are reliant on CP to provide ATP for normal contraction); macromolecular synthesis (CK inhibition results in parallel inhibition of lipid and protein synthesis); and maintenance of ion gradients (CK is associated with ATP-dependent calcium transport and with sodium-potassium ATPase).[6]

Tissues where creatine kinase is found most, and thus where creatine's role is most important, are in the human muscle, heart, and brain. The creatine pathway is thought to be associated with two distinct functions in these tissues: (1) To deliver creatine as the signal or stimulus for oxygen uptake and (2) to provide CP as an energy source. Creatine kinase has also been found in other tissues (eg, spermatozoa, uterus, leukocytes, macrophages) and here generally appears to be associated with contractile proteins and cell movement.[6,25]

Ergogenic properties: An inverse relationship has been noted between exercise intensity and CP levels. CP is not a primary substrate during submaximal exercise; however, it is estimated that with high-intensity exercise, CP stores can be depleted within 10 seconds. Degradation is higher in type ?? muscle fibers and may be a rate-limiting factor for maintaining muscle force during intense, anaerobic bouts of short-term exercise. Approximately 50% of CP is restored within 1 minute of recovery, with the rate of resynthesis occurring faster in type ? fibers. This difference in rate of CP resynthesis is possibly attributed to the higher aerobic potential (and smaller decrease in pH) of type ? vs type ?? fibers.[3]

Creatine supplementation has been shown to increase pre-exercise total creatine (TCr), increase availability of CP, yield smaller decreases in muscle pH, and allow for a higher rate of CP resynthesis during recovery.[3] This increased availability of creatine augments the physiological capacity for activities that are primarily limited by the rapid availability of ATP to produce high force of power and short-term repetitive force production. This is supported by the ergogenic benefit reported in most studies; improved performance in high-intensity, short duration, intermittent exercise, and improved fatigue resistance.[1,3,7,10,11,13,14,16,17,19,21,22] Some anaerobic studies have reported no ergogenic benefit, and studies of endurance exercise have shown decreased performance, which has been attributed to the increased total body weight associated with creatine ingestion.[5,12,18,20]

Acute increases in strength or power performances may improve quality of training in some individuals and thus provide quicker gains toward an individual's genetic potential.[7] This is most likely to be of benefit in elite athletes training intensely who would benefit from the smallest gains in exercise performance. The positive effect of creatine loading on CP resynthesis and improvement in exercise performance is highly variable among individuals and appears to be closely related to the extent of muscle creatine uptake during supplementation.[24,28]

The benefit of creatine supplementation on post-exercise CP resynthesis is not apparent if creatine uptake is < 20 mmol/kg.[24,28] Approximately 20% to 30% of individuals are considered "non-responders" and show a < 10 mmol/kg (8%) increase in TCr following the standard creatine loading regimen used in most studies (20 g/day for 5 to 7 days).[24,28] Individuals with an initial TCr near or at the creatine saturation point (150 to 160 mmol/kg) do not appear to show improved uptake or performance following creatine ingestion.[1] Normal muscle creatine concentrations average 120 mmol/kg (range, 100 to 140 mmol/kg); the maximum TCr concentration of 150 to 160 mmol/kg is achieved by only about 20% of subjects.[3,5,7,28,29]

Creatine uptake has been shown to be augmented by up to 10% when supplementation is given in conjunction with submaximal exercise and by an average of 60% when given in combination with carbohydrates (20 g/day creatine for 5 days with 370 g/day simple carbohydrates).[5,29,30] The administration of carbohydrates yields an increase in insulin that has been found to enhance the transfer of creatine into muscle cells and increase skeletal muscle creatine retention.[24] No additional benefit in creatine uptake was observed with carbohydrate ingestion plus exercise.[29] Conversely, muscle creatine loss has been reported to be increased during fasting.[29]

Caffeine has been shown to stimulate the sodium-potassium ion pump in muscle directly as well as indirectly via stimulating the release of epinephrine. Contrary to expectations of one small study, administration of caffeine did not improve performance related to oral creatine supplementation and appeared to fully abolish the ergogenic effects of muscle creatine loading.[31,32] While both the creatine and creatine plus caffeine regimens increased CP to the same extent, only the creatine group exhibited improved performance.[32] It was concluded that caffeine-containing beverages were an inappropriate vehicle for creatine supplementation; it is worth noting the average caffeine dose studied (400 mg/day) and usual caffeine content in soft drinks (40 to 60 mg) and coffee (50 to 200 mg).[28,32,33] Conclusions on caffeine's effect on creatine uptake would be premature based on data to date.

Studies evaluating the ergogenic properties of creatine supplementation have routinely used a loading dose of 20 to 30 g/day divided into 4 to 5 equal doses for 5 to 9 days (0.3 g/kg/day), following a 1992 study that first reported an ability to increase skeletal muscle TCr content after dietary supplementation for more than 2 days.[7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,23,34] One recent study has reported improved performance subsequent to a 6-day, low-dose creatine regimen of 0.1 g/kg of lean body mass (average, 7.7 g/day).[22] A maintenance dose of 2 to 5 g/day for up to 10 weeks has been used in an effort to determine the lowest dose required to maintain creatine stores over the long-term.[7,19,34] However, further studies are needed as it has been shown that creatine levels at one month were not significantly different between healthy subjects who ingested only a 6-day loading dose and those who followed the loading dose with 2 g/day for 30 more days.[15]

Endogenous production of creatine is reversibly inhibited after creatine supplementation, as indicated by the return of muscle creatine concentrations to presupplementation levels within 4 weeks of discontinuing supplementation.[1,15,18]

Pathophysiology: Possible pathological significance of the creatine pathway and phosphate shuttle would fall into two categories: (1) Diseases presenting with a deficiency in CK and (2) diseases resulting from a deficiency in creatine.[6]

Several diseases are related to energy deficiencies, some of which may be related to creatine metabolism disturbances.[24] Muscular dystrophy may be related to myofibrillar or mitochondrial CK deficiencies; heart and muscle disease caused by phosphate depletion may be a result of defects in the CP shuttle; liver disease can impair the synthesis of the creatine precursors, arginine and glycine. The liver is also the site of methylation of guanidoacetic acid and requires methionine; deficiency of this amino acid might be responsible for muscle weakness, and in the brain, for functional problems caused by creatine deficiency. It is also possible that creatine synthesis from arginine is impaired in gyrate atrophy of the retina that presents as a failure in retinal energy generation.[6]

Muscle hypertrophy of exercise is accompanied by the increased delivery of CP to protein synthesis sites, which may provide insight to hypertensive cardiac hypertrophy; increased vascular resistance in hypertension would stimulate increased cardiac contraction and protein synthesis resulting in an enlarged myocardium.[6]

Animal studies using creatine analogs (which inhibit the uptake of creatine) reported smaller and lighter muscles, growth retardation and weakness, and loss of thick and thin filaments microscopically.[6] The gene for the creatine transporter protein has been mapped to the human chromosome Xq28; this locus has also been linked to the genes for several neuromuscular disorders such as Emery-Dreifuss muscular dystrophy, Barth syndrome, infantile cardiomyopathy, and myotubular myopathy.[24]

CP levels decrease in rat brains injected with ammonium chloride in a model of hepatic coma, accompanied by a decrease in protein synthesis. Protein synthesis in brain tissue has been shown to be even more sensitive to CK inhibition than muscle tissue.[6]

While no effect of creatine supplementation was seen on the lipid profiles of healthy young men, preliminary data in men and women with total cholesterol > 200 mg/dL suggest that creatine supplementation (5 g/day for 56 days) may modulate lipid metabolism in the hyperlipidemic patient.[35,36]

Creatine supplementation has been evaluated in patients with various diseases and an array of signs and symptoms caused by possible defects in creatine metabolism, including gyrate atrophy of the choroid and retina, myophosphorylase deficiency (type 5 glycogenesis; McArdle disease), mitochondrial cytopathies, rheumatoid arthritis, and congestive heart failure. Improvement in skeletal muscle performance, physiology, and symptomology was noted in several patients, but more studies are needed before clinical benefit can be determined in these conditions. [37,38,39,40,41,42,43,44,45,46] A potential problem with long-term supplementation could be the down-regulation of the creatine transport protein, which would antagonize such treatment. [24]

TOXICOLOGY: There are no safety data available regarding creatine use in athletes < 18 years of age. [7]

A theoretical concern exists regarding the extra creatine load placed on developing organs, particularly the kidneys, as well as the effects on muscle and bone junctions in the skeletally immature.[47]

Creatine supplementation elevates urinary and serum creatine, which can increase the creatine load on the kidneys; healthy kidneys appear to manage short-term creatine loading without compromised function.[32,34] However, patients with a history of renal dysfunction or diabetes or those taking concomitant nephrotoxic agents should avoid creatine supplementation or be monitored closely if supplementation is necessary. [47,48,49,50,51] Healthy individuals should consider regular testing to detect any potential renal dysfunction that may develop because of unknown decreased compensatory mechanisms. [50]

Anecdotal reports of adverse effects include dehydration, heat-related illnesses, reduced blood volume, electrolyte imbalances, and muscle cramping. [2,7,50] Intracellular fluid retention in the muscle cell may predispose to dehydration, but studies are lacking; a dehydrated state before exercise decreases renal concentrating ability.[47,50] Optimal hydration is recommended during supplementation to reduce risk of these hydration-related side effects. [47,50]

Most studies indicate an increase in total body mass by about 0.7 to 1.6 kg following short-term supplementation (20 to 25 g/day for 5 to 7 days), which appears most likely to be due to water retention as it is unlikely that protein synthesis changes would be reflected in this time frame. Long-term supplementation trials (20 to 25 g/day for 5 to 7 days and 2 to 25 g/day for up to 84 days) have reported significantly greater gains (0.8 to 3 kg) in total body mass and fat-free mass with no change in the percentage of total body water; suggesting enhanced lean tissue accretion. [5,16] A study in 1985 of gyrate atrophy patients receiving creatine 1.5 g/day for one year reported that the diameters of type ?? muscle fibers increased significantly over the placebo group ($p < 0.001$). [37] This could have negative effects on mass-dependent activities such as running and swimming.[47]

A theoretical concern exists regarding the neurological effect of oral creatine supplementation as 3 of 32 documented complaints to the FDA regarding creatine supplementation have involved seizures. [47,50] No causal relationship has been established. [47] Conversely, creatine has been linked to neuroprotection in animal models of Huntington's chorea and has shown potential clinical benefit in a patient with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes). [50]

There have been anecdotal claims of minor GI distress (eg, nausea, diarrhea, GI pain), but no direct relationship has been established, and no studies have reported cramping as a side effect of creatine supplementation.[7,48] Supplementation studies using creatine for up to 8 weeks have reported minimal or no liver enzyme elevation; however, some concern exists regarding the reversibility of suppression of endogenous creatine synthesis after long-term supplementation. [47]

Data are limited in the elderly; one study (n = 32) evaluating the effects of creatine ingestion in sedentary and weight-trained older adults (67 to 80 years of age) reported no side effects with a 52-day oral supplementation regimen (20 g/day for 5 days, followed by 3 g/day for 47 days). [34] Small studies of gyrate atrophy patients receiving supplementation of normal dietary intake (1.5 to 2 g/day) for up to 6 years reported no untoward effects. [37,38] Additionally, no evidence for significant alterations in blood pressure, renal indices, or plasma CK activity was found in a study in young healthy men and women. [51]

SUMMARY: The beneficiaries of creatine's positive ergogenic properties are those who would benefit from the smallest of gains in anaerobic exercise performance (eg, elite athletes requiring short bursts of high power).

Creatine monohydrate supplementation of 20 g/day for 5 to 9 days has been shown to enhance performance of short-duration, dynamic, high-intensity, intermittent exercise.[3,6,10] By improving the ability of muscle to sustain ATP resynthesis during exercise and by reducing the extent of fatigue in type ?? muscle fibers, creatine supplementation preserves the ability of the muscle to perform exercise requiring speed and power. [1,8,9,10,11,13,14] Creatine supplementation does not appear to enhance endurance exercise performance, nor does it modify the metabolic response during this type of exercise. [3,5]

Positive effects on performance have been reported with short-term loading doses (20 to 30 g/day in 4 to 5 divided doses for 5 to 7 days) and with loading doses followed by a maintenance regimen of 2 to 5 g/day for up to 10 weeks. [2,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23] Alternatively, an equally effective benefit may be seen with 3 g/day over at least 4 weeks but is likely to be at a slower rate. [28] Evidence does not support potentiation of benefit with higher doses and further supplementation will simply result in urinary excretion of excess creatine. [1]

The therapeutic role of creatine supplementation has yet to be determined for diseases related to abnormalities in creatine metabolism; however, improvement in skeletal muscle metabolism or symptomology has been demonstrated in a few patients.[37,38,39,40,41,42,43,44,45,46]

Short-term creatine supplementation appears to be well tolerated in healthy subjects and patients; no untoward effects have been noted in the scientific literature except for weight gain. Intracellular fluid retention in the muscle following creatine ingestion may be a predisposing factor to dehydration-related effects; optimal hydration is therefore recommended to decrease the risk of these effects. There are reports of minor GI distress, dehydration, heat-related illnesses, reduced blood volume, electrolyte imbalances, muscle cramping, and weight gain.

PATIENT INFORMATION— Creatine

Uses: Creatine has been shown to enhance performance of short-duration, dynamic, high-intensity, intermittent exercise. The therapeutic role of creatine supplementation has yet to be determined for diseases related to abnormalities in creatine metabolism; however, improvement in skeletal muscle metabolism and/or symptomology has been demonstrated in a few patients.

Side Effects: There are reports of minor GI distress, dehydration, heat-related illnesses, reduced blood volume, electrolyte imbalances, muscle cramping, and weight gain.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CREATINE

CUCURBITA

DATE OF ISSUE: FEB 2000

REPLACES MONOGRAPH DATED: MAY 1990

SCIENTIFIC NAME(S): *Cucurbita pepo* L. (pumpkin or pepo), *C. maxima Duchesne* (autumn squash), *C. moschata* Poir. (crookneck squash). Family: Cucurbitaceae.

BOTANY: The members of this genus are plants that develop long vine-like stems that produce large edible fruits. The large, yellow flowers are eaten in some Mediterranean cultures; whereas, the fruits are eaten worldwide. Many cultivated varieties can be found throughout the world.

HISTORY: The seeds of several species of cucurbita have been used in traditional medicine for centuries. They have been used to immobilize and aid in the expulsion of intestinal worms and parasites. Traditionally, the seeds of *Cucurbita* species are ingested after grinding or as a tea. The amount of seeds that can exert a pharmacologic effect appears to vary by species, from as few as 50 g to more than 500 g. These are usually taken in several divided doses. Some cultures suggest eating small amounts of the seeds on a daily basis as a prophylactic against worm infections. The seeds also have been used in the treatment of prostate gland disorders.[1]

CHEMISTRY: The pharmacologically active anthelmintic component of cucurbita seeds appears to be cucurbitin, a carboxypyrrolidine. The distribution of this compound is limited to seeds of this genus. The concentration of cucurbitin can vary from 0.53% to 1.94% in *C. maxima*, from 0.4% to 0.84% in *C. moschata*, and from 0.18% to 0.66% in *C. pepo*. A 1-dose pumpkin seed extract prepared from a Lebanese variety of cucurbita contained about 1.5 g of cucurbitin. [2]

Cucurbita is rich in carotenoids. Pressed seeds of *C. pepo* contain lutein, carotene, and beta-carotene.[3] *C. moschata* contains 19 carotenoids, with beta-carotene accounting for 74% of total carotenoid content. This "Baianinha" squash is one of the richest sources of provitamin A. [4] The species *C. maxima* is also high in carotenoid content containing 11 carotenoids, which include lutein and beta-carotene. [4,5]

C. pepo has a high fatty acid content containing mainly palmitic, stearic, oleic, and linoleic acids. The oil content of the seed is 50%. Vitamin E content, primarily gamma-tocopherol, is very high, making certain pumpkin varieties desirable. [6,7] Long chain hydrocarbons and fatty acids have been reported in fruits of *C. maxima*.[8]

Amino acid content in cucurbita has been reported. Amino acid patterns and certain protein isolates have been studied in the species *C. moschata*, evaluating nutritional characteristics.[9] Computer analysis of amino acids in *C. pepo* has been performed to find properties of phytochromes in the plant. [10]

Flavonol content from *C. pepo* has been discussed[11] and sterols in *C. moschata* seed oil have been reported.[12] *C. maxima* flowers contain spinasterol.[13] Sterols and triterpenoids in *C. maxima* tissue cultures also have been evaluated.[14]

Other reports concerning cucurbita chemistry include *C. pepo* male flower constituents,[15] lectins from related species of *C. ficifolia* seedlings,[16] and root starches from *C. foetidissima* and *C. digitata*.[17]

PHARMACOLOGY: Cucurbitin inhibits the growth of immature *Schistosoma japonicum* in vivo, and a patent has been granted for an effective aqueous extract of the seeds for use as a human anthelmintic.[2] Anthelmintic activity has been demonstrated in mice.[18] In certain species of parasites, cucurbita had no effect. A dried-seeds diet of *C. maxima* given to mice infected with *Vampirolepis nana* tapeworm had no anthelmintic actions.[19] Because cucurbitin varies widely among plants of the same species, it has often been difficult to replicate the efficacy of the crude preparations. Cucurbitin has been generally supplanted by more effective single-dose vermifuges.[2] In one report, *C. maxima*in an oral preparation displayed strong antimalarial activity in mice, reducing the parasites by 50%. [20] In another report, an extract of *C. maxima* demonstrated antitumor potential against *Neurospora crassa*.[21]

Characteristics[22] and nutritional aspects[23] of cucurbita have been addressed. Studies on antilipolytic activity of *C. maxima* also have been performed.[24]

The influence of *C. maxima* on age-associated impairments has been reported.[25]

In a randomized, 3-month, double-blind study, a preparation of *C. pepo* (curbicin) improved certain parameters of benign prostatic hyperplasia including urinary flow, micturition time, residual urine, and urinary frequency vs placebo. [26]

Related species *C. ficifolia* exhibits hypoglycemic actions in rabbits.[27,28]

TOXICOLOGY: Severe toxicity has not been reported with the use of cucurbita extracts. In a 53-patient, randomized, double-blind trial, no side effects from *C. pepo* were noted.[26] Ingestion of *C. maxima* seeds by rats and pigs over a 4-week period resulted in no changes in glucose, urea, creatinine, liver enzymes, blood counts, etc.[29] One report on *C. moschata*describes dermatitis.[30]

SUMMARY: Seeds of *Cucurbita* species have been used throughout the world for centuries as a vermifuge. The active component, cucurbitin, is an effective vermifuge agent in vitro and may also be effective in humans. Cucurbita also demonstrates antimalarial and antitumor activities. The plant improved symptoms of BPH in one trial. It may be useful in diabetes, but more human research is warranted. Preparations of this plant have not been generally associated with toxicity.

PATIENT INFORMATION— Cucurbita

Uses: Squashes, pumpkins, and other fruits of this family are consumed throughout the world. Flowers and seeds of some species are eaten. Seeds of some species are a traditional vermifuge. Also, components of some seeds may be useful in treating prostatic disorders.

Side Effects: Severe toxicity has not been reported with the use of cucurbita extracts.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CUCURBITA

CUMIN

DATE OF ISSUE: APR 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Cuminum cyminum* L. also referred to as *C. odorum* Salisb. Family: Apiaceae (Umbelliferae)

COMMON NAME(S): Cumin, cummin

BOTANY: This small annual plant is native to the Mediterranean region where it is cultivated extensively. The cumin seed is widely used in cooking. The dried seeds resemble those of caraway, but are straighter in form and have a coarser taste and odor than caraway seeds. [2] Major cumin seed producers include Egypt, Iran, India and Morocco.[1] The United States is among the largest producers of cumin oil.This spice should not be confused with sweet cumin, which is a common name for anise (*Pimpinella anisum*).[3] Black cumin (*Bunium persicum*) has smaller and sweeter seeds than *C. cyminum*, but is not commercially important. Another black cumin (*Nigella sativa*) is not related to cumin.[4]

HISTORY: Cumin is a major component of curry and chilir powders[1] and has been used to flavor a variety of commercial food products. The oil, which is derived by steam distillation,[4] is used to flavor alcoholic beverages, desserts and condiments, and has been used as a fragrant component of creams, lotions and perfumes. [1]

CHEMISTRY: Cumin seeds contain up to 5% of a volatile oil. In addition, the seeds yield about 22% fats, numerous free amino acids and a variety of flavonoid glycosides, including derivatives of apigenin and luteolin. [1]

The volatile oil is composed primarily of aldehydes (up to 60%) and the cuminaldehyde content varies considerably depending on the source of the oil (ie, fresh versus ground seeds). Fine grinding of the seed can result in the loss of up to 50% of the volatile oil, [1] with the greatest loss occurring within one hour of milling. Other major components of the oil include monoterpene hydrocarbons, and sesquiterpenes constitute minor constituents of the oil. The chief components of the characteristic aroma of unheated whole seeds are 3-p-menthen-7-al and cuminaldehyde in combination with other related aldehydes.

PHARMACOLOGY: The petroleum ether soluble fraction of cumin has been reported to have antioxidant activity when mixed with lard. [1] No in vivo inhibition of hepatic peroxidation has been observed, even with high concentrations of cuminaldehyde. [5] However, cuminaldehyde scavenges the superoxide anion.[6]

The spice appears to have and anticancer effect as demonstrated by the ability of cumin seeds to inhibit the induction of gastric squamous cell carcniomas in mice. [7] Furthermore, cumin seeds were not carcinogenic when tested by the reverse mutation *Salmonella typhimurium* test.[8]

Cumin, given at a level 5-fold higher than the normal human intake level, did not reduce serum or liver cholesterol levels in rats fed a hypercholesterolemic diet. [9]

Cumin oil and cuminaldehyde have been reported to exhibit strong larvicidal and antibacterial activity. At in vitro concentrations of 300 or 600 ppm, cumin oil inhibited the growth of *Lactobacillus plantarum*.[10]

TOXICOLOGY: Cumin is generally recognized as safe for human consumption as a spice and flavoring. [4] Cumin oil components appear to be absorbed rapidly through shaved intact abdominal mouse skin and undiluted cumin oil has phototoxic effects that are not related to cuminaldehyde, but to another photosensitizing component.[1]

SUMMARY: Cumin, a widely used spice, is a major ingredient in curry and chilies. Its aromatic fragrance makes it valuable in cooking and perfumery.

PATIENT INFORMATION— Cumin

Uses: The seeds are used in cooking. The oil flavors food and scents cosmetics. Components may have antioxidant, anticancer, larvicidal and antibacterial effects.

Side Effects: The oil may have photosensitizing effects.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "C" MONOGRAPHS
    CUMIN

"D" MONOGRAPHS

DAMIANA

DATE OF ISSUE: JUL 1996

REPLACES MONOGRAPH DATED: FEB 1989

SCIENTIFIC NAME(S): *Turnera diffusa* Willdenow et Schultes var. *aphrodisiaca* Urban. Also known as *T. aphrodisiaca* Ward. and *T. microphylla* Desv. Family: Turneraceae

COMMON NAME(S): Damiana, herba de la pastora, Mexican damiana, old woman's broom, rosemary (not to be confused with the spice *Rosmarinus officinalis* L.)

BOTANY: Damiana is a Mexican shrub also found throughout the southern US and many parts of South America. It has small, yellow-brown aromatic leaves. The leaves are broadly lanceolate, 10 to 25 mm long with three to six teeth along the margins. The red-brown twigs are often found mixed in the crude drug along with the spherical fruits.

HISTORY: The scientific literature on the plant dates back more than 100 years when reports described its aphrodisiac effects. [1] Damiana history began with its early use by the Maya (under the name mizibcoc) in the treatment of giddiness and loss of balance. Its primary use in the last century has been as an aphrodisiac. [2] Father Juan Maria de Salvatierra, a Spanish missionary, first reported that the Mexican Indians made a drink from the damiana leaves, added sugar and drank it for its love-enhancing properties. In the 1970s, it was imported into the US as a tincture and advertised as a powerful aphrodisiac, to improve the sexual ability of the enfeebled and the aged and to provide increased activity to all the pelvic secretions. Suffice to say that in this patent medicine era, it enjoyed some success.

Damiana was admitted into the first edition of the National Formulary (NF) in 1888 as an elixir and fluid extract. However, it never made it into the US Pharmacopeia and the elixir was finally dropped from the NF in 1916. The fluid extract and the crude drug (leaves) were listed in the NF until 1947. Although some commercial companies continued to sell it to the American market, damiana had almost disappeared until the 1960s "hippy" movement brought it back into popularity.

Today, damiana has found its way into a number of herbal OTC products, in particular those claiming to induce a legal herbal "high." In the Caribbean, damiana leaves are boiled in water and the vapors inhaled for the relief of headaches. Teas are said to aid in the control of bed wetting. [3]

CHEMISTRY: Damiana contains from 0.5% to 1% of a complex volatile oil that gives the plant its characteristic odor and taste. Analysis of the oil has identified a low-boiling fraction composed mainly of 1,8-cineol and pinenes, but their consistent presence in all forms of the plant has been disputed. [4] A fraction with a higher boiling point is believed to contain thymol and a number of sesquiterpenes. In addition, the plant contains gonzalitosin, a cyanogenic glycoside and a brown amorphous, bitter substance (damianin) among other components.[5]

PHARMACOLOGY: No substantive data is available to support the aphrodisiac effects of damiana. Although it has been postulated that the plant may contain the central nervous system stimulant caffeine, the aphrodisiac effect has not been attributed to any specific components. The volatile oil in damiana might be sufficiently irritating to the urethral mucous membranes to account for its so-called aphrodisiac effects. [2] Despite containing a complex mixture of components, there is no evidence to support claims for an aphrodisiac or hallucinogenic effect.

TOXICOLOGY: No significant adverse effects have been reported in the literature. However, persons claiming to experience damiana-induced hallucinations should be monitored closely and the possibility of ingestion of other drugs should be considered.

SUMMARY: Damiana is a plant that has received considerable attention for its purported aphrodisiac and hallucinogenic effects. Although there are anecdotal reports of these effects, the plant lacks any verifiable pharmacologic activity. No new significant chemical or pharmacological studies could be found in the scientific literature up to mid-1996.

PATIENT INFORMATION — Damiana

Uses: Damiana is reportedly an aphrodisiac and hallucinogen.

Side Effects: Significant adverse effects have not been reported.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DAMIANA

DANDELION

DATE OF ISSUE: AUG 1998

REPLACES MONOGRAPH DATED: DEC 1987

SCIENTIFIC NAME(S): *Taraxacum officinale* Weber, also referred to as *Leontodon taraxacum* L. Family: Compositae

COMMON NAME(S): Dandelion, lion's tooth

BOTANY: The dandelion is a weedy composite plant with a rosette of leaves radiating from its base. The stem is smooth and hollow and bears a solitary yellow head consisting solely of ray flowers, which produces a cluster of numerous tiny, tufted, single-seed fruits. The plant has a deep taproot. The leaves may be nearly smooth-edged, toothed or deeply cut; the toothed appearance gives rise to the plant's name (dent-de-lion means "lion's tooth" in French). [1] This perennial plant can reach 20 inches in height. It grows wild in most parts of the world and is cultivated in France and Germany. [2]

HISTORY: The dandelion is mentioned as early as the 10th century by Arab physicians, who used it for medicinal purposes. [3] The plant was also recommended in an herbal written in the 13th century by the physicians of Myddfai in Wales. [2] It is native to Europe and Asia, but was naturalized in North America and now grows widely as a weed in nearly all temperate climates. It is cultivated by some European growers, and more than 100 specialized varieties have been developed. The bitter greens are used raw in salads, in wine making or cooked like spinach. The root is roasted and used to brew a coffee-like beverage said to lack the stimulant properties of coffee. Dandelions have long been used in herbal remedies for diabetes and disorders of the liver (the sugars in the plant are said not to aggravate this disease) and as a laxative and tonic. The juice of the leaves has been used to treat skin diseases, loss of appetite and to stimulate the flow of bile. [3]

CHEMISTRY: Dandelions are one of nature's richest green vegetable source of beta-carotene, from which vitamin A is created (14,000 IU/100 g leaf vs. 11,000 IU/100 g in carrots). They are also a very good source of fiber, potassium (297 mg or 7.6 mEq/100 mg leaf), iron, calcium, magnesium, phosphorus, thiamine and riboflavin. Sodium and vitamins C and D are also present. [4]

Dandelions contain acids including caffeic, p-hydroxyphenyl-acetic, chlorogenic, oleic, palmitic and the fatty acids linoleic and linolenic. Other acids found are gallic and ascorbic acids.

The plant also contains terpenoids, sesquiterpenes (responsible for the bitter taste), triterpenes (beta-amyrin, taraxol and taraxerol), luteolin and the glycoside apigenin. Other reported constituents in dandelion include choline, inulin, pectin, glutin, gum, resin, sterols (ß-sitosterol, stigmasterol, taraxasterol, homotaraxasterol) coumestrol and sugars (fructose, sucrose, glucose). [2,5,6]

Reports are available evaluating fructofuranosidases from dandelion roots, [7] taraxinic acid 1´-O-beta-D-glucopyranoside [8] and furan fatty acid content. [9]

PHARMACOLOGY: Dandelion has been classified as a hepatic, mild laxative, cholegogue, diaphoretic, analgesic, stimulant, tonic and a regulator of blood glucose. [5,6,10,12,13,14,15] The roots have been used as a laxative, diuretic, tonic, hepatic and for spleen ailments. [6,12,14] Root and leaves have been used for heartburn, bruises, chronic rheumatism, gout, diabetes, eczema and other skin problems as well as for cancers. [12,14]

Diuretic effects of dandelion extracts have been documented in mice. [5] One reported animal study indicated a greater diuretic effect achieved from herbal extracts than root extracts and compared the effects of a 50 ml/kg body weight dose (2 g dried herb/kg) to the effects achieved with 80 mg/kg of furosemide. [5] This study also reported the effects of dandelion to be greater than other plant diuretics, including Equisetum and Juniper berry. [5,10] This diuretic effect, likely a result of sesquiterpene lactone activity and high potassium content, [10] has been used to treat high blood pressure. [2,10] A later report observed no significant diuretic activity from the plant. [11] These same sesquiterpene lactones may contribute to dandelion's mild anti-inflammatory activity demonstrated. [5,12]

It is effective as a detoxifying herb, working primarily on the liver and gallbladder to remove waste. It may aid gallbladder ailments and help "dissolve" gallstones. [2] However, dandelion should only be used for gallstones under a physician's direction; it is generally contraindicated in bile duct obstruction, empyema or ileus. [5,10,12,13] Increases of bile secretion in rats (= 40%) have been attributed to activity of bitter sesquiterpene lactones in the root. [12] These lactones also increase gastric secretions that can cause gastric discomfort. [10,12] Use for dyspeptic disorders may be attributed to the anti-ulcer and gastric antisecretory activity of taraxerol, one of the terpenoid alcohols also found in the root. [4] Dandelion is also considered an appetite-stimulating bitter. [4,10] The bitter principles, previously known as taraxacin which have recently been identified as eudesmanolides, are contained in the leaves and appear to be unique to dandelion. [10]

Hypoglycemic effects have been demonstrated in healthy, non-diabetic rabbits with a maximum decrease in blood glucose achieved at a dose of 2 g/kg. [5] The maximum effect of dandelion was reported to be 65% of the effect produced by tolbutamide 500 mg/kg. [5] Another report found no effect on glucose homeostasis in mice. [16] Inulin, reported to have antidiabetic activity, may contribute to dandelion's glucose regulating properties. [14,17]

In vitro antitumor activity with a mechanism similar to that of lentinan (a tumor polysaccharide) has been reported. [5] , *Taraxacum* species have been used in China for over 1100 years in treating breast cancer and other breast ailments. [12] Clinical studies using Chinese *Taraxacum* species also support the use of dandelion to treat hepatitis as well as various respiratory infections. [12]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Like many plants in this family, dandelions are known to cause contact dermatitis in sensitive individuals. [18,19] A case report of a 9-year-old boy describes positive patch test reactions to dandelion and other compositae-plant oleo resins. [20] Two out of seven patients, each with histories of dandelion dermatitis, reacted not only to dandelion extracts, but to a sesquiterpene mix. [21] These sesquiterpene lactones are believed to be the allergenic principles in dandelion. [2] Taraxinic acid 1´-O-beta-D-glucopyranoside has also been identified as an allergenic component. [22]

Acute toxicity of dandelion is low. LD_{50} values in mice for the root are 36.8 g/kg and for herb are 28.8 g/kg. [2] A case report describes toxicity in a patient taking an herbal combination tablet that included dandelion. It was unclear as to which constituents were responsible. [23] Dandelion may be potentially toxic because of the high content of potassium, magnesium and other minerals. [24]

SUMMARY: The dandelion is a common weed that has been collected and used as a salad green, an ingredient for wine and an herbal medicine. It has limited documented pharmacological activity, but its use persists in herbal medicine for minor medicinal and nutritional purposes. The principal hazard appears to be contact dermatitis.

PATIENT INFORMATION — Dandelion

Uses: Dandelion has been used for its nutritional value in addition to other uses including diuresis, regulation of blood glucose; liver and gall bladder disorders; an appetite stimulant; and for dyspeptic complaints.

Side Effects: Contact dermatitis and gastric discomfort have been reported.

Dosing: Dandelion root has been used as a tonic for digestive complaints in doses of 9 to 12 g/day, prepared as a tea. [25]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DANDELION

DANSHEN

DATE OF ISSUE: JUL 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Salvia miltiorrhiza* Bunge Family: Labiatae

COMMON NAME(S): Danshen, Tan-Shen, Tzu Tan-Ken (roots of purple sage), Hung Ken (red roots), Shu-Wei Ts'ao (rat-tail grass), Ch'ih Shen (scarlet sage), Pin-Ma Ts'ao (horse-racing grass)

BOTANY: Danshen is a perennial herb found mainly on sunny hillsides and stream edges. Violet-blue flowers bloom in the summer. The leaves are oval, with finely serrated edges. The fruit is an oval brown nut. Danshen's roots, from which many of the common names are derived, are a vivid scarlet red. [1] Danshen is related to common sage (of the same genus *Salvia*), the culinary herb.

HISTORY: Used in ancient Chinese medicine for generations, danshen joins many other of these remedies that must be evaluated scientifically to separate fact from myth in the therapeutic claims. In the mid-1980s, danshen (among other Chinese medicinal herbs similar in structure) was presented at the Chinese University of Hong Kong for discussion of its vasoactive properties. [2] The herb has also been used for menstrual irregularity, to "invigorate" the blood and for other ailments such as abdominal pain and insomnia.[1]

CHEMISTRY: Derivatives isolated from danshen include protocatechualdehyde and 3,4-dihydroxyphenyl-lactic acid, both of which are derived from a 4-substituted catechol structure. Structures of this type play a role as vasoactive agents. [2] Twenty-eight compounds, including tanshinones and related terpenoids, have been identified, using both HPTLC and mass spectrometric analysis.[3] Miltirone, an "active central benzodiazepine receptor ligand," has been isolated from the plant, from which twenty-one 0-quinonoid-type compounds and one coumarin-type compound have been synthesized. [4] Another report discusses the structure of "dihydroisotanshinone ?" from danshen.[5] Salvianolic and rosmarinic acids have also been isolated from the plant. [6,7,8]

PHARMACOLOGY: Circulation improvement from danshen's use has long been practiced. Its ability to "invigorate" the blood is now being proven in many Chinese studies. Danshen has been used for menstrual problems, to relieve bruising and to aid in granulation. [1]

Pharmacokinetic studies of constituent 3,4-dihydroxyphenyl-lactic acid have been performed in rabbits. [9]

In animal studies, a mixture of danshen with chuanxiong excelled in preventing capillary contraction, thus improving circulation in a hypoxic, high-altitude environment.[10] However, this same mixture was not satisfactory to prevent cardiopulmonary changes caused by high altitudes in humans. [11]

Another danshen mixture, this time with foshousan, may offer protection to erythrocytes, improving blood flow to the placenta and increasing fetal birth weight in pregnant rats exposed to cigarette smoke.[12]

Danshen use in ischemic stroke has been reported.[13]

Danshen has been studied for its effects on mechanical activity and coronary flow rate in isolated rat hearts. After 30 minutes of ischemia, reperfusion was then allowed for 30 minutes. Although danshen exerted a negative inotropic effect, it caused an increase in coronary flow rate, suggesting some protective actions of the drug in ischemic situations.[14]

Antithrombotic actions of danshen have also been reported. A proposed mechanism of this effect may be related to a semisynthetic analog of plant constituent "salvianolic acid A." This "acetylsalvianolic acid A" reduced cerebral infarction and lessened neurological deficits in ischemic rats with cerebral artery thrombosis. [7] In another report, acetylsalvionolic acid A was also found to exert suppressive effects on collagen-induced platelet 5-HT release while inhibiting aggregation in vitro. [6] The rosmarinic acid isolate from danshen also displayed antithrombotic effects when injected into rats. This was because of platelet aggregation and promotion of fibrinolytic activity as well. [8]

Danshen use results in possible dilation of blood vessels, increase in portal blood flow and prevention of coagulation to improve tissue ischemia. This accelerates repair and enhances nutrition in hepatic cells. [2]

More than 70% of chronic hepatitis patients responded to danshen therapy in areas such as LFTY improvement and relief of symptoms such as nausea, malaise, liver pain and abdominal distention.[2] Another report confirms danshen therapeutic effects in chronic active hepatitis as well. [15]

Other effects of danshen include: Cytotoxic activities (of tanshinone analogs) against certain carcinoma cell lines, many of which were effective at concentrations less than 1 mcg per ml;[16] marked protective action against gastric ulceration; [17] and CNS effects[18] including neurasthenia and insomnia treatments.[1]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Coadministration of danshen and warfarin result in exaggerated warfarin adverse effects. Both pharmacodynamic and pharmacokinetic parameters were affected when studied in rats. Observed interactions such as increased warfarin bioavailability, decreased warfarin clearance and prolonged prothrombin times are all indicative of clinically important interactions if danshen and warfarin are taken together. [19,20] Severe clotting abnormalities have been reported in a case where danshen induces overcoagulation in a patient with rheumatic heart disease. [21] Another case report is available describing an interaction between danshen and methylsalicylate medicated oil.[22]

SUMMARY: Danshen has been used in ancient Chinese medicine for circulatory and related disorders. Some of its constituents are derived from a 4-substituted catechol structure responsible for the drug's vasoactive characteristics. Studies on dashen's effects on circulation improvement, protective actions against ischemia, antithrombotic effects and hepatitis are ongoing. Clinically important adverse interactions between warfarin and danshen have been reported more than once.

PATIENT INFORMATION — Danshen

Uses: Danshen's effects on circulation improvement have long been utilized. Danshen has also been used to alleviate menstrual irregularity, abdominal pains and insomnia.

Interactions: Adverse effects of warfarin are exaggerated when danshen and warfarin are coadministered.

Side Effects: The most prominent side effect of danshen seems to be blood clotting disorders. Danshen can also cause difficulties when taken with warfarin or methylsalicylate medicated oil.

Dosing: The recommended dose of danshen root is 9 to 15 g/day. Exercise caution because of the potential drug interaction with warfarin. [21,22,23,24]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DANSHEN

DEER VELVET

DATE OF ISSUE: OCT 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Antler velvet of species *Cervus nippon* T., *Cervus elaphus* L. (Wapiti), *Cervi parvum*

COMMON NAME(S): Deer velvet, velvet antler, *Cornu cervi parvum*, lu rong (hairy young horn)

SOURCE: Deer antlers are the only mammalian bone structures to regenerate completely every year.[1] Deer antler velvet is the epidermis covering the inner structure of the growing bone and cartilage, which develops into antlers.[2] This tissue grows each spring on male *Cervus sp*. (North American elk and red deer) and should be removed by a veterinarian or certified farmer. The ethics, including use of local anesthetics, and procedures of harvesting antler velvet have been reported.[3,4,5,6] Velvet yield depends on several factors, including season, parasites, or injury.[7] After removal of the deer velvet, it is collected and then frozen or dried prior to its manufacture into various "medicinal" forms including powders, extracts, teas, capsules, and tablets. Each part of elk velvet contains varying compounds, but the deer antler velvet contains the largest concentrations of those found to be beneficial. (Antler also has been sold by the slice). Heating during processing may reduce or destroy the purported beneficial effects of velvet antler. Various preparation methods, including freeze-drying and non-heat-producing methods have been reported.[8,9,10,11,12,13]

HISTORY: The word *antler* is derived from the Latin Anteoculae, meaning "in front of the eyes." Antlers are present in almost all members of the deer family *Cervidae*. The first documented evidence of deer velvet as a medicinal was found on a scroll recovered from a tomb in Hunan China dating back 2000 years. The use of antler dates back to the Han Dynasty 206 BC to 220 AD. A 16th century medical text, *Pen Ts'ao Kang Mu*, lists several antler preparations including pills, tinctures, and ointments. In traditional chinese medicine, velvet antler has been used for over 2000 years as a tonic, to improve bone health, to nourish the blood, reduce swelling, and to treat impotence. Later research on deer antler dates back to the 1980s in Russia. Hundreds of articles have since been published including those documented by Chinese, Korean, and Japanese scientists. In 1999, the use of velvet antler was scientifically supported by clinical research in compliance with FDA regulations for its beneficial effects in treating arthritis. However, empirical evidence suggests several other therapeutically valuable actions including immune stimulation, antiaging, protective and rejuvenating effects, and beneficial effects in blood and circulation.[14,15] Certain Web sites (eg, http://qeva.com/research/batch.htm and http://www.vitaminexpress.com/news/velvet.htm) offer similar but unsubstantiated information. Further study into future directions in antler research has been addressed, mentioning unsolved problems of antler evolution, development, and other areas of investigation.[16]

CHEMISTRY: Chemical comparison of various sections of growing antler (eg, tip, upper, middle, base) finds different concentrations of collagen, ash, calcium, phosphorus, magnesium, protein, lipids, amino and fatty acids, uronic acid, proteoglycans, glycosaminoglycans, and others. Collagen and minerals had higher concentrations at the base, where as the antler tip was found to be rich in the chrondroiton, containing 6-fold greater amounts than in the middle and base sections.[17,18,19,20,21] Chondroitin structures and other anti-inflammatory moieties have been reported from deer velvet as well.[22,23] Fat-soluble constituents from antler velvet[24] and certain lipids from both antler velvet and antler have been reported.[25,26] Hairy young horn of *C. nippon* also contains amino acids, fatty acids, sugars, vitamin A, sex hormones, estrone and estrandiol, sphingomyeleine, ganglioside, and prostaglandins.[27] Prostaglandins A, E, and F (primarily PGF1 alpha and PGF2 alpha) have all been reported from velvet antler.[28,29] In vivo and in vitro production of 1,25-dihydroxy, vitamin D precursors, and calcium from deer antler cells has been also investigated.[30] Gelatin components of antler velvet vs antler were compared. They were found to contain similar amino acids (glycine, proline, glutamic acid) trace elements, and polysaccharides.[31] *Cervi parvum* horn contains lecithin, choline, and uracil.[32,33] Epidermal growth factor from *C. nippon* velvet antler has been isolated.[34] Habitat has marked influence on quality of velvet antler.[35]

PHARMACOLOGY: In Chinese medicine, deer velvet has been used to treat impotence, female disorders, urinary problems, skin ailments, and knee weakness. It is also employed as a tonic in children with learning disabilities or insufficient growth.[36] Koreans use antler velvet to treat anemia and impotence and to stimulate the immune system, treat impotence, improve heart function, muscle tone, lung efficiency, and nerve function.[37]

Velvet antler's effects on cell growth and repair have been investigated in several areas. Antler regeneration not only involves bone, but nerves as well, which can grow up to 1 cm/day, an exceptional rate of growth.[38,39,40] In velvet antler, expression of neurotropin-3 mRNA in the growing process has been studied.[41] Pantocrin, a preparation of deer velvet, improved induced, whiplash-type injury in rats and rabbits by enhancing glycolysis in nervous tissue.[42,43] Insulin-like growth factors (IGF-1 and IGF-2) are important mediators for antler growth as well.[44,45,46] Insulin-like growth factors and their receptors have been isolated from deer blood during periods of antler growth. These growth factors augment cell division, suggesting a possible role in cell regeneration and repair processes in humans. In chickens administered velvet antler, growth rate and testes weight were both increased.[15] Other factors contributing to deer antler's effects in growth, include the fact that the tissue contains many cell types besides nutrients such as fibroblasts, chrondroblast, and chondrocytes.[15] Deer velvet has been shown to improve wound healing in a like manner.[15,27] Stimulation of body tissue/cell growth, such as reticuloendothelial cells and leukocytes improve metabolism and overall health. It comes with no surprise then, that velvet antler has been promoted for performance-enhancing effect on the human body.[27] Russian bodybuilders have claimed to benefit from velvet antler by increasing muscle and nerve strength.[47] Earlier studies found similar results in laboratory animals and athletes given pantocrin.[10,15,48] Later reports in this area were not reliable with regard to scientific methods (eg, double-blind, placebo-controlled studies, mainstream medical literature searches). Instead, certain commercially-oriented Web sites (eg, http://www.vitaminexpress.com/news/velvet.htm and http://www.sexualboost.com/anti-aging.htm) contained incomplete information related to performance enhancement. Some of these include positive outcomes in police recruits, male university athletes, and New Zealand rugby players and rowers given deer velvet. In addition, sexual enhancement and antiaging effects because of deer velvet were claimed.

Deer velvet is reported to have accelerated the body's natural restorative processes, reduced liver damage in mice, and through its active compounds, promoted synthesis of proteins and RNA.[49,50] Another report confirms these effects in induced liver injury in rats.[51] Velvet antler products also are claimed to demonstrate the ability to prevent/reduce shock and stress responses. Pretreatment in rats reduced cell degradation and improved recovery times from extreme temperature and electric shock exposure.[52] Velvet antler has shown marked effects on biochemical parameters related to aging in "senescence - accelerated" mice, a model for senility.[53] Deer velvet's protective effects are also apparent in the area of cancer research. Pantocrine (deer velvet preparation) increased the survival rate of mice exposed to radiation.[54] Extracts of deer antler have reduced tumor cell growth.[9] Reports of enhancement of immune function from velvet antler demonstrate significant immune stimulatory activity from several preparations,[11] as well as enhancement of phagocytes and immunoglobulin levels in mice.[55] An increase in monocytes in rats, cells necessary to the immune function of lymph, spleen, bone marrow, and loose connective tissue also has been reported.[15]

Beneficial effects of deer velvet in the area of blood/circulation are also apparent. Preparations have been shown to stimulate red blood cell synthesis in induced anemia in laboratory animals.[13,56] Antler extract also has increased neutrophil levels in mice, improving their ability to resist injury and disease.[9] Growth of fibroblasts from antler also has been reported.[57] Other positive cardiovascular effects from velvet antler include hypotensive, cholesterol reduction, circulation improvement, and reduction of blood clotting.[15,37,58]

Glycosaminoglycans, chondroitin sulfate, and glucosamine sulfate are potent anti-inflammatory agents used in arthritis treatment. As a source for the agents, velvet antler has been considered to help treat rheumatoid and osteoarthritis. (GAGRA, a glycosaminoglycan-containing product from antlers, is commercially available). The main glycosaminoglycan in velvet antler, chondroitin sulfate, binds to certain proteins to form proteoglycans (as do other lesser glycosaminoglycans [eg, decorin, keratin sulfate, hyaluronic acid, and dermatan sulfate]). These molecules regulate water retention and are important to proliferate and differentiate chondrocytes. Chondrocytes are cells that synthesize collagen and, eventually, cartilage. Type 2 collagen is necessary in the formation of elastic cartilage and is abundant in

cartilaginous antler.[12,17,19,59,60] Degenerative conditions caused by alterations in collagen synthesis include rheumatoid and osteoarthristis. Other research suggests that supplementation with type 2 collagen, like that found in antler, may help treat these conditions as well. [61,62,63]

Prostaglandins, also present in velvet antler, are known for their anti-inflammatory effects, reducing swelling in injury, infection, pain, and arthritis. [15]

The polysaccharides in velvet antler seem to be responsible for its antiulcer effects. [64] Treatment with rantarin (a deer velvet preparation), prior to GI tumor surgery, reduced stress responses in patients.[25]

TOXICOLOGY: A possible interaction of velvet antler with morphine has been reported. Velvet antler has inhibited the development of tolerance to repeated doses of morphine in mice. The article suggests that it may even be useful for prevention and therapy of the adverse actions of morphine. [65,66]

Toxicity studies of deer antler powder in rats have been assessed. A 2 g/kg dose demonstrated no mortality or adverse events on a short-term (14 days) basis. In a 90-day study, a 1 g/kg/day regimen also found no observable, significant adverse effects, except for a minor change in liver weight. [67]

Use caution due to lack of scientific evidence supporting toxicities such as those from drug residues, in pregnancy, or allergic reactions. [68]

Reliable medical literature searches (eg, *PubMed*) found no direct reports of chronic wasting disease (CWD) related to deer velvet supplementation. However, certain Web sites mention the possibility of the disease being present in antler products. The CDC has not yet found a relationship between CWD and any neurological disease that affects humans with deer velvet use.

SUMMARY: Deer velvet is the rapidly growing tissue covering the inner structure of the bone and cartilage that develops into antlers. It is rich in nutrients, containing such constituents as prostaglandins and glucosaminoglycans (chondroitin and glucosamine) that are known anti-inflammatory agents. Supplementation with deer velvet may be of benefit in these inflammation-type diseases, including arthritis and GI complaints. Velvet antler also has had beneficial effects on cell growth and repair including improved muscle and nerve strength. Performance-enhancing effects of deer antler also have been reported, as have its ability to accelerate the body's restorative processes. Velvet antler also may play a role in improving blood/circulation, cholesterol reduction, and ulcer treatment. Deer antler powder was nontoxic in rats, but evidence is lacking in humans. Chronic wasting disease may pose a potential problem, but the relationship between this and deer velvet supplementation has not been found to date.

PATIENT INFORMATION — Deer Velvet

Uses: The use of velvet antler was scientifically supported in compliance with FDA regulations for its beneficial effects in treating arthritis. Other therapeutically valuable actions include immune stimulation, antiaging, protective and rejuvenating effects, and beneficial effects in blood and circulation.

Side Effects: Chronic wasting disease may be present in antler products.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DEER VELVET

DEVIL'S CLAW

DATE OF ISSUE: MAR 1996

REPLACES MONOGRAPH DATED: JUL 1987

SCIENTIFIC NAME(S): *Harpagophytum procumbens* DeCandolle. Family: Pediliaceae

COMMON NAME(S): Devils' claw, grapple plant

BOTANY: Devil's claw grows naturally in the Kalahari desert and Namibian steppes of southwest Africa. The secondary roots are used in decoctions and teas.

HISTORY: Devil's claw has been used by native Africans as a folk remedy for diseases ranging from liver and kidney disorders to allergies, headaches and, most commonly, rheumatisms. This drug, however, is more widely used in South Africa, expecially by Bushmen, Hottentots and Bantu.[1] Devil's claw is marketed in Canada and Europe as a home remedy for the relief of arthritic disease.[2]

CHEMISTRY: The major chemical component, which has been thought to be responsible for the anti-inflammatory activity of devil's claw, is harpagoside, a monoterpenic glucoside. Harpagide has also been shown to be one of the active principles of devil's claw.[3] Harpagoside is found primarily in the roots; secondary tubers contain twice as much glucoside as the primary roots. Flowers, stems and ripe fruits are essentially devoid of the compound while traces have been isolated from the leaves.[4] Harpagoside can be progressively hydrolyzed to harpagid and harpagogenin.[5] Commercial sources of devil's claw extract contain 1.4% to 2% harpagoside.[6]

The plant also contains procombide, a diasterio-isomer of antirrhinoside[7,8] and a variety of other glycosides, the pharmacologic significance of which is unknown.[9]

PHARMACOLOGY: Studies of the crude methanolic extract of the secondary roots of *Harpagophytum procumbens* indicate that its effect on smooth muscles is due to a complex interaction of the different active principles of the drug at the cholinergic receptors.[3] The dried crude methanolic extract, harpagoside, causes significant dose-dependent reduction in blood pressure, decreased heart rate and anti-arrhythmic activity on isolated rabbit heart and on intact rats.[10] The extract has shown that harpagoside interferes with the mechanisms that regulate the influx of calcium in cells of smooth muscles.[3] The methanolic extract also causes a mild decrease in the heart rate with a concomitant and positive inotropic effect at higher doses. The coronary flow decreases at higher doses only.

The negative chronotropic and positive inotropic effects of harpagoside are comparatively higher with respect to that of the extract, whereas harpagide has only a slight negative chronotropic effect and a considerable negative inotropic one.[11] In experiments on intact rats and on isolated rabbit heart, the *H. procumbens* extract has demonstrated a protective action with regard to arrhythmias induced by aconitine, and particularly to those provoked by calcium chloride and epinephrine chloroform.[11]

Aqueous extract of *H. procumbens* significantly reduces the carrageenan-induced edema at 400 and 800 mg/kg 4 hours after carrageenan injection. Orally administered extracts are inefficient, which could be attributed to the time in transition in the stomach, where the pH is acidic, causing a decrease in activity of the extract.[11]

The results of a German clinical study indicate that devil's claw has anti-inflammatory activity comparable to that of phenylbutazone. Analgesia was observed, along with a reduction in abnormally high uric acid and cholesterol levels.[12]

The suggestion that devil's claw possesses oxytocic or abortive properties has been largely disproved.

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Harpagoside has been found to be of low toxicity with an LD_{50} of greater than 13.5 g/kg in mice. Although no chronic toxicity studies have been reported, rats given oral doses of 7.5 g/kg/day harpagoside showed no clinical, hematologic or gross pathologic changes.[13] Adverse effects in human trials have been rare, generally consisting of headache, tinnitus or anorexia.

SUMMARY: Devil's claw extracts contain harpagoside and harpagide which possess anti-inflammatory activity, the ability to reduce blood pressure, decrease heart rate and slow anti-arrhythmic activities in animal studies. These extracts appear to be free of significant toxicities when given for short periods of time to animals and humans; little is known about their long-term toxicity or potential for interactions with other commonly used anti-inflammatory agents. Additional human clinical studies need to be conducted before the true efficacy of devil's claw can be stated.

PATIENT INFORMATION — Devil's Claw

Uses: Devil's claw is a folk remedy for an extensive range of diseases, including arthritis and rheumatism. Research suggests it may be useful as a hypotensive, anti-arrhythmic, anti-inflammatory, and analgesic.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Significant toxicity has not been observed in limited use.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DEVIL'S CLAW

DEVIL'S CLUB

DATE OF ISSUE: DEC 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Oplopanax horridus* (Sm.) Miq. Also referred to as *Panax horridum* Sm., *Echinopanax horridum* (Sm.) Decne. & Planch., *Fatsia horrida* (Sm.) Benth. & Hook. Family: Araliaceae (the ginseng family)

COMMON NAME(S): Devil's club, cukilanarpak (native Alaskan for "large plant with needles") [1]

BOTANY: This hardy plant grows in moist ravines and well-drained soils along much of the Alaskan coast and adjacent regions of Canada and northwestern United States; it can be found up to 100 miles inland, forming nearly impenetrable thickets. [2] The plants attain heights of 5 m, and the densely thorned stem can reach 3 cm in diameter.[2] Greenish-white flowers appear in June, producing scarlet berries in late summer.

HISTORY: This plant has a long tradition of use, particularly among native Alaskans and other populations in the Northwestern regions of the United States and Canada. The prickly outer bark sometimes is scraped from the stem, leaving the cambium for use in the preparation of decoctions and poultices; others, however, use both the cambium and stem together.[1] The cambium sometimes is softened by chewing prior to being placed on a cut or burn. In many cultures, the plant is believed to possess "magical" powers that impart great strength.[2] Traditional uses of extracts of the plant have included the treatment of arthritis, as a purgative and emetic, for the treatment of body pain, to promote wound healing, to control fever, tuberculosis, stomach trouble, coughs and colds and pneumonia. [1,2] The berries are not eaten and are considered useless or toxic by some.

CHEMISTRY: Preliminary chemical investigations into the constituents of devil's club reported the absence of alkaloids and gallic acid, and the presence of oleic and unsaturated fatty acids, saponins, glycerides and tannins. [3] An ether extract of the root yielded two oils, equinopanacene (a sesquiterpene) and equinopanacol (a sesquiterpene alcohol).[4]

PHARMACOLOGY: Several animal investigations were conducted in the 1930s and 1940s in an attempt to characterize the pharmacologic activity associated with the traditional uses of devil's club. Following reports that patients with diabetes could be managed successfully using water extracts of the root bark, animal-based investigations suggested that the extract had hypoglycemic activity in the hare and that the plant was not associated with toxicity. [5] Further investigations were unable to verify the hypoglycemic effect in rabbits. [3,6] No pharmacologically active component could be identified in the plant. [3] A report of a case study of two patients given extracts of the plant in conjunction with a glucose tolerance test found no hypoglycemic effects that could be attributed to devil's club. [2]

The dried roots and stalk have been reported to inhibit the effects of pregnant mare serum on the growth of the ovaries of the white rat. The ovaries of control rats weighed more than eight times those of test animals that received the serum together with 40 mg of dried plant per dose. [7]

TOXICOLOGY: Although no cases of significant toxicity have been reported, several points should be kept in mind regarding devil's club. The spiny covering of the stem can cause painful irritation and scratches upon contact. The use of devil's club extract as an emetic and purgative are reflective of potential toxicity from use of the plant. Although the hypoglycemic effect has not been confirmed, the continued traditional use of this plant for the management of diabetes suggests that some persons may be sensitive to the hypoglycemic effects of devil's club and should use the plant with caution.

SUMMARY: The use of devil's club is steeped in tradition, particularly among native Alaskans. Although the plant has been reported to have hypoglycemic activity, no strong evidence supports this effect.

PATIENT INFORMATION— Devil's Club

Uses: Devil's club has been traditionally made into decoctions and poultices for diabetes, arthritis, wounds, fever, pain, and as a purgative and emetic.

Side Effects: Traditional use as a hypoglycemic, purgative, and emetic suggests potential toxicity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DEVIL'S CLUB

DEVIL'S DUNG

DATE OF ISSUE: JAN 1993

REPLACES MONOGRAPH DATED: MAR 1990

SCIENTIFIC NAME(S): *Ferula assafoetida* L., *F. foetida* Regel, *F. rubricaulis* Boissier and possibly other sp. Family: Umbelliferae

COMMON NAME(S): Asafetida, asafoetida, devil's dung, gum asafetida

BOTANY: Indigenous to eastern Iran and western Afghanistan, asafetida is the gum resin obtained from the dried roots and rhizomes of this plant. This perennial herb branches up to 9 feet and appears as a soft, almost semiliquid mass of tears, as irregular masses of agglutinated tears or as separate egg-shaped tears. This tear-like part of the plant undergoes a gradual change from a shimmering yellowish white to a violet-streaked pink and finally to reddish brown. [1]

HISTORY: The resin has been used as an expectorant, carminative and intestinal spasmodic, and was administered rectally to control colic. A suspension of the product has been used as a repellent against dogs, cats and other wildlife. Its use continues especially within African-American communities. [1] Asafetida has been used for tumors in the abdomen, corns and calluses, as an aphrodisiac, diuretic, sedative and stimulant. In folk remedies, it is used for amenorrhea, asthma, convulsions, croup, insanity and sarcomas.[2] However, its main use is as a fragrance component in perfumes.

With a taste stronger than onion or garlic, the product continues to be available as the gum resin or as a solution. It is found in pharmacies and ethnic and health food stores where it is sold as a food preservative and spice. At very low levels, it is sometimes used in candies, beverages, relishes and sauces. [2]

CHEMISTRY: Despite its popularity, asafetida gum has a major drawback — a putrid, almost nauseating odor and bitter, acrid taste — which serves as the basis for its common name, devil's dung. Asafetida contains a number of terpenes and lipid-soluble substances, which have not been well characterized. It is composed of up to 20% volatile oil, 65% resin and 25% gum. Isobutylpropanyldisulfide, pinene, cadinene and vanillin are found in the oil. Umbelliferone, asaresinotannol and ferulic acid have been found in the resin.

PHARMACOLOGY: There are no animal or clinical studies evaluating the efficacy of devil's dung in any disorder. In a study in rats, asafetida did not reduce serum cholesterol levels.[3] In vitro, an alcoholic extract of asafetida showed some cytotoxicity against lymphoma ascites, tumor cells and human lymphocytes. [4]

TOXICOLOGY: The topical use of asafetida may result in skin irritation. Ingestion of the product has not been associated with severe toxicity in adults. However, one report described the case of a 5-week-old child who developed severe methemoglobinemia after being given an undetermined amount of glycerated asafetida solution (a mixture of asafetida, glycerol, propylene glycol and calcium carbonate, available over the counter). [5] In vitro testing found gum asafetida to exert a strong oxidative effect on purified fetal hemoglobin, leading to the recommendation that this folk remedy should be considered potentially life threatening if given to infants.

SUMMARY: Asafetida persists as a folk remedy, especially among the African-American population in the United States. There is no evidence that the material exerts any therapeutic effect, and its use should be discouraged in children because of a potential to induce methemoglobinemia. The resin is used safely in small quantities as a spice.

PATIENT INFORMATION — Devil's Dung

Uses: The gum resin, asafetida, is used as a flavoring, food preservative, and fragrance. It is used as a folk remedy for a wide variety of ills and as an aphrodisiac, diuretic, sedative, and stimulant.

Side Effects: It should be considered potentially life threatening to infants, although ingestion has not been associated with severe toxicity in adults. It may cause topical irritation.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
      DEVIL'S DUNG

DIACYLGLYCEROL OIL

DATE OF ISSUE: NOV 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Diacylglycerol oil

COMMON NAME(S): *Enova*, *Healthy Econa*, DAG[1]

HISTORY: Diacylglycerol (DAG) oil was developed in Japan and launched in February 1999 by Kao Corporation as Healthy Econa cooking oil. According to the manufacturer, sales exceeded 4 million dollars within 7 months and the product became the best-selling cooking and salad oil in Japan. Kao Corporation also has introduced DAG in other products such as mayonnaise, margarine, and canned tuna. [1,2]

In 2000, the FDA granted Kao (and its partner, Archer Daniels Midland Company) generally recognized as safe (GRAS) status for their DAG product. In the United States, DAG is commercially available as Enova oil and may be used in home cooking oil and vegetable oil spreads. [1,2]

CHEMISTRY: DAG is a constituent of cellular phospholipids and consists of glycerol and 2 fatty acyl groups. Enova oil contains increased concentrations of DAG and is made from soybean and canola oil. DAG oil contains 2 fatty acids, not 3 like conventional oils; therefore, DAG is primarily utilized as an energy source v being stored as fat. DAG oil is readily absorbed and metabolized by the body and does not affect the absorption of the fat-soluble vitamins A, D, E, or K. [1,3]

DAG oil is more hydrophilic and water soluble when synthesized enzymatically with the reverse reaction of 1,3-specific lipase. DAG oil contains 70% of the 1,3-diacylglycerol species and has metabolic characteristics distinct from those of the similar fatty acid triacylglycerol (TAG). [3] The proposed mechanism of action involves the main digestive product of DAG oil, 1 (or 3)-monoacylglycerol, which is poorly re-esterified into TAG in the small intestinal mucosa. Postprandial elevations of TAG chylomicrons are smaller after consuming DAG v TAG oil; therefore, long-term use of DAG oil may help reduce body fat. Consuming DAG oil also increases oxygen utilization and hepatic beta-oxidase enzyme activity. [4]

PHARMACOLOGY: A review of the scientific literature primarily reveals studies of DAG oil on lipid metabolism and its potential role in preventing accumulation of body fat in animals and in humans.

The potential health benefit of DAG oil v TAG oil was assessed in a double-blind, controlled trial involving 38 men. Subjects were divided into 2 groups of 19; 1 group followed the DAG oil diet and the other group the TAG oil diet. Anthropometric measurements, body fat, and serum lipid profiles were compared in both groups before and after 16-weeks of treatment. Body weight, body mass index, waist circumference, and total fat (including visceral and subcutaneous fat) significantly decreased for subjects on the DAG v TAG oil diet. Hepatic fat content decreased significantly for subjects on the DAG oil diet. [5] Another randomized, double-blind, clinical trial of 131 women revealed the potential use of DAG oil as an adjunct to diet therapy in the management of obesity. [6] Over a period of 24 weeks, body weight and fat mass decreased more significantly for subjects in the DAG group than in the TAG group ($P = 0.025$ and 0.037).[6]

Dietary DAG also may reduce postprandial serum and chylomicron TAG. In a double-blind, controlled study, 40 normolipidemic male subjects ingested fat emulsions containing either DAG oil or TAG oil. Two test emulsions were administered randomly, so that half of the subjects received the DAG oil emulsion and the other half the TAG oil emulsion. Fasting and postprandial serum lipid concentrations for each group were measured. The results of the study indicated that the DAG oil group had lower concentrations ($P < 0.05$) of chylomicron TAG, cholesterol, and phospholipids, indicating that DAG oil may be less atherogenic than TAG oil. No marked differences were observed for VLDL, LDL, and HDL lipids in either group. [7]

DAG oil was used as adjunctive therapy to the standard diet regimen in the management of patients with type II diabetes with hypertriglyceridemia. The effects of daily consumption of dietary DAG oil on serum lipid concentrations were examined in patients whose serum TAG levels were persistently increased despite continuous nutritional counseling at the outpatient clinic. Over a period of 12 weeks, DAG oil was incorporated in their diet by substituting the oil (80 g DAG/100 g oil) for ordinary TAG cooking oil. Dietary records indicated that there were no differences between groups in total energy intake or percentage of energy from fat. In the DAG oil group, serum triglyceride levels decreased 39.4% and serum glycosylated hemoglobin decreased by 9.7%. In contrast, there were no changes in these variables in the control group. Serum total and HDL cholesterol were not affected in either group. [8]

TOXICOLOGY: In Japan, the safety and function of DAG oil has been approved for consumption and it is sold as a "Food for Specified Health Use." A 2-year chronic rat toxicity study revealed no treatment-related effects of DAG oil consumption at levels of up to 5.3% of the diet. [9]

SUMMARY: Food and related products containing DAG oil may be used as adjunctive therapy for weight loss, body fat reduction, and obesity management.

PATIENT INFORMATION — Diacylglycerol oil

Uses: DAG oil has been used as a replacement of regular cooking oil and in foods to promote weight loss and body fat reduction. Clinical trials have focused on its use as adjunctive therapy for weight loss, body fat reduction, and management of obesity.

Side Effects: According to the manufacturer, millions of people have used DAG oil with no known adverse side effects. [1]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DIACYLGLYCEROL OIL

DICHROA ROOT

DATE OF ISSUE: OCT 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Dichroa febrifuga Lour.*Family: Saxifragaceae.

COMMON NAME(S): Dichroa root, ch'ang shan (Chinese), huang ch'ang-shan(yellow alum root), t'u ch'ang-shan (native alum root), chi-ku feng, chi-ku ch'ang-shan (chicken-bone alum root), pai ch'ang-shan(white alum root), ta chin-tao(big golden sword), chi-fen ts'ao (chicken-droppings grass).

BOTANY: Dichroa root comes from a deciduous shrub that prefers damp areas such as wooded valleys or stream edges. The roots and leaves are used medicinally. The plant bears light-blue flowers and blue-colored berries. [1,2]

HISTORY: For many centuries in China, dichroa root was used to treat malaria.[3,4] One of the earliest recorded uses of "plants as medicine" include dichroa root. [5] Chinese scholar/emperor Shen Nung (c. 2735 BC) recorded the plant's effectiveness in treating fevers caused by malaria parasites. [6]

CHEMISTRY: Alkaloid febrifugine and its isomer isofebrifugine were isolated during World War II in order to study their effects against malaria. [3,4] Febrifugine is the main alkaloidal constituent present.[7]

PHARMACOLOGY: With drug resistance from medications such as chloroquine and quinine becoming prevalent, researchers sought other possible antimalarial sources. Isolates of *D. febrifuga*, febrifugine, and isofebrifugine were found to be the active principles against malaria. However, chemists could not separate adverse effects such as nausea, vomiting, and diarrhea from its beneficial actions. [6,8,9] Febrifugine and isofebrifugine in certain preparations (eg, acetone extract) demonstrated high antimalarial activity against *Plasmodium falciparum* and *P. berghei*.[4] Aqueous extract of dichroa studied in mice against *P. berghei* demonstrated an inhibition of infection rate and an increase in mean survival time. [10] Two reports suggest that dichroa extracts alter nitric oxide (NO) concentrations. It was found that infected mice administered febrifugine at 1 mg/kg/day orally increased NO production, thus contributing to host defense against malaria infection. Febrifugine reduced mortality and parasitemia, as well as increased plasma NO concentrations. [7] Febrifugine had the same NO increasing effects in mice peritoneal macrophages with dose-dependent activations.[11] However, another report demonstrates aqueous extract of dichroa decreasing NO production as well as tumor necrosis factor, which plays a role in endotoxin-mediated shock and inflammation. In mouse macrophages, NO synthase and NO serum levels were decreased by the extract, suggesting a suppression of inflammatory response and possible use as an anti-inflammatory drug. [12]

Changrolin, a Chinese antiarrhythmic drug derived from dichroa, has been studied for its antiarrhythmic effects in small mammal cardiac cells. [13]

Other claims from animal studies for dichroa root include its use for bronchitis to remove sputum, as an emetic, and as an antipyretic. [1,3]

TOXICOLOGY: Little information concerning toxicity of dichroa root is available, except for the previously mentioned nausea, vomiting, and diarrhea. [6,14]

SUMMARY: Dichroa root has been used for many centuries in China, and its effectiveness in treating malaria has been noted as far back as 2735 BC. The active alkaloids are febrifugine and isofebrifugine. Modern studies in animals have shown febrifugine and isofebrifugine are active against malaria parasites, involving possible alteration of NO, which is important in host defense. Nausea, vomiting, and diarrhea are some adverse effects observed in animal studies.

PATIENT INFORMATION— Dichroa Root

Uses: Dichroa root has been used to treat malaria for centuries in China.

Side Effects: Possible adverse effects include nausea, vomiting, and diarrhea.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DICHROA ROOT

DIGITALIS

DATE OF ISSUE: OCT 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Digitalis purpurea* L.; *D. lanata* Ehrh. Family: Scrophulariaceae, the figwort family. Related species that have found some use in traditional medicine include *D. lutea* (straw foxglove), *D. grandiflora* and D. ambigua (yellow foxglove), and *D. ferriginea* (rusty foxglove).[1]

COMMON NAME(S): Foxglove, purple foxglove, throatwort, fairy finger, fairy cap, lady's thimble, scotch mercury, lion's mouth, witch's bells, dead man's bells, wolly foxglove, digitalis.[1,2,7,8]

BOTANY: The foxglove is typically a biennial plant (but may be annual or perennial depending on the species) characterized by a thick, cylindrical downy stem that reaches a height of up to 6 feet. The leaves form a thick rosette during the first year of growth. The leaves, which are wooly and veined and covered with whitish hairs on the underside, have a very bitter taste. The flowers grow in the first or second year, depending on the species, and are tubular and bell-shaped, growing to 3 inches in length. Although many colors of flowers have been bred from digitalis, the flowers are rarely white. The plant is native to the British Isles, Western Europe and parts of Africa, but today is found as an ornamental throughout the world.

HISTORY: Although the use of foxglove has been traced back to 10th century Europe, it was not until its scientific investigation by William Withering in the late 1700s that the plant became widely used as a diuretic for the treatment of dropsy.[1] In South America, preparations of the powdered leaves are used to relieve asthma, as sedatives and as diuretic/cardiotonics. In India, an ointment containing digitalis glycosides is used to treat wounds and burns.[1] Today, digitalis glycosides are widely used in the treatment of congestive heart failure; however, because of their narrow therapeutic margin and high potential for severe side effects, the use of these products is beginning to be supplanted by newer agents including the angiotensin converting enzyme inhibitors and the calcium channel blocking agents.

CHEMISTRY: Ornamental strains of *D. purpurea* typically have low concentrations of active compounds. Leaves of wild varieties that have been used for medicinal purposes contain at least 30 different glycosides in total quantities ranging from 0.1% to 0.6%; these consist primarily of purpurea glycoside A (yielding digitoxin) and glycoside B, the precursor of gitoxin. Upon hydrolysis, digitoxin and gitoxin loose sugar molecules producing their respective aglycones, digitoxigenin and gitoxigenin. Seeds also contain digitalis glycosides.[1]

The main glycosides of *D. lanata* are the lanatosides, designated A through E. Removal of acetyl groups and sugars results in formation of digitoxin, gitoxin, digoxin, digitalin and gitaloxin.[1,3] *D. lanata* is not typically used in powder form in the United States, but serves as a major source of lanatoside C and digoxin.

PHARMACOLOGY: Digitoxin is 1000 times more potent than the powdered leaves and is completely and rapidly absorbed from the gastrointestinal tract.[1] Digoxin is 300 times more potent than the powder prepared from *D. purpurea*. All cardiac glycosides share the characteristic of improving cardiac conduction, thereby improving the strength of cardiac contractility. These drugs also possess some antiarrhythmic activity, but will induce arrhythmias at higher dose levels.

Digitoxin has shown antitumor activity in the KB tumor system.[2] Some investigators have suggested that the incidence of cancers is lower among patients receiving digitalis glycosides[4] and that these compounds may offer some protection by virtue of their structural similarity to estrogens. Tumors from patients receiving these glycosides were found to be smaller in size, less prone to distant metastasis, more uniform in morphology and their small nuclei had lower RNA and DNA contents than did those of breast cancer patients not taking digitalis glycosides.[5]

The pharmacology and pharmacokinetics of the digitalis glycosides have been extensively studied. For a concise review on the medicinal use of commercial products, please refer to a standard reference book.[9]

TOXICOLOGY: All parts of the plant are toxic. Animal toxicity occurs during grazing. Children have been made ill by sucking the flowers or ingesting seeds or parts of the leaves. The toxic doses of fresh leaves are reported as 6 to 7 ounces for an ox, 4 to 5 ounces for a horse, and 0.5 to 0.75 ounces for a pig.[1] Deaths have been reported among persons who drank tea made from foxglove mistakenly identified for comfrey.[2]

Digitalis glycosides are excreted slowly and accumulate; therefore, intoxications during therapy are common. The incidence of digitalis toxicity had been estimated to range from 5% to 23%. More stringent dosing guidelines and monitoring techniques have dramatically reduced the incidence of therapeutic overdose.

Signs of poisoning by the plant or purified drug include contracted pupils, blurred vision, strong but slowed pulse, nausea, vomiting, dizziness, excessive urination, fatigue, muscle weekness and tremors; in severe cases, stupor, confusion, convulsions and death occur.[1,10] Cardiac signs include atrial arrhythmias and atrioventricular block.[1] Chronic digitalis intoxication is characterized by visual halos, yellow-green vision and gastrointestinal upset.

Gastric lavage or emesis together with supportive measures such as electrolyte replacements, antiarrhythmias, such as lidocaine and phenytoin, atropine and other agents that can antagonize the cardiovascular effects of the glycosides, have been used to manage acute poisonings.[2,10] Digoxin-specific Fab antibody fragments *(Digibind)* are effective in managing acute intoxications caused by digitalis and related cardioactive glycosides.[6,9,10] This therapy is revolutionary for the severely poisoned patient.

SUMMARY: Foxglove and its derivatives are critically important in the management of congestive heart failure and related cardiac disorders. Their uses continue to be strong in underdeveloped countries where they can be used cost effectively. The plants are grown ornamentally throughout much of the world, and vigilance must be used if children or animals can come in contact with the potentially lethal plants.

PATIENT INFORMATION — Digitalis

Uses: In addition to a range of other traditional uses, digitalis has long been used as a recognized treatment for heart failure. The plant is cultivated as an ornamental.

Side Effects: Ingestion of extremely small amounts of the plant may be fatal to humans, especially children and to animals. Toxicity is cumulative.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DIGITALIS

DOLOMITE

DATE OF ISSUE: OCT 1991

REPLACES MONOGRAPH DATED: N/A

COMMON NAME(S): Dolomite, dolomitic limestone

HISTORY: Dolomite has long been used as a source of calcium and magnesium for animal feeds. Dolomite is now available in a number of dosage forms including tablets and chewable wafers, to be taken as dietary supplements.

CHEMISTRY: Dolomite is a form of limestone rich in approximately equal parts of magnesium carbonate and calcium carbonate. It is found widely throughout the world. Dolomitic limestone contains about five times as much magnesium and five eighths as much calcium as ordinary limestone. Dolomite also contains small amounts of chlorine, phosphorus, and potassium,[1] in addition to more than 20 other trace minerals.[2]

PHARMACOLOGY: Dolomite appears to be a good source of magnesium and calcium supplementation. In animal models, minerals from dolomite are well absorbed.[3]

TOXICOLOGY: Although the use of pure dolomite supplements has not been associated with toxicity, concern has arisen over the use of dolomite preparations contaminated with heavy metals.

Dolomite mined from a location near a lead mine was found to contain up to 2,700 ppm (after addition to animal feed), a level that would have induced lead toxicity in the cattle that ingested it; milk and meat products from these animals would have been unsafe for human consumption.[4]

Of similar concern has been the detection of elevated levels of heavy metals in dolomite preparations intended for human consumption. One product, for example, that was used as a mineral supplement was contaminated with aluminum (187 ppm), lead (35 ppm), nickel (13 ppm), arsenic (24 ppm) and mercury (12 ppm), among other trace elements.[5]

Contaminated dolomite products have been reported to precipitate psychomotor seizures in otherwise controlled epileptics. [2]

SUMMARY: Dolomitic limestone preparations are good sources of calcium and magnesium for dietary supplementation. In general, they may be taken with little concern about toxicity or side effects. Some products, however, have been shown to be contaminated with often significant levels of heavy metals, which may pose a toxicologic hazard.

PATIENT INFORMATION — Dolomite

Uses: Dolomitic limestone is a supplementary source of magnesium and calcium.

Side Effects: Products contaminated with heavy metals are considered hazardous.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DOLOMITE

DONG QUAI

DATE OF ISSUE: JUL 2000

REPLACES MONOGRAPH DATED: MAR 1997

SCIENTIFIC NAME(S): *Angelica sinensis* (Oliv.) Diels, synonymous with *A. polymorpha* var. *sinensis* Oliv. Family: Apiaceae (carrot family)

COMMON NAME(S): Dong quai, danggui, tang-kuei, Chinese angelica

BOTANY: Three species of *Angelica* are monographed separately in the Chinese pharmacopeia: Dong quai, the root of *Angelica sinensis*; Bai zi, the root of *Angelica dahurica* (Fisch.) Benth. et. Hook. f. or *A. dahurica* var. *formosana* (Boiss.) Shan et Yuan; and Du huo, the root of *A. pubescens* Maxim. *f. biserrata* Shan et Yuan.[1] In Korea, *A. gigas* Nakai is used medicinally, while in Japan, *A. acutiloba* Kitagawa is used. The European *A. archangelic* L. is used to flavor liqueurs and confections. While botanically related, do not confuse the various species of *Angelica*, which differ in chemistry, pharmacology, and toxicology. A molecular biology study of *A. acutiloba*may lead to efficient methods for distinguishing raw materials.[2]

HISTORY: Dong quai is widely used in traditional Chinese medicine and continues to be popular in China and elsewhere. It is used to treat menstrual disorders, as an analgesic in rheumatism, and in suppressing allergy symptoms. It is promoted for similar uses in the American herb market.

CHEMISTRY: The chemistry of *A. sinensis* is distinct from the other species. While coumarins have been reported from this species,[3] a recent comparative study of commercial dong quai products and related species[4] found coumarins to be lacking, while the lactone Z-ligustilide was a major constituent. In fact, in this study, *A. sinensis* more closely resembled *Levisticum officinale* in chemical composition than it did the other species of *Angelica*. Thus, there is good justification for terming the latter plant "European dong quai." Several other lactones related to ligustilide have been found in *A. sinensis*.[5,6,7] Ferulic acid and its esters were also found in *A. sinensis*. A capillary electrophoresis method for measuring ferulic acid in *A. sinensis* has been published.[8]

In contrast, the roots of *A. dahurica* have been found to contain an abundance of coumarins. Imperatorin and isoimperatorin are the major constituents, with many other related compounds (eg, bergapten, phellopterin, scopoletin) reported.[9] Ferulic acid was also detected in this species.[10]

The root of *A. pubescens* contains coumarins, but with some differences from *A. dahurica*. The simple prenylcoumarin, osthole, and the linear furocoumarins, columbianadin and columbianetin acetate, are the major constituents while the coumarins, angelols A-H, are characteristic of the species.[11,12]

The common polyacetylene falcarindiol has been isolated from various species of *Angelica*.[4] Polysaccharides have been isolated from different species of *Angelica*; however, they have not been characterized sufficiently to permit comparison.[13] Simple plant sterols and lipids have also been found.[14]

PHARMACOLOGY

Antiallergy effects: A water extract of *A. sinensis* inhibited IgE-antibody production in a mouse model of atopic allergy. The extract was active orally and the activity was retained on dialysis, indicating that it was caused by high molecular weight components of the extract.[15]

Antispasmodic effects: The simple lactone ligustilide is thought to be a major bioactive principle of dong quai. Its antiasthmatic action was studied in guinea pigs.[16] Ligustilide and the related butylidenephthalide and butylphthalide were found to have antispasmodic activity against rat uterine contractions and in other smooth muscle systems. The compounds were characterized as nonspecific antispasmodics with a mechanism different from papaverine.[17] The ligustilide and butylidenephthalide constituents of Japanese angelica root were found to reverse the decrease in pentobarbital sleep induced by either isolation stress or yohimbine, implicating central noradrenergic or GABA systems in their actions.[18]

Anticoagulant effects: The coumarins of *Angelica* species have been associated with both bioactivity and toxicity of the plants; however, the low coumarin content of *A. sinensis* minimizes its importance in dong quai pharmacology. In other species of *Angelica*, coumarins clearly play an important role. Simple coumarins often have anticoagulant effects, while the linear furocoumarins are well known as photosensitizing agents.[19]

Anti-inflammatory effects: The simple prenylcoumarin, osthole, is a major constituent of *A. pubescens* (Du huo).[20] Osthole showed anti-inflammatory activity in carageenan-induced rat paw edema and acetic acid-induced writhing in mice.[20] Osthole also caused relaxation of rat thoracic aorta preparations[21] and inhibited proliferation of rat vascular smooth muscle cells.[22] Another study found that osthole inhibited the second phase of edema caused by formalin in the rat.[23] An inhibitory effect was also seen for osthole on 5-lipoxygenase and cyclooxygenase.[24] The related prenylcoumarin angelols were shown to inhibit platelet aggregation.[25]

The linear furocoumarin phellopterin was found to bind with high affinity to benzodiazepine receptors in vitro; however, other closely related furocoumarins were weaker or inactive.[26] Phellopterin was characterized as a competitive partial agonist of central benzodiazepine receptors by GABA and TBPS shift assays.[27] No in vivo experiments were reported. Other furocoumarins from *A. dahurica* inhibited histamine release in a mouse peritoneal cavity assay,[28] while isoimperatorin was analgesic; columbianadin, columbianetin acetate, and bergapten were anti-inflammatory and analgesic.[23] Finally, the action of various coumarins from *A. dahurica* on lipolysis in fat cells of rats were examined, with some coumarins activating lipolysis and other coumarins inhibiting lipolysis.[29]

Menopause: Dong quai is widely used in the US to treat hot flashes and other symptoms of menopause. A randomized, double-blind, placebo-controlled trial of *A. sinensis* as a single agent found no effect on vasomotor flushes, endometrial thickness, or on the level of estradiol or estrone. The study material was standardized for ferulic acid content.[30] A polyherbal preparation including dong quai was shown to reduce menopausal symptoms in a much smaller clinical trial.[31]

INTERACTIONS: The possibility of herb-drug interactions between *Angelica* coumarins and warfarin has been postulated[32] and is supported by one case report,[33] a patient stabilized on warfarin therapy experienced more than a 2-fold increase in prothrombin time and international normalized ratio 4 weeks after starting dong quai.[33] The values returned to the therapeutic range 4 weeks after discontinuing dong quai. Monitor patients receiving warfarin.

TOXICOLOGY: Coumarins are the focus of toxicology in *Angelica*. Furanocoumarins such as bergapten and psoralen have been widely studied for their photoactivated toxicity; however, only *A. gigas*(Korean angelica) has been demonstrated to cause photodermatitis.[34] Clearly the risk of phototoxicity should be correlated with the content of specific toxic furocoumarins. In the case of *A. sinensis*, there appears to be little risk, but with *A. gigas*, *A. dahurica*, and *A. pubescens*, there is a very reasonable cause for caution. Possible synergism with calcium channel blockers may occur. *Angelica archangelica* L. is reported to be an abortifacient and to affect the menstrual cycle. *A. sinensis*has uterine stimulant activity.

SUMMARY: Dong quai is monographed in the Chinese Pharmacopeia, the British Herbal Pharmacopeia (vol. 2), and by WHO (vol. 2). An American Herbal Pharmacopeia monograph is in progress.

Dong quai is a Chinese medicine used widely to treat menopause symptoms; however, convincing proof of efficacy in humans is lacking. Animal studies support anti-inflammatory, antiasthmatic, and antiallergy effects, but these observations require clinical study. Monitor the potential interaction with warfarin and other anticoagulants. Phototoxicity appears to be a problem with related species of *Angelica*, but not with authentic dong quai.

PATIENT INFORMATION— Dong Quai

Uses: Traditionally used as an analgesic for rheumatism, an allergy suppressant, and in the treatment of menstrual disorders, dong quai has been shown to possess

antiasthmatic, antispasmodic, anti-inflammatory, and anticoagulant properties. It has also been used to flavor liqueurs and confections.

Interactions: The possibility of dong quai interactions with warfarin has been postulated and is supported by at least one report. Possible synergism with calcium channel blockers may occur.

Side Effects: No reported side effects have occurred with authentic dong quai, but with *A. gigas*, *A. dahurica*, and *A. pubescens* , there is a very reasonable risk of phototoxicity. *Angelica archangelica* L. is reported to be an abortifacient and to affect the menstrual cycle. *A. sinensis* has uterine stimulant activity.

Dosing: Crude dong quai root has been given in doses ranging from 0.75 g/day to as much as 30 g/day. More typical doses are around 4.5 g/day. [30,31]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DONG QUAI

DRAGON'S BLOOD

DATE OF ISSUE: APRIL 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Croton lechleri* Muell.-Arg. Fam. Euphorbiaceae (spurges)

COMMON NAME(S): Dragon's blood, sangre de grado, sangre de drago, drago

BOTANY: The genus croton contains about 750 species of trees and shrubs commonly found in tropical and subtropical regions of both hemispheres. This tree grows from 10 to 20 m in height. The trunk is covered with smooth, mottled bark, which when cut or "wounded," oozes a red, sappy resin that makes it appear as if the tree is "bleeding."[1]

Red resin from the genus *Daemonorops draco*, used to color varnishes and lacquers, is the common dragon's blood of commerce,[2] and is an entirely different plant than *C. lechleri*. Since *C. lechleri* latex is sold in Peru and elsewhere, it is also "of commerce" though not as widespread as the *Daemonorops* resin.

HISTORY: Sangre de grado, Spanish for "blood of the dragon," has a long history of use for both the bark and the resin. An early reference dating back to the 1600s notes that Spanish explorer P. Bernabe Cobo found the sap was being used by indigenous tribes throughout Peru and Ecuador. They used it internally and externally to stop bleeding, help heal wounds, and treat intestinal problems.[1] Studies regarding this plant date back to the late 1970s. Preparations made from dragon's blood are found in several pharmaceutical products, some of them patented.

CHEMISTRY: Alkaloid taspine has been isolated from *C. lechleri*.[3] Diterpenes and polyphenolic compounds including proanthocyanidins (90%), catechins, epicatechins, gallocatechins, and related structures have been found in the sap.[4,5] Clerodane diterpenoids including korberin A and B have been isolated as well.[6] A dihydrobenzofuran lignan; 3´,4-O-dimethylcedrusin, has been found in the latex.[7] Volatile constituents from *C. lechleri* sap, as determined by GC/MS analyses, include ethyl acetate, ethyl propionate, 2-methylbutanol, 2-methyl-bu acetate, Pr acetate, 3-methyl-bu acetate, eucalyptol, 1-bu acetate, and 3-methyl-2-pentanol.[8] Other phytochemicals reported from the plant include pinenes, camphene, eugenol, linalool, pectic acid, tannin, vanillin, and resin.[1] One report suggests the presence of pro-oxidant compounds.[9] Another report provides the synthesis of methyl dihydrohardwickiate from crolechinic acid isolated from *C. lechleri*[10] with the goal of generating useful derivatives.

Sinoacutine has been isolated from *C. lechleri* leaves.[11] A review on certain techniques for isolation of natural products is available, including chemical and biological investigations of dragon's blood in particular.[12]

PHARMACOLOGY: *C. lechleri* resin and bark are used in traditional medicine in South America. Externally, it is employed as an antiseptic, as a wound-healing agent, and for skin disorders. Internally, it is used for hemorrhaging, mouth and throat ulcers/infections, and intestinal disorders.[1] This important "rainforest resource" has several uses that have been validated by several studies.

Antibacterial and antiviral effects: Several phenolic compounds and diterpenes have demonstrated potent antibacterial activity.[6,13] Antiviral effects are seen from *C. lechleri* as well. A large proanthocyanidin oligomer isolated from the latex demonstrates broad activity against DNA and RNA viruses, including RSV, influenza A, parainfluenza virus, herpesvirus types 1 and 2, and hepatitis A and B viruses.[14] Constituent taspine inhibited RNA-directed DNA polymerase activity from certain virus types, including leukemia and sarcoma virus.[15]

Wound-healing effects: The taspine alkaloid from dragon's blood was first documented with anti-inflammatory actions in 1979.[3] Later studies confirmed these actions, leading to further studies in the area of wound healing. Taspine was found to be the healing principle, as in 1 study by in vivo testing in mice. Increased migration of human fibroblasts was suggested as the probable mechanism in this acceleration of the wound-healing process.[16] Another report evaluating taspine's wound-healing properties demonstrated positive results (with higher dosing, earlier seen than later), using such parameters as wound tensile strength and histology. Taspine also was found to stimulate chemotaxis for fibroblasts. Data from the report suggest that taspine promotes early phases of wound healing in a dose-dependent manner.[17] A patent was issued for taspine in DMSO (solvent), which healed wounds faster than DMSO alone or no treatment at all.[18] Another dragon's blood constituent, a dihydrobenzofuran lignan also involved in wound healing actions, was isolated in 1993.[7]

GI effects: Dragon's blood also plays a role in GI health. Practitioners are reporting it beneficial for stomach ulcers, ulcerative colitis, and Crohn's disease when taken internally. Ten to 20 drops of the resin in water once to twice daily is the regimen based on South American herbal medicine practices.[1] A patent describing use of the proanthocyanidin polymer from croton species as an antidiarrheal was issued to Shaman Pharmaceuticals, Inc. USA.[19] The company's natural dietary supplements containing standardized extract from *C. lechleri* sap are called NSF[20] and NSF-1B.[21] The products claim "clinically demonstrated relief from diarrhea that won't cause constipation." Normalization of diarrhea caused by excess fluid secretion into the intestinal tract is the suspected mechanism of action.[22] A double-blind, randomized, placebo-controlled trial of the principal ingredient (SP-303) in patients with HIV-associated diarrhea demonstrated beneficial effects.[23]

Other effects: One report describes protective effects of *C. lechleri* latex on spontaneous lipid peroxidation in rat livers.[24] Taspine, isolated from *C. palanostigma* sap, has been isolated as a cytotoxic substance.[25]

TOXICOLOGY: No major toxicity has been reported from dragon's blood. The natural product (NSF) web page mentions its safety and efficacy in clinical testing involving > 1200 patients. No interactions were observed.[20] One report found taspine to be nontoxic to human foreskin fibroblasts.[16]

There is no safety data regarding pregnancy. The American Herbal Products Association lists dragon's blood as Class I, meaning it can be consumed safely when used appropriately.[26]

SUMMARY: Use of dragon's blood dates back to the 1600s. Central and South American tribes used the resin internally and externally for wound healing and intestinal problems. Certain compounds from the sap possess antibacterial and antiviral properties. Constituent taspine demonstrates anti-inflammatory actions, and accelerates wound healing. Dragon's blood has been beneficial for GI disorders, including diarrhea. No major toxicity has been associated with the plant.

PATIENT INFORMATION — Dragon's Blood

Uses: Dragon's blood has been used for its antiviral, wound healing, and GI benefits.

Side Effects: There have been no major toxicities reported with the use of dragon's blood.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "D" MONOGRAPHS
    DRAGON'S BLOOD

"E" MONOGRAPHS

ECHINACEA

DATE OF ISSUE: JUL 2000

REPLACES MONOGRAPH DATED: DEC 1996

SCIENTIFIC NAME(S): *Echinacea angustifolia* DC. The related species *E. purpurea* (L.) Moench and *E. pallida* (Nutt.) Britton have also been used in traditional medicine. Family: Compositae

COMMON NAME(S): American coneflower, black susans, comb flower, echinacea, hedgehog, Indian head, Kansas snakeroot, narrow-leaved purple coneflower, purple coneflower, scurvy root, snakeroot

BOTANY: There are at least 9 species of echinacea. The ones most commonly studied are *E. purpurea*, *E. pallida*, and *E. angustifolia*.[1]

Echinacea is native to Kansas, Nebraska, and Missouri. There has been confusion regarding the identification of echinacea. Because of this confusion, it should be recognized that much of the early research conducted on this plant (in particular with European *E. angustifolia*) was probably conducted on *E. pallida*.[2] At least 6 synonyms have been documented for these plants.

E. angustifolia is a perennial herb with narrow leaves and a stout stem that grows to 90 cm in height. The plant terminates in a single, colorful flower head. The plant imparts a pungent, acrid taste when chewed and causes tingling of the lips and tongue.

Echinacea products have been found to be adulterated with another member of the family Compositae, *Parthenium integrifolium*L. This plant has no pharmacologic activity.

HISTORY: Echinacea is a popular herbal remedy in the central US, an area to which it is indigenous. The plant was used in traditional medicine by the American Indians and quickly adopted by the settlers. During the 1800s, claims for the curative properties of the plant ranged from a blood purifier to a treatment for dizziness and rattlesnake bites.[3] During the early part of the 20th century, extracts of the plant were used as anti-infectives; however, the use of these products fell out of favor after the discovery of modern antibiotics.

The plant and its extracts continue to be used topically for wound-healing action and internally to stimulate the immune system. Most of the research during the past 10 years has focused on the immunostimulant properties of this plant.

CHEMISTRY: Echinacea contains about 0.1% echinacoside, a caffeic acid glycoside. The pungent component of the plant is echinacein, a isobutylamide. [4] This compound is toxic to adult houseflies. The plant also contains a complex mixture of components that are now being elucidated. Depending on the species, the essential oil obtained from the root may be high in unsaturated alkyl ketones or isobutylamides. [2] Fresh aerial portions of echinacea contain a highly volatile germacrene alcohol that is not usually identified in dried plant material. [5] In addition, a number of alkamides have been found in the lipophilic fraction of *E. angustifolia* and *E. purpurea*roots.[6]

PHARMACOLOGY: A small but growing body of evidence is developing to support the traditional uses of echinacea as a wound-healing agent and immunostimulant.

Most studies have indicated that the lipophilic fraction of the root and leaves contains the most potent immunostimulating components. Although a number of pharmacologically active components have been isolated, no single compound appears to be responsible for the plant's activity. Polyunsaturated alkamides from *E. angustifolia* have been shown to inhibit in vitro the activity of sheep cyclooxygenase and porcine 5-lipoxygenase assays. [7]

Treatment of the common cold: Nineteen German controlled clinical trials examined the efficacy of 7 different echinacea preparations, alone or in combination, for the prevention or treatment of upper respiratory tract infections (URIs) including the common cold. The authors rated the overall quality of the studies, with a median score of 37% and a range of 7% to 70%.[8] These results correspond to the average scores (38.5%) found for other clinical trials in journals from 1990. [9] The authors of this review determined that the studies available as of 1993 revealed that echinacea may have an effect on the immune system, but that there is insufficient evidence to provide specific recommendations.[8]

Barrett and colleagues published an evidence-based clinical review of echinacea in 1999. They examined 13 trials, 9 of which were reviewed by Melchart in 1994, and 4 additional studies (1 unpublished report). Barrett et al, found conclusions similar to those of Melchart in that there is some evidence that echinacea is effective for treatment, not for the prevention of URIs, but there is still a lack of definitive information to provide specific recommendations. [10] Brinkeborn and colleagues reported that patients receiving a commercially available echinacea product in Germany with 6.78 mg, 95% herb, and 5% root or a concentrate with 48.27 mg of the same crude extract, had a 50% reduction in 12 cold symptoms as judged by the patient and 60% as judged by physicians compared with placebo (see Table 1 for description of clinical trials). In addition, approximately 70% of physicians and 80% of patients judged the treatment to be effective. There was no information on whether echinacea decreased the duration of a cold. The authors did not speculate as to why it was effective while the fresh plant preparation was not. [11] Degenring provided information concerning an open-label, "adjunctive treatment" (term not described) trial in 77 patients receiving echinacea. Results showed that 72% of patients became symptom-free within 14 days. However, without a placebo-control, it is impossible to determine if patients would have improved without treatment. [12] Dorn and colleagues used an unidentified *E. pallida radix*extract 900 mg/day in an unspecified divided dose regimen for 8 to 10 days to determine its effect on both viral and bacterial infections compared with a placebo. *E. pallida* decreased the length of the illness from 13 to 9.8 days compared with placebo for bacterial infections and 12.9 days to 9.1 days for viral infections ($p < 0.0001$). [13]

Another study used a commercially available echinacea product in Germany. Results showed a direct correlation to time of administration with patients taking the medication during the early phase ("...identified by the course of an indicator symptom during the first three days of observation") showing faster improvement than those who started echinacea later. In the treatment group, 55.3% had greater than or equal to 50% improvement in global score compared with 27.3% in the placebo group.[14] Hoheisel and colleagues demonstrated that another commercially available product in Germany was more effective in shortening the duration of a cold and required treatment of a cold than placebo using subjective measures such as "Did you have a 'real cold'?" (fully expressed symptoms of acute respiratory tract infection). Although more patients experienced a "real cold" with placebo than echinacea, the severity of symptoms were similar in the 2 groups. [15] Thom and colleagues used a commercially available *E. pallida* root extract combination product (Kanjang mixture) in Scandinavia. Compared to placebo, the Kanjang mixture caused a decrease in subjective symptoms such as degree and frequency of cough, quality of sleep, efficacy of mucus discharge, nasal congestion, and global evaluation compared with placebo. These improvements were noted as early as 2 days after initiation of treatment and were more prominent at day 4. Patients took the echinacea treatment for an average of 5.2 days vs 9.2 days for placebo. No side effects were reported in either group; however, 2 patients discontinued the active treatment because they could not tolerate the taste of the medication.[16]

There were several limitations of the studies listed in Table 1. Only 2 studies measured patient compliance and 3 studies addressed concomitant medication use that might affect cold symptoms.[11,14,16] Inclusion and exclusion criteria were not always provided, and if provided, they were poorly defined. Four studies mentioned that the placebo product was similar to the echinacea preparation to help ensure blinding. However, one of these studies reported that the treatments "...could almost not be distinguished from one other by their smell or taste." However, Melchart mentioned that "because of the characteristic taste of echinacea extracts it is almost impossible to prepare a completely indistinguishable placebo." [11,14,17] None of the studies asked patients if they had tried an echinacea product before. If so, what kind was it and did it work? The methods for randomization and verification were not provided. The studies used subjective measures of a cold that can be highly variable from patient to patient, and the methods for measuring these subjective outcomes varied greatly. Some of the studies used plant parts (*purpurea* root) that are not approved by The German Commission E because they lack documentation pertaining to efficacy. There were 6 different preparations (extract vs. tab vs

squeezed sap vs combination product), 2 different species (*E. purpurea* or *pallida*), and 6 different doses used in the 6 studies. None of the studies tested the products for quality high-pressure (performance) liquid chromatography (HPLC) testing procedures currently available or standardized the products prior to initiation of the study.[18] Two of the studies used patients who were more prone to the common cold.[11,15] One of the studies lacked a placebo control, which makes it virtually impossible to reach a conclusion regarding efficacy.[12] The exact time of initiation of echinacea treatment was not well defined in the studies. Some mentioned echinacea was taken at the first sign of a cold, others did not mention when therapy was initiated.

Prevention of the common cold: Three clinical trials, 2 were randomized, double-blind, placebo-controlled English-language trials, and 1 placebo-controlled have been conducted that examined the effectiveness of echinacea in the prevention of the common cold and other URIs (see Table 2). None of the studies found echinacea to be effective. However, 1 study did not calculate power (ie, the ability of a study to find a significant difference, if in fact, one exists). One calculated the study power at only 20% and the other 75%, suggesting that neither study probably enrolled enough subjects.[17,19,36] Melchart and colleagues commented that echinacea may cause a 10% to 20% relative risk reduction for the occurrence of a cold; however, larger sample sizes than those used would be required to prove this theory.[17] As with the treatment trials, 2 of the studies determined whether the placebo was a true placebo.[17,19] The other study questioned whether patients thought they were receiving a placebo, and the investigators found no significant difference between groups. However, the dosage form used in this study was not described. Only 1 of the studies tested the products for quality.[36] However, the study did not list the species they used or if the product contained the desired components. None of the studies standardized their products prior to initiation of the study.[18] Melchart and colleagues reported that 45% of the subjects had tried echinacea before, which could have affected the results. This study also used an echinacea species (*angustifolia*) and plant parts (*purpurea* root) that are not approved by The German Commission E because they lack documentation of efficacy.[17]

When injected IV in mice or rats, echinacea extract almost completely inhibited carrageenan-induced mice or rat paw edema. Similarly, when the extract was applied topically, it inhibited almost completely the inflammation induced by croton oil applied to the mice or rats' ear.[20] Its activity was slightly less than that of topical indomethacin. The most active anti-inflammatory compound(s) has a molecular weight of between 30,000 and 100,000.[21]

Several caffeoyl conjugates have been isolated from *E. angustifolia* that demonstrate antihyaluronidase activity; these include chicoric acid, cynarine, chlorogenic acid, and caftaric acid.[22] The inhibition of this enzyme is believed to limit the progression of certain degenerative inflammatory diseases.

Perhaps the most intriguing activity of this plant rests in the ability of its extracts to enhance the immune response. A number of in vitro and animal studies have documented the activation of immunologic activity. These extracts appear to exert their effects by stimulating phagocytosis, increasing cellular respiratory activity, and increasing the mobility of leucocytes. When ethanolic extracts were administered orally to rats, phagocytosis was enhanced. The lipophilic fraction was more active than the polar fraction.[23]

The purified polysaccharide arabinogalactan, isolated from *E. purpurea*, was effective in activating macrophages to cytotoxicity against tumor cells and microorganisms following intraperitoneal injection in mice.[24] Arabinogalactan induces macrophages to produce tumor necrosis factor, interleukin-1, and interferon beta-2. Polysaccharides derived from *E. purpurea* enhance the cytotoxic activity of treated macrophages against tumor cells and the intracellular parasite *Leishmania enrietti*.[25] The research suggests that this activity may be of clinical value in the defense against tumors and infectious diseases, particularly in immunocompromised patients. However, a study involving 23 patients with tumors showed that an echinacea complex made with *E. angustifolia* had no effect on cytokine or leukocytes.[26]

Dietary supplementation with *E. purpurea* to rats who were undergoing experimental irradiation resulted in the mobilization and enhancement of vitamin E-mediated oxidation/reduction pathways, suggesting that echinacea could have potential as a radioprotector.[27]

One study found the administration of echinacea extracts to humans stimulated cell-mediated immunity following a single dose, but that repeated daily doses suppressed the immune response.[28] In a more recent German study conducted in a small number of patients (15) with advanced metastasized colorectal cancer, echinacin (a component of the plant) was added to treatment consisting of cyclophosphamide and thymostimulin; the mean survival time was 4 months, and two patients survived for more than 8 months, suggesting that this form of immunotherapy may have some value in treating these ill patients.[29]

Although the results are encouraging, they are too preliminary to draw conclusions about the appropriate therapeutic uses of echinacea extracts. Similarly, there are no well-controlled studies that have evaluated the effects of OTC echinacea supplements. Consequently, dosages are not well defined.

Photodamage prevention/treatment : An in vitro study demonstrated that typical constituents of echinacea species applied topically were effective in prevention/treatment of photodamage of the skin caused by UV/UVB radiation.[30]

TOXICOLOGY: Little is known about the toxicity of echinacea despite its widespread use in many countries. It has been documented in American traditional medicine for more than a century and generally has not been associated with acute or chronic toxicity. Purified echinacea polysaccharide is relatively nontoxic. Acute toxicity studies found that doses of arabinogalactan as high as 4 g/kg injected intraperitoneally or IV were essentially devoid of toxic effects.[24]

High-dose oral and IV administration (ie, several times the normal human therapeutic dose) of the expressed juice of *E. purpurea* to rodents for 4 weeks demonstrated no acute, subacute, genotoxic, carcinogenic, mutagenic, or other toxic reactions.[31]

Side effects: Exclusion criteria from clinical trials provide information regarding patients who should not receive echinacea. Some of the exclusion criteria were the following: Childhood, chronic diseases such as diabetes, bronchial asthma, allergy, or autoimmune deficiency, tuberculosis, leukemia, collagenous disease, multiple sclerosis, polyarthritis, HIV infection, organ transplantation, pneumonia, or fungal infections, other infections not involving the respiratory tract, known inflammatory GI disease or impairment of resorption, acute influenza, chronic diseases of the respiratory tract; patients taking any immunosuppressants including corticosteroids, antibiotics, or cytostatic therapy; pregnancy or lactation; fever; hypersensitivity to plants of the Asteraceae/Compositae family; and any type of acute infection.[11,12,13,14,15,16,17,19] Some of the exclusion criteria were taken from parenteral echinacea product information. Most of the contraindications and some of the possible side effects are theoretical and are not derived from actual case reports or studies of oral echinacea. According to The German Commission E, *Echinacea purpurea* and *pallida*, when taken orally, do not cause any side effects.[32] Parnham and colleagues reported results from an unpublished practice study to determine adverse effects and safety of the squeezed sap of *E. purpurea*. A total of 1231 patients with relapsing respiratory and urinary infections given echinacea for 4 to 6 weeks demonstrated the following side effects: Unpleaseant taste (1.7%); nausea or vomiting (0.48%); abdominal pain, diarrhea, sore throat (0.24%). The authors reported that 90% of patients took the medication as directed. Parenteral administration was associated with immunostimulating-type reactions such as shivering, fever, and muscle weakness.[33] Degenring reported that 1 out of 77 patients who received the 6.78 mg, 95% herb, and 5% root formulation experienced nausea, restlessness, and aggravation of cold symptoms 4 days after starting the medication.[12] The symptoms were severe enough to require discontinuation of therapy.

Other side effects reported in clinical trials were primarily GI in nature, such as mild nausea.[11,12,14,19] At the American Academy of Allergy, Asthma and Immunology 2000 annual meeting, 23 unpublished cases (2 "certain," 10 "probable," and 11 "possible") of allergic reaction to echinacea consistent with IgE-mediated hypersensitivity were reported. Of the 23 cases, 34% were atopic, 13% were nonatopic, and 44% did not provide this information. Of another 100 atopic patients who had never taken echinacea, 20% had positive skin test reactions to echinacea, indicating a hypersensitivity without prior exposure to echinacea.[34] There was also a case of anaphylaxis caused by a combination echinacea product (*E. angustifolia* and *E. purpurea*) with other dietary supplements. The amount of echinacea product consumed was approximately double that recommended by the manufacturer. The patient had a high incidence of allergies to other substances. Of an additional 84 patients with asthma or allergic rhinitis, 16 subjects (19%) reacted to an echinacea skin prick. Only 2 patients had prior exposure to echinacea.[35]

SUMMARY: Echinacea is a native American plant that has been documented in traditional herbal medicine for more than a century. Its uses have included topical application to stimulate wound healing and ingestion to improve immune function. Studies have indicated that the plant does possess pharmacologic activity that supports some of these traditional uses.

Echinacea has been shown to have some beneficial effects on the symptoms of the common cold. A few studies have shown echinacea (*E. purpurea* and *E. pallida*) to be effective for the treatment, but not prevention, of the common cold. However, the variation in products used in clinicial trials (some products are not available in the US), including part of the plant used, variable dosing, treatment duration, and different extraction methods (eg, alcoholic extraction, pressed juice) makes specific dosing recommendations difficult to determine (see Table 1). There are 9 species of echinacea found in the US and south central Canada.[19] Many different parts of

the plants can be used in formulations, such as the root, upper parts, sap, or the whole plant. There is a lack of large clinical trial information. However, The German Commission E gives a positive rating to 2 echinacea monographs, *E. pallida* root (not herb or leaf) and *E. purpurea* herb or leaf (not root).[32] Some of the studies listed in the pharmacology section used parts of the herb that are not approved by The German Commission E.

PATIENT INFORMATION— Echinacea

Uses: There is some evidence that echinacea (*purpurea* and *pallida* species) is effective in shortening the duration of symptoms of URIs, including the common cold, but it has not been shown to be effective as a preventative. The variation in available products makes specific recommendations difficult to determine.

Side Effects: Side effects are rare. Patients with allergies, specifically allergies to daisy-type plants (Asteraceae/Compositae family) might be more susceptible to reactions. Nausea and other mild GI effects have been reported in clinical trials. Because of the potential immune stimulating property of echinacea, patients who are immunocompromised should not take echinacea. Many patients were excluded from clinical trials (see Pharmacology, Clinical Trials, Toxicology).

Dosing: Echinacea clinical trials for prevention or treatment of cold symptoms have been run primarily on the frest pressed juice of the herb, which is preserved with 22% alcohol. Typical daily doses are 5 to 10 mL of the juice. *Echinacin* (Madaus, EC31) and *Echinagard* are fresh juice prepared from the herb. Extracts of the root are available, including *Echinaforce* and *Echinacea Plus*. These have been given at doses corresponding to 1 g of the crude herb or root 3 times/day.[11,14,15,17,19,37,38,39,40]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    ECHINACEA
    DATE OF ISSUE

Table 1: English-Language Studies of Echinacea for the Treatment of the Common Cold

Study & country	N	Study design	Species	Formulation	Dose	Outcome
Brinkeborn (1999) Sweden	246	R, D-B, P-C, intent-to-treat, healthy volunteers "prone to common cold"	*E. purpurea*	(1) Echinaforce (6.78 mg, 95% herb, and 5% root) or(2) Echinaforce concentrate (48.27 mg of the same crude extract) or (3) special *E. purpurea* extract preparation (29.6 mg crude extract based on root only).	2 tabs tid at the first sign of a cold for =7 days or until pt felt better	Echinaforce and the concentrate were more effective at relieving 12 symptoms[1] of the common cold compared with special *Echinacea* extract and placebo.
Degenring (1995) Austria	77	Open-label, 4-week observation	*E. purpurea*	Echinaforce (6.78 mg, 95% herb, and 5% root) "made from stems and leaves, together with the root." Alcohol content, 57%.	30 drops tid × 14 days at the first sign of a cold; = 3 days after	88.2% of pts and 86.8% of physicians rated echinacea to have clinically relevant efficacy (very good, good, or satisfactory).
Dorn (1997) Germany	160	R, D-B, P-C, single-center	*E. pallida*	Liquid form of *E. pallida radix* extract.	90 drops (900 mg) in divided doses for 8 to 10 days	Length of illness, overall symptom scores, and whole clinical scores were decreased compared with placebo.
Henneicke-von Zepelin (1999) Germany	259	R, D-B, P-C, multi-center, intent-to-treat	*E. purpurea*, *E. pallida*	Esberitox N tablets (ethanolic-aqueous extracts of 2 mg of *herba thujae occidentalis*, 7.5 mg of *radix echinaceae* [*purpureae*+ *pallidae* = 1+1], 10 mg *radix baptiaiae tinctorae* , plus other ingredients).	"3 tabs tid for 7 to 9 days, and at least until the final visit to the investigator"	Esberitox N was more effective in relieving 18 cold symptoms than placebo. Mean time to response was 4.8 days in the echinacea group vs 7 days in the placebo group.
Hoheisel(1997) Sweden	120	R, D-B, P-C, intent-to-treat, healthy volunteers with history of recurrent URIs.	*E. purpurea*	Echinagard ("squeezed sap of the herb").	20 drops q2hrs for the first day, at the first sign of URI then tid for = 10 days	60% of placebo and 40% of echinacea pts experienced a "real" cold, with faster improvement time by 4 to 5 days. Pts stopped treatment median 6 days on echinacea vs 10 on placebo.
Thom (1997) Norway	60	R, D-B, P-C pts with the common cold	*E. pallida*	Kanjang mixture with *E. pallidia radix* 10 g/100 ml mixed with 4 other "active ingredients."	15 ml tid for 5 to 10 days	Kanjang mixture improved symptoms compared with placebo on days 2 and 4.

[1]Severity of illness, runny nose and sneezing, tearing/burning eyes, sore throat, headache, dizziness, weakness, drowsiness, muscle pain, limb pain, fever, cough, blocked nose, ear other complaint most probably related to the cold. R = randomized; D-B = double-blind; P-C = placebo-controlled;pt = patients.

Table 2: English-Language Studies of Echinacea for Prevention of the Common Cold

Study & country	N	Study design	Species	Formulation	Dose	Outcome	Side effects
Grimm (1999) Germany	108	R, D-B, P-C, pts with a history of cold > 3x/yr	*E. purpurea*	Echinacin-Liquidum made from fresh expressed juice of whole flowering plants of *Echinacea purpurea* (verum) harvested without its roots with 22% alcohol.	4 ml bid for 8 weeks	No difference in occurrence, severity, or duration.	Similar to placebo.
Melchart (1998) Germany	289	R, D-B, P-C	*E. purpurea*, *E. angustifolia*	Ethanolic extracts (plant ratio 1:11 in 30%alcohol) from the roots of *E. angustifolia* or *E. purpurea*.	50 drops bid, M-F × 12 weeks	Not an effective preventative.	Similar to placebo.
Turner(2000) USA	92	P-C, experimental rhinovirus	Possibly *E. pallida*, *E. angustifolia* but not directly stated	0.16% cichoric acid with almost no echinacosides or alkamides.	300 mg tid × 14 days prior to virus challenge	Not an effective preventative.	Similar to placebo.

R = randomized; D-B = double-blind; P-C = placebo-controlled; pt = patients.

ELDERBERRY

DATE OF ISSUE: JUL 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): The American elder (*Sambucus canadensis* L.) and the European Elder (*Sambucus nigra* L.). Family: Caprifoliaceae

COMMON NAME(S): Sweet elder, common elder, elderberry, sambucus[1]

BOTANY: The American elder is a tall shrub that grows to 12 feet. It is native to North America. The European elder grows to about 30 feet and while native to Europe, has been naturalized to the United States.

HISTORY: Elder flowers and berries have been used in traditional medicine and as flavorings for centuries. In folk medicine, the flowers have been used for their diuretic and laxative properties and as an astringent. Various parts of the elder have been used to treat cancer and a host of other unrelated disorders. [2] Distilled elder flower water has been used as a scented vehicle for topical preparations and extracts are used to flavor foods, including alcoholic beverages. The fruits have been used to prepare elderberry wine.

CHEMISTRY: European elder flowers contain about 0.3% of an essential oil composed of free fatty acids and alkanes. Triterpenes (alpha- and beta-amyrin), ursolic acid, oleanic acid, betulin, betulic acid and a variety of other minor components have been identified. [1,3] The elder leaf contains sambunigrin, a cyanogenic glucoside (0.042% by weight).[1]

The *Sambucus* species are now undergoing significant scrutiny because they contain a number of plant lectins that have hemagglutinin characteristics. These compounds are useful in blood typing and defining other hematologic characteristics. [4,5]

PHARMACOLOGY: Elder flowers are considered to have diuretic and laxative properties; however, the specific compounds responsible for these activities have not been well established. The compound sambuculin A and a mixture of alpha- and beta-amyrin palmitate have been found to exhibit strong antihepatotoxic activity against liver damage induced experimentally by carbon tetrachloride. [6]

TOXICOLOGY: Because of the cyanogenic potential of the leaves, extracts of the plant may be used in foods, provided HCN levels do not exceed 25 ppm in the flavor. Toxicity in children who used pea shooters made from elderberry stems has been reported. [2]

One report of severe illness following the ingestion of juice prepared from elderberries has been recorded by the Centers for Disease Control. [7] Persons attending a picnic who ingested several glasses of juice made from berries picked the day before reported nausea, vomiting, weakness, dizziness, numbness and stupor. One person who consumed five glasses of juice was hospitalized for stupor. All recovered. Although cyanide levels were not reported, there remains the possibility of cyanide-induced toxicity in these patients. While elderberries are safe to consume, particularly when cooked (uncooked berries may produce nausea), leaves and stems should not be crushed when making elderberry juice.

SUMMARY: Elderberries are edible berries (particularly when cooked) from the elder bush. They have been used medicinally although they are not typically associated with strong medicinal characteristics. One report of toxicity following the ingestion of elderberry juice has been recorded, but this appears to have been an isolated incident.

PATIENT INFORMATION — Elderberry

Uses: Elder flowers and berries have been used in flavorings and in traditional medicines.

Side Effects: There have been reports of toxicity, particularly involving the stems and leaves.

Dosing: A tea made from elder flowers has been used for coughs and colds, with a daily dosage of 10 to 15 g. [8]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    ELDERBERRY

ELEUTHEROCOCCUS

DATE OF ISSUE: AUG 2000

REPLACES MONOGRAPH DATED: MAY 1996

SCIENTIFIC NAME(S): *Eleutherococcus senticosus* Maxim. *Acanthopanax senticosus* Rupr. et Maxim. *Hedera senticosa*. Family: Araliaceae

COMMON NAME(S): Devil's shrub, eleutheroccoc, shigoka, Siberian ginseng, touch-me-not, wild pepper

BOTANY: *E. senticosus* belongs to the same family as (Araliceae) *Panax ginseng*. The geographical distribution of eleutherococcus coincides with the borders of the distribution of *P. ginseng*. Eleutherococcus is found in forests of broadleaf trees, broadleafs with spruce, and broadleafs with cedar. It grows at elevations of up to 800 m or more above sea level. The plant is a shrub, commonly attaining a height of 2 to 3 m or, less commonly, 5 to 7 m. It possesses gray or grayish-brown bark and numerous thin thorns. The leaves are long-stalked and palmate. Eleutherococcus has male and female forms with globular umbrella-shaped flowers. Male plants produce violet flowers, while female plants have yellowish flowers; the fruit takes the form of black, oval berries. Most commonly, the root is used in herbal medicine; however, it was found that leaves and berries also produce pharmacologically active metabolites. Because it grows abundantly in areas such as Russia and China, it has become a popular substitute for ginseng.[1]

HISTORY: Eleutherococcus has been studied extensively in Russia. It is used as a health food in China, but Asian folk medicine has largely ignored eleutherococcus in favor of its relative, ginseng. As with ginseng, root extracts of the plant have been promoted as "adaptogens" that aid the body in responding to external (eg, environmental) and internal (eg, a disease) stress. The plant extracts have been used to normalize high or low blood pressure, to stimulate the immune system, and to increase work capacity. Reputed effects include increasing body energy levels, protection from motion sickness and against toxins, control of alloxan-induced diabetes, reduction of tumors, and control of atherosclerosis.[1,2]

CHEMISTRY: The chemical composition of the roots and leaves varies with season. It was observed that the roots contain the maximum active ingredient in October and drops sharply in July.[1,2] Methanolic extracts of eleutherococcus roots have been found to contain a glycoside fraction that includes different eleutherosides (isofraxidin, sesamin, syringin) as well as glucose, sucrose, betulinic acid, vitamin E, ß-carotene, caffeic acid, and ß-sitosterol. The eleutherosides found in the root, leaves, and berries are designated as A through M and have different structures belonging to different groups of chemical compounds.[1,3]

Several studies have differentiated between the botany, chemistry, and pharmacology of common ginseng (*P. ginseng* and *P. quinquefolium*) and Siberian ginseng (*E. senticosus*).[4] Only eleutheroside A has similar saponins structure (ginsenosides/panaxosides) to ginseng.[5] While some eleutherosides share common properties with panaxosides, others exhibit very different effects. Seven glycans (eleutherans A, B, C, D, E, F, G) have been isolated from aqueous extract of the crude drug shigoka (Siberian ginseng) roots.[6] New lignans have been isolated from the root of eleutherococcus: 7SR,8RS-dihydrodrodiconiferyl alcohol, dehydrodiconiferyl alcohol, 7,8-trans-dihydrodehydrodiconiferyl alcohol-4-O-ß-D-glucopyranoside, meso-secoisolariciresinol, and (-)-syringoresinol-4-O-ß-D-glucopyranoside.[7] The antiplatelet compound 3,4-dihydroxybenzoic acid has also been isolated from this species.[8] Eleutherosides have been isolated, identified, and measured in the rhizomes, roots, and liquid extracts of eleutherococcus.[9] Other relatively new compounds that have been isolated include phenylpropanes and polysaccharides, ciwujianosides C1 and D1,[10] and at least 10 phenolic compounds such as isofraxidin.[11] Chemical analysis is still in progress on eleutherococcus and indicates that there have been improvements in the procedures of isolation and analysis methods (such as reverse-phase HPLC) of the plant.[12,13,14]

PHARMACOLOGY: An animal study examined the effect of acute (4 to 320 mg/kg) or 4- to 5-day treatment (80 to 320 mg/kg/day) via intraperitoneal injection of eleutherococcus extract on the response of mice to hexobarbital. Both single dose and 4- to 5-day treatments increased sleep latency and duration. This may have drug-drug interaction implications if these 2 agents are taken together. Findings support the contention that the extract acts by inhibiting an enzyme system of hexobarbital metabolism.[15]

In another study with mice, intraperitoneal injection of an aqueous extract of eleutherococcus root reduced plasma sugar levels. Fractionation studies of the extract identified 7 eleutherosides, designated A through G, that produced synergistic hypoglycemic effects in normal mice and in mice with alloxane-induced diabetes.[6] Water-soluble, branched-chain heteroglycans isolated from polysaccharide fractions of extracts have been shown to have such properties in granulocyte and carbon-clearance tests.[16] However, in rats, oral administration of extracts did not affect plasma lactic acid, glucagon, insulin, or liver glycogen, nor did they increase swimming times in endurance tests. Thus, this study did not confirm an endurance-boosting effect of eleutherococcus. Decreased plasma glucose levels were found in resting rats.[17] Another study compared the effects of various orally administered infusions of *P. ginseng* and eleutherococcus for endurance effects in mice. Treatments lasting up to 96 days failed to show any increases in swimming endurance or longevity with any of the infusions. However, eleutherococcus was associated with increased aggressive behavior.[18] There is evidence that the adaptation effect of eleutherococcus may act through the pituitary-adrenocortical system.[19]

In vitro experiments have shown some activity of eleutherococcus against L1210 murine leukemia cells. When root extract was added to cytarabine or N-6-(delta-2-isopentenyl)-adenosine, the extract had an additive effect with conventional antimetabolite drugs, with an ED50 of about 75 mcg/ml. This suggests that addition of the extract to anticancer regimens might make it possible to reduce the doses of toxic drugs.[20] *P. ginseng* has been shown to protect cell cultures from the effects of gamma radiation. The mechanism seems to involve alteration of cellular metabolism rather than DNA repair. Eleutherococcus extract has a similar action, but only to a slight degree.[21]

The eleutherosides have 36 to 143 times the physiologic activity of the roots from which they are extracted.[2] Eleutherococcus extracts, like those of *P. ginseng*, bind to progestin, mineralocorticoid, and glucocorticoid receptors. In addition, eleutherococcus extracts bind to estrogen receptors. This may explain the observed glucocorticoid-like activity of the extracts.[22]

There is evidence of therapeutic benefits of eleutherococcus in humans. In 1 study of 36 healthy volunteers, a 3-times-daily injection of an ethanolic extract for 4 weeks produced increases in the absolute numbers of immunocompetent cells, particularly T-cells. The increase was most marked for helper/inducer cells, although cytotoxic and natural killer cells also increased in number. A general enhancement of the activation state of T cells was evident.[23]

In hypotensive children between 7 and 10 years of age, an eleutherococcus extract improved subjective signs, significantly raised systolic and diastolic blood pressures, and increased total peripheral resistance.[24]

Other studies have described the wide range of eleutherococcus properties, including the effects on the human physical working capacity,[25] the immune systems of cancer patients,[26] the heart structure in MI,[27] malignant arrhythmias,[28] myocarditis and other coronary heart diseases,[29] radiation recovery,[30] diabetes,[31] hyperlipemia,[32] its antimicrobial actions,[33] prenatal prevention of congenital developmental anomalies in rats,[34] and enhanced proliferation of human lymphocytes.[35] Although preparations from *E. senticosus* have been found to be effective against a variety of somatic disorders, the labels on otc preparations do not supply adequate directions for taking the product or clarify the ingredients.[36,37]

INTERACTIONS: Possible assay interference with digoxin may occur; concomitant therapy increased digoxin level to greater than 5 mg/ml without symptoms of toxicity.[38]

TOXICOLOGY: There are possible estrogenic effects in females. Side effects, toxicity, contraindications, and warnings similar to those for *Panax* species (see ginseng) apply. Experience suggests that this product should not be used for people under the age of 40 and that only low doses be taken on a daily basis. Patients are advised to abstain from alcohol, sexual activity, bitter substances, and spicy foods. Avoid use during pregnancy and lactation. High doses of eleutherococcus are

associated with irritability, insomnia, and anxiety. Other adverse effects include skin eruptions, headache, diarrhea, hypertension, and pericardial pain in rheumatic heart patients. Use of eleutherococcus extract has been associated with little or no toxicity. No pathologic, cytotoxic, or histologic changes were noted in mice that ingested infusions of the plant for up to 96 days.[18] In 1 human study, there were no side effects during the 6 months of follow-up.[23] However, use is not recommended for patients in febrile states, hypertensive crisis, or those with MI. Use is contraindicated in hypertensive patients. Rare reported side effects have included slight languor or drowsiness immediately after administration; this may be the result of a hypoglycemic effect of the extract.[2]

Most of the reviewed literature on eleutherococcus suggests that the plant preparations bear minimal toxicity and are fairly safe to use. There was a case in which an eleutherococcus preparation caused severe side effects, but it was later discovered that the preparation did not include eleutherococcus but rather another related species.[1,4,5]

SUMMARY: Eleutherococcus is a plant botanically related to the more familiar *P. ginseng*. Eleutherococcus has a different chemical composition but has been named Siberian ginseng because of purported similar activities. Ethanol and water extracts of the roots of eleutherococcus have been used for a wide variety of therapeutic purposes in which they are said to have an adaptogenic effect. Among the studied properties of eleutherococcus are adaptogenic, hemodynamic, immunoboosting, cardioprotective; usefulness in treatment of hyper- and hypotonia, inhibitory effects on platelet aggregation, potentiation of radioprotective agents, hypoglycemic properties, cytotoxicity against various cancer cells, usefulness in the treatment of hyperlipemia, potential histamine-inhibiting effects, and potential prevention of congenital defects. Continued studies on standardized extracts or isolated active constituents are needed to verify all of eleutherococcus' purported activities.

PATIENT INFORMATION— Eleutherococcus

Uses: Eleutherococcus is similar to ginseng in its properties and alleged effects. It has been used as a hypotensive, immunostimulant, energy enhancer, and aphrodisiac. Extracts of the roots have been used for a wide variety of therapeutic purposes in which they are said to have an adaptogenic effect. Although preparations from *E. senticosus* have been found to be effective against a variety of somatic disorders, the labels on *otc* preparations do not supply adequate directions for taking the product or clarify the ingredients. In addition, standardization of the active ingredients is not clear.[36,37] The German Commission E recommends limiting use to 3 months.[39]

Interactions: Possible assay interference with digoxin may occur; concomitant therapy increased digoxin level to greater than 5 mg/ml without symptoms of toxicity.[38]

Side Effects: Although side effects appear to be rare, eleutherococcus should not be used by patients in febrile states, hypertensive crisis, or those with MI. Use is contraindicated in hypertensive patients. In some individuals it may produce drowsiness or nervousness.

Dosing: As an adaptogen, Eleutherococcus has been given as the powdered root in doses of 1 to 4 g/day. Extracts of *E. senticosus*are recommended at less than 1 g/day.[25,40]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    ELEUTHEROCOCCUS

EMBLICA

DATE OF ISSUE: JAN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Emblica officinalis* Gaertn, *Phyllanthus emblica* L. Family: Euphorbiaceae

COMMON NAME(S): Indian gooseberry, Amla (Hindi), Amalaki (Sanskrit), Emblic Myrobalan (English).

BOTANY: Emblica is a deciduous tree native to India and the Middle East. The round greenish-yellow fruits are commonly used in the Indian diet. Its leaves are feather-like with pale green flowers.[1]

HISTORY: Emblica is mentioned in an Ayurvedic text dating back to the 7th Century.[1]

CHEMISTRY: A fixed oil, volatile oil, and tannins are also present in the plant. [1]

PHARMACOLOGY: Emblica has documented effects on cholesterol levels. Various reports from the 1980s demonstrated reduced serum, aortic, and hepatic cholesterol in rabbit experimentation.[2,3,4,5] A later report confirms the earlier studies reducing lipids and exhibiting atherosclerotic effects in rabbits. Parameters that decreased were serum cholesterol (82%), triglycerides (66%), phospholipids (77%), and LDL (90%). [6] In a human clinical trial, normal and hypercholesterolemic men (35 to 55 years of age) given emblica supplementation experienced a decrease in serum cholesterol levels, which was reversible upon discontinuation of the drug. [7] The plant also has inhibited lipid peroxidation in biological membranes [8] and has displayed a protective effect in myocardial necrosis in rats. [9]

Ancient Ayurvedic medicine also employs emblica, in the form of fruit juice, as therapy for diabetic patients to strengthen the pancreas. [1] Current investigation in this area was studied in dogs with acute pancreatitis. The treated group showed less cell damage and marked inflammatory score decreases confirmed by microscopic examination.[10]

Emblica has also been studied for its anticancer and antimicrobial effects. It has inhibited induced mutagenesis in *Salmonella* strains.[11] In another study, the plant significantly inhibited dose-dependent hepatocarcinogenesis as measured by parameters such as tumor incidence, enzyme measurements, and other liver injury markers.[12] Emblica has reduced cytotoxic effects in mice given carcinogens.[13] However, in 1 report emblica had no significant effect in reducing lung cancer parameters in mice.[14] Alcoholic extracts of emblica showed activity against a number of test bacteria in another report. [15] In addition, the plant was effective against certain dermatophytes in another study.[16]

Other reported effects of emblica include the following: Anti-inflammatory (in water fraction of methanol leaf extract), [17] dyspepsia treatment,[18] organ restoration, and treatment for eye problems, joint pain, diarrhea, and dysentery. [1]

TOXICOLOGY: No major reported toxicities have been associated with the fruit.

SUMMARY: Emblica, or Indian gooseberry, has been used in Ayurvedic medicine for thousands of years. Emblica has cholesterol-lowering effects, and other positive effects in certain heart diseases. The plant has also exhibited antimicrobial, anticancer, and anti-inflammatory actions. Little information on toxicity is available.

PATIENT INFORMATION — Emblica

Uses: Emblica has cholesterol-lowering, antimicrobial, anticancer, and anti-inflammatory effects.

Side Effects: No major toxicities have been reported.

Dosing: Emblic fruits often are taken in doses from 0.25 to 3 g/day as a source of vitamin C. There are no published clinical studies to support this dosage; however, it is a reasonable dose given the high vitamin C content of emblic fruits.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    EMBLICA

EMU OIL

DATE OF ISSUE: JAN 2004

REPLACES MONOGRAPH DATED: NA

SCIENTIFIC NAME(S): *Dromaius Novae-Hollandiae*[1]

COMMON NAME(S): Emu

HISTORY: The Aboriginal people of Australia have used emu oil for centuries. The oil was collected by either hanging the emu skin from a tree or wrapping it around an affected area and allowing the heat of the sun to liquefy the emu fat to enhance absorption or penetration into the skin. [2]

Emu oil was used medicinally to treat muscle and joint problems (ie, painful joints, swollen muscles) and a variety of skin conditions (ie, burns, eczema). Other purported medicinal uses include psoriasis and rheumatoid arthritis. The oil has also been used for cooking as well as for keeping leather riding tackle supple. [2]

The Emu Producers International Cooperative (EPIC) oil refinery produces 5000 pounds of oil daily for commercial use in cosmetics such as eye creams, moisturizers, and hair products.[3]

CHEMISTRY: There are limited chemical data on emu oil. The *International Emu Oil Standards* state that emu oil contains myristic, palmitic, palmitoleic, steraic, oleic, elaidic, linoleic, linolenic, and eiconsenoic fatty acids. Oleic acid is the main fatty acid. [4,5]

PHARMACOLOGY: Nearly all clinical and scientific studies focus on the anti-inflammatory properties of emu oil.

The anti-inflammatory activities of 5 different preparations of emu oil were examined in Wistar rats. The oils came from birds raised in different habitats. Adjuvant arthritis was induced by caudal injection of a mixture of *M. tuberculosis* in squalane. The rear paw diameters were measured for signs of inflammation on days 10 and 14. The oil mixtures were applied at the rate of 2 mL/kg on days 10 through 13. Topical application of 3 of the oil preparations reduced the increase in paw diameter caused by arthritis inflammation over the treatment period. The topical applications of 2 of the oils had effects comparable to the oral administration of ibuprofen (40 mg/kg).[1] A similar study which generated data over a 24-month period provides further evidence of anti-inflammatory activity. [6]

Emu oil was evaluated as a lubricant and aid in reducing scar formation in healed burns. Ten male patients, ranging from 24 to 62 years of age, were evaluated over a 6-month period in a randomized, double-blinded study. Patients were instructed to apply the placebo or emu oil lubricant daily on independent sites as needed. Wound areas treated with emu oil healed significantly better ($P < 0.02$) than the control in photo analysis.[7]

Another study examined the efficacy of emu oil lotion, 100% emu oil, furasin, polysporin, hydrocortisone 1% ointment, and no ointment (control) on full-thickness skin defects in rodents after surgery. Six days postoperatively, wound contraction and infiltration of epithelialized and granulation tissue were assessed; results indicated a 2-fold promotion ($P < 0.05$) of wound contraction, epithelialization, and infiltration of organized granulation tissue with emu oil lotion only. [8]

Topically applied emu oil reduced the severity of acute auricular inflammation in mice induced by croton oil. The magnitude of swelling and degree of edema were reduced in mice treated with emu oil as compared with controls.[9,10]

TOXICOLOGY: There is limited clinical toxicological data on emu oil in the scientific literature. Anecdotal information suggest a lack of obvious toxicity. [2]

SUMMARY: The indigenous people of Australia have used emu oil for centuries for treating muscle and joint problems and for a variety of skin conditions; limited clinical and scientific evidence suggest that emu oil has important anti-inflammatory activity.

PATIENT INFORMATION — Emu oil

Uses: Historically, the oil has been primarily used topically for its anti-inflammatory effects; limited clinical data are available to support this use.

Side Effects: There is limited clinical toxicological data on emu oil in the scientific literature.

Dosage Concerns: Although not supported by clinical trial data, dosage regimens marketed by commercial Web sites include topical application 2 to 3 times/day to the affected site.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    EMU OIL

EVENING PRIMROSE OIL (EPO) (OEP)

DATE OF ISSUE: AUG 1997

REPLACES MONOGRAPH DATED: NOV 1993

SCIENTIFIC NAME(S): *Oenothera biennis* L. Family: Onagraceae

COMMON NAME(S): Evening primrose

BOTANY: The evening primrose is a large, delicate wildflower native to North America and is not a true primrose. The blooms usually last only 1 evening. Primrose is an annual or biennial and can grow in height from 1 to 3 meters. The flowers are yellow in color and the fruit is a dry pod about 5 cm long that contains many small seeds.[3] The small seeds contain an oil characterized by its high content of gamma-linolenic acid (GLA). [1] Wild varieties of *O. biennis* contain highly variable amounts of linoleic acid and GLA; however, extensive cross-breeding has produced a commercial variety that consistently yields an oil with 72% cis-linoleic acid and 9% GLA. This is perhaps the richest plant source of GLA. A commercially grown mold has been reported to produce an oil containing 20% GLA, and newer strains may produce even greater yields.[2]

The oil from evening primrose (OEP) seeds is cultivated in at least 15 countries and is available in more than 30 countries as a nutritional supplement or as a constituent in specialty foods. US and Canadian production total more than 300 to 400 tons of seeds yearly. US production centers are in California, North Carolina, South Carolina, Oregon and Texas.[4]

CHEMISTRY: Seeds from *O. biennis* L. contain 14% of a fixed oil known as OEP. This oil can contain from 50% to 70% cis-linoleic acid and from 7% to 10% cis-GLA.[3] Plants of varying age and location have been studied for different GLA content. [5] Also found is cis-6,9,12-octadecatrienoic acid; small amounts of oleic, palmitic and stearic acids; steroids; campesterol; and beta-sitosterol. [3] Mucilage and tannin presence in plant parts of evening primrose has also been analyzed. [6]

PHARMACOLOGY: Essential fatty acids (EFAs) are important as cellular structural elements and as precursors of prostaglandins. Prostaglandins help regulate metabolic functions.[3] EFAs are the biologically active parts of polyunsaturated fats. Ingestion of EFAs is believed to help reduce the incidence of cardiovascular disease and obesity. EFAs cannot be manufactured by the body and must be provided by the diet in relatively large amounts. It has been recommended that 1% to 3% of total daily caloric intake should be in the form of EFAs. [7] The World Health Organization recommends 5% for children and pregnant or lactating women. [8]

Animal studies have shown that dietary EFA deprivation can lead to eczema-like lesions and hair loss, a generalized defect in connective tissue synthesis with poor wound healing, failure to respond normally to infection with poor immune function, infertility (especially in males), fatty degeneration of the liver, renal lesions with a lack of normal water balance and atrophy of exocrine glands (lacrimal, salivary). This suggests that a variety of human illnesses with similar symptoms may result from poor EFA metabolism or insufficient dietary EFA. Because OEP represents a rich source of EFAs, particularly GLA, its use has been suggested in the treatment of these deficiency syndromes. Theoretically, the GLA provided by EPO can be converted directly to the prostaglandin precursor dl-homo-GLA (DGLA) and might be beneficial to persons unable to metabolize cis-linoleic acid to GLA or with low dietary intake of cis-linoleic acid.

It has been postulated that GLA, DGLA and arachidonic acid are present in human milk for a very important and specific purpose. [9,10] It is believed that the conversion of linoleic acid to GLA in humans is a rate-limiting metabolic step, [11] with only a relatively small amount of dietary linoleic acid (LA) being converted to GLA and to other metabolites.[12] The delta-6-desaturase enzyme is required for this conversion. Factors interfering with this GLA production include aging, diabetes, high alcohol intake, high fat diets, certain vitamin deficiencies, hormones, high cholesterol levels and viral infections. [8] The essential fatty acids beyond this rate-limiting step are crucial for proper development of many body tissues, especially in the brain. The brain contains about 20% of 6-desaturated EFAs by weight. Infants cannot form an adequate amount of EFAs if linoleic acid is the only dietary source of n-6-EFA; this may be why preformed GLA, DGLA and arachidonic acid are present in human milk. Studies have compared fatty acids in the phospholipids of red blood cells from infants fed human milk with those from infants fed artificial milk formulas. Infants fed artificial formulas showed phospholipids containing higher levels of linoleic acid and significantly lower levels of DGLA and arachidonic acid. Dietary supplementation to pregnant women with OEP results in an increase of total fat and EFA content in breast milk. [13] The presence of linoleic acid metabolites in human milk can affect the composition of red blood cell membranes.[14]

Taking large amounts (30 g/day to 40 g/day) of linoleic acid has little effect on DGLA or arachidonic acid blood levels. [15,16,17] However, taking less than 500 mg GLA/day can produce a significant increase in DGLA concentration and a smaller increase in arachidonic acid in plasma phospholipids. [12] These elevated levels do not exceed normal amounts found in the American population.[18] Therefore, GLA, not linoleic acid, is capable of elevating the levels of linoleic acid metabolites in human blood. Below-normal plasma or adipose-tissue concentrations of GLA, DGLA or arachidonic acid may occur in: Healthy middle-aged men who will later develop heart disease;[19,20,21,22] healthy middle-aged people who will later suffer stroke; [23] diabetics;[24,25] patients with atopic dermatitis;[25,26,27] heavy drinkers;[28,29] females with premenstrual syndrome;[30] older people.[31,32]

The commercial product *Efamol* (Efamol Research Institute, Nova Scotia, Canada) is a standardized dosage form of EPO and has been tested clinically in a variety of illnesses. A large number of independently conducted studies and clinical trials, mainly sponsored by Efamol, Ltd., provide preliminary evidence that GLA in the form of EPO can be beneficial in certain conditions.

The effects of OEP can be categorized as follows:

Cardiovascular disease: Linoleic acid can reduce elevated serum cholesterol levels, but GLA has cholesterol-lowering activity about 170 times greater than the parent compound.[33] In 79 patients who took 4 g *Efamol*/day in a placebo controlled study, a significant ($P < 0.001$) decrease of 31.5% in serum cholesterol was noted after 3 months of treatment. A nonsignificant (NS) decrease was observed in the placebo group. [34] Preliminary unpublished data from double-blind trials suggest that EPO given to overweight patients with a family history of obesity results in a significant weight loss and a reduction in skin-fold thickness and systolic and diastolic blood pressures after 6 weeks of therapy. There is evidence that the oil inhibits ADP-induced platelet aggregation in treated guinea pigs, suggesting that an increase in the formation of the antithrombotic-1-series prostaglandins may inhibit in vivo thrombosis. [35] In some studies, GLA has lowered plasma cholesterol and triglycerides and inhibited in vivo platelet aggregation. [36] Elevated plasma lipids and in vivo platelet aggregation are risk factors for heart disease and stroke, and GLA lowers both of these.[37] In a later report in 20 hyperlipidemic patients, 2.4 to 7.4 ml/day of *Pre-Glandin ?* (containing 9% GLA) was administered. There were no changes in serum cholesterol, HDL cholesterol or triglyceride levels. [38]

Breast cancer and related disorders: Animal studies indicate that subcutaneous OEP injections (25 to 200 mcL/day) produced statistically significant reductions in transplanted mammary tumors from baseline size, while an olive oil control did not. [39] An in vitro experiment found a dose-related inhibition of the growth rate in the malignant BL6 tumor system.[40]

Improvement in serum fatty acid levels by OEP supplementation in women with benign breast disorders has not been associated with a clinical response. [41] In women with proven recurrent breast cysts, OEP treatment for 1 year resulted in a slightly lower (NS) recurrence rate compared with placebo. [42]

Premenstrual syndrome (PMS) and mastalgia: Clinical studies investigating OEP use in these conditions have had positive results. PMS involves a variety of symptoms, the most common being cyclical mood changes, fluid retention or redistribution, breast tenderness and discomfort and tension headaches. A variety of pharmacologic therapies have been suggested with variable results, including the use of progestogens, oral contraceptives, pyridoxine (vitamin B_6), bromocriptine, danazol, mineral supplements, opioid antagonists, diuretics, antidepressants, mefenamic acid, clonidine, lithium carbonate, ibuprofen and GLA. [43,44,45]

It has been suggested that an abnormal sensitivity to prolactin or a deficiency of PGE1 (thought to attenuate the biologic activity of prolactin) may contribute to PMS. Levels of GLA and subsequent metabolites were lower in women with PMS than in controls, indicating a possible defect in the conversion of linoleic acid to GLA. This may result in an exceptional sensitivity to normal changes in prolactin levels. [46] In 19 PMS patients receiving evening primrose oil each morning and evening during the last 14 days before menstruation for five consecutive cycles, PMS symptoms were decreased. OEP was most effective during the fifth cycle. [47]

PMS and breast pain are common with high fat intake. Women with breast pain may be unable to convert LA to GLA. [8] In some studies, PMS and premenstrual breast pain (cyclic mastalgia) have been relieved by GLA to a significantly greater degree than with placebo. [48] However, a placebo controlled evaluation of OEP found the oil to have no effect and that the effects observed in women with moderate PMS were solely due to a placebo effect. [49]

A number of clinical studies have evaluated the effect of OEP in women with nodular or polycystic breast disease. Treatments such as bromocriptine, danazol or OEP have been associated with improvement in breast pain in up to 77% of patients with cyclical mastalgia and 44% of those with noncyclical mastalgia. [50]

Further etiology and assessment of breast pain has been reported, along with OEP treatment in this condition. [51] PMS assessment and recommendations to affected patients can also be referenced. [52]

A recent report on the use of OEP to treat menopausal flushing concluded that there were no benefits over placebo in this condition. [53]

Rheumatoid arthritis: A double-blind, placebo controlled study investigated the effects of altering dietary EFAs on requirements for nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis. The major aim was to determine whether OEP or OEP/fish oil could replace NSAIDs. An initial 1 year treatment period was followed by 3 months of placebo. At 1 year, OEP and OEP/fish oil produced significant subjective improvement compared with placebo. Furthermore, by 1 year, the patients taking OEP or EPO/fish oil had significantly reduced their use of NSAIDs. Following 3 months of placebo, those receiving initial NSAID treatment had relapsed. Despite decreased NSAID use, measures of disease activity did not worsen. However, there was no evidence that OEP and OEP/fish oil acted as disease-modifying agents. [54] OEP therapy for rheumatoid arthritis requires longer than 3 months for any beneficial effects. [8] A study of OEP vs olive oil found that OEP use resulted in a significant reduction in morning stiffness after 3 months. [55]

Properties, adverse effects, mechanism of action and clinical study overview of evening primrose oil for rheumatoid arthritis are further discussed. [56,57]

Multiple Sclerosis: In MS there is evidence of abnormality in both EFA metabolism and lymphocytic function. Several studies have shown slight but variable improvement in patients fed diets high in linoleic acid. In an open trial of OEP, three of eight patients with MS showed improvement in the manual dexterity test, but no improvement was noted in grip strength. When the oil was given with colchicine, four of six patients improved in their general physical tone. [58] Others have noted similar improvement with GLA therapy. [59,60,61]

Atopic dermatitis and dermatologic disorders: In atopic dermatitis, GLA was significantly more effective than placebo in improving skin condition, providing relief from pruritus and allowing reduced reliance on corticosteroid medication. [62,63] Other reports exist (most double-blind, crossover, randomized or placebo controlled) that evaluate OEP in atopic dermatitis treatment. These studies include: 15 adults and 17 children given 500 mg OEP (*Efamol*) orally twice daily for 3 weeks; [64] 60 adults and 39 children given higher EPO doses compared with lower doses; [63] 20 adults; [62] 24 children for a 4-week period, then 12 children for a long-term 20-week follow-up period; [65,66] 52 patients, age 16 to 64 years, given 500 mg OEP frequently for 4 months. [67] All reports suggest improvement in atopic eczema, regarding factors such as itch, scaling, disease severity, grade of inflammation, percent of body surface area involvement, dryness, [62,63] erythema and surface damage. Women with "premenstrual flare" of eczema reported improvement in their condition. [67] A meta-analysis involving 311 patients (age 1 to 60) in nine randomized, double-blind, placebo controlled studies determined OEP to be more effective than placebo. [68]

A defect in the function of delta-6-desaturase, the enzyme responsible for the conversion of linoleic acid to GLA, has been found in patients with atopic dermatitis. [69] Forty-eight children (age 2 to 8 years) administered 0.5 g/kg/day of *Epogam* showed significant improvement in disease severity independent of whether the patients had IgE-mediated allergy manifestations. OEP also increased percent content of n-6 fatty acids in red blood cell membranes, without affecting membrane microviscosity. [70] OEP doses of 6 g/day in a double-blind, placebo controlled study of 102 patients improved the lipid profile of the epidermis in patients with atopic dermatitis [71] but it was not effective in treatment of the disease itself. [72]

A recent report discusses OEP and fish oil in the treatment of atopic dermatitis and psoriasis. [73]

Other diseases: In diabetic patients, GLA has been shown to reverse neurological damage. [74] GLA supplementation to children with IDDM (insulin-dependent diabetes mellitus) indicated that favorable and statistically significant increases in serum essential fatty acid levels and decreases in PGE2 levels occurred, which may provide a therapeutic benefit. [75] One study demonstrated that GLA accelerated recovery of liver function in alcoholics and reduced the severity of withdrawal symptoms. [28]

OEP has been tested for use in diagnosis and symptom relief of myalgic encephalomyelitis (Tapanui flu). [76] OEP may be of use to prevent or slow the development of hypertension in pregnancy by its pressor response to angiotensin ??. [77] In combination therapy, three patients with Crohn's disease remained in relapse-free remission after OEP administration. [78]

The value of a drug that is effective in a wide variety of EFA-deficiency disorders cannot be overstated. The treatment of several unique medical conditions with OEP has been undertaken, often with excellent results. Many of the published studies have been open trials that require confirmation through double-blind testing; however, these studies generally have been well designed and their results adequately analyzed. The disorders treated include autoimmune diseases, childhood hyperactivity, chronic inflammation, ethanol-induced toxicity and acute alcohol withdrawal syndrome, icthyosis vulgaris, scleroderma, Sjogren's syndrome and Sicca syndrome, brittle nails, mastalgia, psychiatric syndromes, tardive dyskinesia, ulcerative colitis and migraine headaches. GLA has shown in vitro antitumor activity against primary liver cancer cells, but this effect was not demonstrated in a clinical trial. [79] Reviews of evening primrose oil are listed in the bibliography. [80,81,82,83,84,85,86,87,88,89,90]

TOXICOLOGY: As a nutritional supplement, the maximum label-recommended daily dose of OEP is approximately 4 g. This dose contains 300 to 360 mg GLA, which contributes: (1) 6 to 7 mg GLA/kg/day likely to be produced from linoleic acid in the normal adult female, (2) 23 to 65 mg GLA/kg/day consumed by a breastfed baby or (3) 70 to 400 mg/kg/day of all the metabolites of linoleic acid consumed by a breastfed infant. According to these estimates, the amounts of GLA in the recommended doses of OEP are in the same range as the amounts of GLA and other related EFAs present in widely consumed foods. Thus, there is little concern about the safety of OEP as a dietary supplement in the recommended dosage range. There are considerable data on the safety of OEP from Efamol, Ltd., a major commercial supplier of oil derived from specially selected and hybridized forms of *Oenothera* species. In toxicological studies carried out for 1 year, OEP at doses up to 2.5 ml/kg/day in rats and 5 ml/kg/day in dogs was found to possess no toxic properties. Similar results were obtained in 2-year carcinogenicity and teratological investigations. With approximately 1000 tons of OEP sold in several countries as a nutritional supplement since the 1970s, there have been no complaints concerning the safety of the product. [91]

SUMMARY: The oil obtained from the seeds of inbred strains of evening primrose is a rich natural source of essential fatty acids, especially cis-linoleic acid and GLA. The biologic importance of these fatty acids in maintaining normal physiologic function is well documented. The use of GLA supplementation by the ingestion of OEP has been shown effective in a variety of medical disorders due to EFA deficiency or problems in EFA metabolism. Some of these illnesses include: Cardiovascular disease, female disorders, rheumatoid arthritis, multiple sclerosis and atopic dermatitis.

Evening primrose oil appears to be devoid of significant adverse effects. A small number of patients in published studies have discontinued therapy for reasons related to OEP, but the symptoms have been variable and usually mild. The use of OEP for periods of up to 18 months did not result in any adverse effects.

PATIENT INFORMATION— Evening Primrose Oil (EPO) (OEP)

Uses: OEP has been used to treat cardiovascular disease, breast disorders, premenstrual syndrome, mastalgia, rheumatoid arthritis, multiple sclerosis, atopic eczema, dermatological disorders and other illnesses.

Side Effects: There have been no adverse effects attributed to oil of evening primrose.

Dosing: Evening primrose oil has been administered orally in clinical trials for arthritis, atopic dermatitis, PMS, and diabetic neuropathy at doses between 3 and 6 g/day. The typical content of gamma-linolenic acid is 8% to 10% in the oil. [72,92,93]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    EVENING PRIMROSE OIL (EPO) (OEP)

EYEBRIGHT

DATE OF ISSUE: SEP 1996

REPLACES MONOGRAPH DATED: APR 1987

SCIENTIFIC NAME(S): *Euphrasia officinale* L. Other species include *E. rostkoviana*Hayne and *E. stricta* J.P. Wolff ex J.F. Lehm. Family: Scrophulariaceae

COMMON NAME(S): Eyebright

BOTANY: This small annual plant grows to about one foot. It has oval leaves but can have a variable appearance. Its flowers are arranged in a spike; the white petals often have a red tinge, but may be purple-veined or have a yellow spot on the lower petal. It blooms from July to September. The flowers have the appearance of blood-shot eyes. It is believed to have originated from European wild plants.

HISTORY: Eyebright was used as early as Theophrastus and Dioscorides, who prescribed infusions for topical application in the treatment of eye infections. This was in large part due to the similarity of the "bloodshot" petals to irritated eyes. The plant has been used in homeopathy to treat conjunctivitis and other ocular inflammations. The plant continues to find use in black herbal medicine. [1]

Further historic data on the use of Euphrasia includes a 14th century cure for "all evils of the eye." An eyebright ale was described in Queen Elizabeth's era. It was a component of British Herbal Tobacco, which was smoked for chronic bronchial conditions and colds. Other early uses include treatments for allergies, cancers, coughs, conjunctivitis, earaches, epilepsy, headaches, hoarseness, inflammation, jaundice, ophthalmia, rhinitis, skin ailments and sore throats.

CHEMISTRY: Eyebright contains the glycoside aucuboside. In addition, the plant contains a tannin, aucubin, caffeic and ferulic acids, sterols, choline, some basic compounds and a volatile oil.[2]

Other components include vitamin C, ß-carotene, glycosides, nonacosame, ceryl alcohol, beta-sitosterol, oleic-, and linoleic-, palmitic- and stearic- acids, fumaric acid, isoquercitrin, quercetin and rutin. [3] Additionally, the iridoid glycosides catalpol, euphroside and ixoroside, the lignan dehydrodiconiferlyl alcohol 4-ß-D-glucoside, the phenyl-propane glycoside eukovoside, the flavonoid apigenin, gallotannins, traces of tertiary alkaloids, steam-volatile substances and a range of free and combined phenol-carboxylic acids, principally caffeic, p-hydroxy-phenylpyruvic and vanillic acids.

Tannins, aucuboside (aucubin), [4] seven known iridoid glycosides and the new compound, eurostoside [5] as well as seven flavonoids [6] have all been isolated from *E. rostkoviana*.

PHARMACOLOGY: None of the chemical components of eyebright have been associated with a significant therapeutic effect. There are no controlled studies in man to evaluate its effectiveness in the treatment of ocular irritations.

Eyebright is commonly used in European folk medicine for blepharitis and conjunctivitis, as well as for a poultice for styes and the general management of eye fatigue. They also use it internally for coughs and hoarseness, as well as a homeopathic remedy for conjunctivitis. [7] The phenol-carboxylic acids are thought to play a role in the antibacterial effects of eyebright.

TOXICOLOGY: While there are no known risks associated with eyebright, its purported activities have not been clinically substantiated and the folkloric use is unacceptable on hygenic grounds.

German studies suggest that 10 to 60 drops of eyebright tincture could induce confusion, cephalalgia, violent pressure in the eyes with tearing, itching, redness and swelling of the margins of the lids, photophobia, dim vision, weakness, sneezing, coryza, nausea, toothache, constipation, hoarseness, cough, expectoration, dyspnea, yawning, insomnia, polyuria and diaphoresis. [3] Hence, ophthalmic use of this material is strongly discouraged.

SUMMARY: Eyebright is an herbal remedy that continues to find use among herbal enthusiasts. Although many adverse effects have been reported with its use, there appears to be little or no evidence in today's scientific literature for its effectiveness.

PATIENT INFORMATION— Eyebright

Uses: Eyebright preparations have been used to treat a variety of complaints, especially inflammatory eye disease.

Side Effects: The range of adverse effects is considered to outweigh the dubious benefits.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "E" MONOGRAPHS
    EYEBRIGHT

"F" MONOGRAPHS

FALSE UNICORN

DATE OF ISSUE: MAY 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Chamaelirium luteum*(L.) Gray, Family: Liliaceae (Lilies)

COMMON NAME(S): False unicorn, helonias root, devil's bit, blazing star, drooping starwort, rattlesnake, fairy-wand

BOTANY: *Chamaelirium luteum* is a native lily of the eastern US. It is considered a threatened species because of a loss of habitat and effects of collection from the wild for herbal use. Cultivation is considered possible, but has not yet become commercially important. The root is collected in autumn. *C. luteum* is a dioecious species (ie, the male and female flowers are borne on separate plants). The plant has been confused with the lilies *Helonias bullata* and *Aletris farinosa*(true unicorn root), because of several shared common names.[1,2,3]

HISTORY: False unicorn root was used by the Eclectic medical movement of the late 19th and early 20th centuries. Its chief use was for female complaints or as a uterine tonic in the treatment of amenorrhea or morning sickness. It has also been used for appetite stimulation and as a diuretic, vermifuge, emetic, and insecticide.[2,3,4,5,6]

CHEMISTRY: The root contains ˜ 10% of a saponin, chamaelirin ($C_{36}H_{62}O_{18}$), but neither its structure nor composition have been fully elucidated. Diosgenin was isolated from a hydrolyzate of the root extract, indicating that some components of the saponin may be based on this genin. [7] The fatty acids oleic, linoleic, and stearic acid were isolated from the root.[8]

PHARMACOLOGY: The fluid extract of false unicorn root was examined for its effects on isolated guinea pig uterus; however, no stimulant or relaxant effect was detected.[9,10,11] Similar experiments in the intact dog were also negative.[12] Nevertheless, a water extract did not block gonadotropin release in the rat. [13] A recent observation suggests, that false unicorn root may act through increasing human chorionic gonadotropin. [14] The notion that the occurrence of diosgenin might be responsible for hormonal effects is incorrect because the parent saponin is unlikely to be hydrolyzed to a free sterol in vivo. An understanding of false unicorn root's effects must await additional modern chemical and pharmacological studies.

TOXICOLOGY: False unicorn root is emetic at high doses. Cattle have died from consumption of the plant. [4] The safety of the plant for use in pregnancy has not been established.

SUMMARY: False unicorn has been used as a uterine stimulant; however, there is no chemical or pharmacological literature that substantiates this use. Its safety cannot be guaranteed in pregnancy; however, its century-long history of use contradicts serious acute toxicity. A monograph of false unicorn can be found in the *British Herbal Pharmacopoeia*, vol. 1.[15]

PATIENT INFORMATION — False Unicorn

Uses: Historically, false unicorn has been used as a uterine tonic for treatment of amenorrhea and morning sickness, as an appetite stimulant, diuretic, vermifuge, emetic, and insecticide.

Side effects: False unicorn can be emetic at high doses. Safety has not been established during pregnancy.

Dosing: Traditional doses of false unicorn root are 2 g as a uterine tonic or diuretic; however, no clinical studies have been performed to support a particular dose.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FALSE UNICORN

FENNEL

DATE OF ISSUE: AUG 1994

REPLACES MONOGRAPH DATED: MAR 1988

SCIENTIFIC NAME(S): *Foeniculum vulgare* Mill. syn. F. *officinale* All. and *Anethum foeniculum* Family: Apiaceae (Umbelliferae) A number of subspecies have been identified and their names add to the potential confusion surrounding the terminology of these plants.

COMMON NAME(S): Common, sweet or bitter fennel, carosella, Florence fennel, finocchio, garden fennel, large fennel, wild fennel [1,2]

BOTANY: Fennel is an herb native to southern Europe and Asia Minor. It is also cultivated in the United States, Great Britain and temperate areas of Eurasia. All parts of the plant are aromatic. When cultivated, fennel stalks grow to a height of about three feet. Plants have finely divided leaves composed of many linear or awl-shaped segments. Grayish, compound umbels bear small, yellowish flowers. The fruits or seeds are oblong ovals about 6 mm long and greenish or yellowish brown in color; they have five prominent dorsal ridges. The seeds have a taste resembling that of anise. Besides *F. vulgare*, *F. dulce* ("carosella") is grown for its stalks, while *F. vulgare* var azoricum Thell. ("finocchio") is grown for its bulbous stalk bases.

HISTORY: According to Greek legend, man received knowledge from Mount Olympus as a fiery coal enclosed in a stalk of fennel. The herb was known to the ancient Chinese, Indian, Egyptian and Greek civilizations, and Pliny recommended it for improving the eyesight. The name "foeniculum" is from the Latin word for "fragrant hay." Fennel was in great demand during the Middle Ages. The rich added the seed to fish and vegetable dishes, while the poor reserved it as an appetite suppressant to be eaten on feast days. The plant was introduced to North America by Spanish priests and the English brought it to their early settlements in Virginia. [3] All parts of the plant have been used for flavorings, and the stalks have been eaten as a vegetable. The seeds serve as a traditional carminative. Fennel has been used to flavor candies, liqueurs, medicines and food, and it is especially favored for pastries, sweet pickles and fish. The oil can be used to protect stored fruits and vegetables against infection by pathogenic fungi. [4] Beekeepers have grown it as a honey plant.[3] Health claims have included its use as a purported antidote to poisonous herbs, mushrooms and snakebites.[5] and for the treatment of gastroenteritis, indigestion, to stimulate lactation and as an expectorant and an emmenagogue.[1] Tea made from crushed fennel seeds has been used as an eyewash.[3] Powdered fennel is said to drive fleas away from kennels and stables. [4]

CHEMISTRY: The oils of sweet and bitter fennel contain up to 90% trans-anethole, up to 20% fenchone and small amounts of limonene, camphor, alpha-pinene and about a half dozen additional minor volatile compounds. [6] The seeds contain between 3% and 6% of an essential oil and about 20% of a fixed oil composed of petroselinic acid, oleic acid and tocopherols.

Sweet fennel contains derivatives of caffeic acid and hydroxybenzoic acid. [7] The fruits (seeds) and leaves have been shown to contain a number of flavonoid compounds. These include quercetin 3-glucuronide, isoquercetin, kaempferol 3-glucuronide and kaempferol 3-arabinoside. Low concentrations of isorhammetin glycosides occur in the leaves.[8]

PHARMACOLOGY: An acetone extract of the seeds of *F. vulgare* has been shown to have estrogenic effects on the genital organs of male and female rats.[9] As an herbal medicine, fennel is reputed to increase milk secretion, promote menstruation, facilitate birth, ease the male climacteric and increase the libido. These supposed properties led to research on fennel for the development of synthetic estrogens during the 1930s. The principal estrogenic component of fennel was originally thought to be anethole, but it is now believed to be a polymer of anethole, such as dianethole or photoanethole. [10] The volatile oil of fennel increases the phasic contraction of ileal and tracheal smooth muscle in the guinea pig. The effect was generally greater with ileal muscle. [11] Administration of the volatile oil to rats has exacerbated experimentally-induced liver damage.[12]

TOXICOLOGY: Ingestion of the volatile oil may induce nausea, vomiting, seizures and pulmonary edema. [13] Its therapeutic use in Morocco has occasionally induced epileptiform madness and hallucinations.[4] The principal hazards with fennel itself are photodermatitis and contact dermatitis. Some individuals exhibit cross-reactivity to several species of Apiaceae, characteristic of the so-called celery-carrot-mugwort-condiment syndrome. [14] Rare allergic reactions have been reported following the ingestion of fennel.

Fennel oil was found to be genotoxic in the *Bacillus subtilis* DNA-repair test.[15] Estragole, present in the volatile oil, has been shown to cause tumors in animals.

A survey of fennel samples in Italy found viable aerobic bacteria, including coliforms, fecal streptococci and *Salmonella* species suggesting the plant may serve as a vector of infectious gastrointestinal diseases. [16]

A serious hazard associated with fennel is that poison hemlock can easily be mistaken for the herb. Hemlock contains highly narcotic coniine, and a small amount of hemlock juice can cause vomiting, paralysis and death.[5]

SUMMARY: Fennel is a popular herb that has been known since ancient times. It is widely used as a flavoring and scent and has served as an herbal remedy. Fennel oil contains compounds with estrogenic activity. The principal hazards associated with the plant are allergic reactions, photodermatitis and contact dermatitis in sensitive individuals, and some samples may be contaminated with pathogenic bacteria. However, poison hemlock can be mistakenly identified as fennel.

PATIENT INFORMATION — Fennel

Uses: Fennel has been used as a flavoring, scent, insect repellent, herbal remedy for poisoning and GI conditions, and as a stimulant to promote lactation and menstruation.

Side Effects: Fennel may cause photodermatitis, contact dermatitis and cross reactions. The oil may induce hallucinations, seizures, etc. Poison hemlock may be mistaken for fennel.

Dosing: Fennel seed and fennel seed oil have been used as stimulant and carminative agents in doses of 5 to 7 g and 0.1 to 0.6 mL, respectively. [17]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FENNEL

FENUGREEK

DATE OF ISSUE: JUL 1996

REPLACES MONOGRAPH DATED: JUL 1987

SCIENTIFIC NAME(S): *Trigonella foenum-graecum*L. Family: Leguminosae

COMMON NAME(S): Fenugreek

BOTANY: Fenugreek spice is commonly sold as the dried ripe seed. The plant is an annual that is native to Asia and southeastern Europe.

HISTORY: The European herb fenugreek has been used for centuries as a cooking spice and has been used in folk medicine for almost as long. The herb has been used in folk medicine in the treatment of boils, diabetes, cellulitis and tuberculosis. Extracts of the seeds are used to flavor maple syrup substitutes. The seeds are rich in protein and the plant is grown as an animal forage. Following commercial extraction of diosgenin (which is used as a natural precursor in commercial steroid synthesis), the nitrogen and potassium-rich seed residue is used as an agricultural fertilizer.

CHEMISTRY: The leaves of the plant contain at least seven saponins called graecunins. These compounds are glycosides of diosgenin. [1] Seeds contain from 0.1% to 0.9% diosgenin and are extracted on a commercial basis.[2,3] Plant tissue cultures from seeds grown under optimal conditions have been found to produce up to 2% diosgenin with smaller amounts of gitongenin and trigogenin. The seeds also contain the saponin fenugrin B. [4]

Several coumarin compounds have been identified in fenugreek seeds. [5] The seeds contain a number of alkaloids (trigonelline, gentianine, carpaine). A large portion of the trigonelline is degraded to nicotinic acid and related pyridines during roasting of the seed. These degradation products are in part responsible for the flavor of the seed. The seeds also yield up to 8% of a fixed, foul-smelling oil.

Several C-glycoside flavones have been identified in the seeds of fenugreek. These include vitexin, vitexin glycoside and an arabinoside of orientin (iso-orientin). [6] Three new minor steroidal sapogenins have also been found in fenugreek seeds: Smilagenin, sarsasapogenin and yuccagenin. [7] The mucilages of the seeds of several plants, including fenugreek, have been determined and their hydrolysates analyzed. [8]

Fenugreek is the source of a galactomannan-like mucilage. Because the seeds contain up to 50% of mucilaginous fiber, they have been used in the preparation of topical poultices and emollients and internally because of their ability to swell and relieve constipation and diarrhea.

PHARMACOLOGY: Fenugreek seeds reduce serum cholesterol levels in lab animals. In one study, fractions of fenugreek seeds were added to the diets of diabetic hypercholesterolemic and normal dogs for 8 days. The defatted fraction, which is rich in fibers (about 54%) and contains about 5% steroidal saponins, significantly lowered plasma cholesterol, blood glucose and plasma glucagon levels from pretreatment values in both diabetic hypercholesterolemic and normal dogs.[9] The hypocholesterolemic effect has also been reproduced in rats. When fenugreek seeds replaced 50% of their diet for 2 weeks, normal rats showed a 42% decreased and hypercholesterolemic rats showed a 58% decrease from baseline in cholesterol levels. [10]

The hypoglycemic effect of the seeds was evaluated further in dogs. Fractions of the seeds were administered orally to normal and diabetic dogs for 8 days. The lipid extract had no pharmacologic effects. The defatted fraction lowered blood glucose levels, plasma glucagon, and somatostatin levels and reduced carbohydrate-induced hyperglycemia. When this fraction was added to the insulin treatment of diabetic dogs, a decrease in hyperglycemia and insulin dose was noted. It is not clear if these changes are due to the common effect of dietary fiber on blood glucose or if the changes are due to a pharmacologically active compound.[11]

Water and alcoholic extracts have been shown to stimulate the isolated guinea pig uterus, indicating that these extracts may have oxytocic activity.

A French patent (2,073,285 Oct 1972) has been granted to a product purported to have antitumor activity, especially against "fibromas." The product contains extracts of tansy, juniper berries, fenugreek seeds, cinnamon, sedum, St. John's wort flowers, bitter orange rind and hydrated ferric oxide. No clinical studies have been reported using this or any other fenugreek extract in the treatment of cancers.

Fenugreek extracts have been shown to exhibit some anti-inflammatory and diuretic activity in animal models. [12] Fenugreek leaf extracts have been shown to repel numerous common insects.[13]

A recent study demonstrated that the steroid saponins of fenugreek enhance food consumption and motivation to eat, and reduce plasma cholesterol levels in rats. [14] Studies continue on the ability of fenugreek to lower blood glucose both in normal as well as in diabetic rats, dogs and humans. [15,16,17,18,19] Similarly, the hypocholesterolemic properties of fenugreek continue to be studies. [20,21] Another property of the plant is under investigation, namely its ability to decrease the quantity of calcium oxalate deposited in the kidneys. [22]

TOXICOLOGY: When ingested in usual culinary quantities, fenugreek is essentially devoid of adverse reactions. An interesting syndrome was noted in a nine-day-old boy who was admitted to the hospital for the treatment of gastroenteritis. Nurses noted that the boy's urine and entire body smelled distinctly of maple syrup. Laboratory tests ruled out the presence of "maple syrup urine" disease (an inborn error of metabolism that results in the abnormal accumulation of leucine, isoleucine and valine and their ketoacid metabolites in the blood and urine). The mother told the physicians that she had been giving the child a tea prepared by boiling fenugreek seeds in water, a common Ethiopian folk remedy for diarrhea and vomiting. The smell of the tea was found to be indistinguishable from that of the child's urine.[23]

The acute toxicity from a large dose of fenugreek has not been characterized, but may result in potentially severe hypoglycemia. Fenugreek may also cause a new type of occupational asthma.[24] Finally, myositis and peritonitis have occurred in chickens given fenugreek crude saponins intramuscularly or intraperitoneally. [25]

SUMMARY: Fenugreek seeds are used as a culinary spice and their extracts as flavorings. Folk uses include the treatment of boils, diabetes, cellulitis, tuberculosis and gastrointestinal problems. Investigations in animals have found the seeds to reduce serum cholesterol and glucose levels. It is not known if these effects are due to the high fiber content or to the saponins or alkaloids found in the seed. Studies continue to elucidate the mechanism of fenugreek's abilities to lower cholesterol and glucose levels. Recent studies also show the ability of the plant to decrease the quantity of calcium oxalate deposited in the kidneys.

PATIENT INFORMATION — Fenugreek

Uses: Fenugreek has been used as a flavoring, animal forage, insect repellent and folk medicine for boils, diabetes and tuberculosis. In lab animals, it has been shown to lower blood cholesterol and glucose, and to exert anti-inflammatory and diuretic effects.

Side Effects: Unusual quantities may result in hypoglycemia.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FENUGREEK

FEVERFEW

DATE OF ISSUE: SEP 1994

REPLACES MONOGRAPH DATED: JUN 1990

SCIENTIFIC NAME(S): *Tanacetum parthenium* Schulz-Bip. synonymous with *Chrysanthemum parthenium* L. Bernh., *Leucanthemum parthenium* (L.) Gren and Godron, and *Pyrethrum parthenium* (L.) Sm.[1] Alternately described as a member of the genus *Matricaria*. Family: Asteraceae Compositae.

COMMON NAME(S): Feverfew, featherfew, altamisa, bachelor's button, featherfoil, febrifuge plant, midsummer daisy, nosebleed, Santa Maria, wild chamomile, wild quinine[2,3,4,5]

BOTANY: A short bushy perennial that grows from 15 to 60 cm tall along fields and roadsides. Its yellow-green leaves and yellow flowers resemble those of chamomile (*Matricaria chamomilla*), for which it is sometimes confused. The flowers bloom from July to October.

HISTORY: The herb feverfew has had a long history of use in traditional and folk medicine, especially among Greek and early European herbalists. However, during the last few hundred years feverfew had fallen into general disuse, until recently. [6] It has now become popular as a prophylactic treatment for migraine headaches and its extracts have been claimed to relieve menstrual pain, asthma, dermatitis and arthritis. Traditionally, the herb has been used as an antipyretic, from which its common name is derived. The leaves are ingested fresh or dried, with a typical daily dose of 2 to 3 leaves. These are bitter and are often sweetened before ingestion. It has also been planted around houses to purify the air due to its strong, lasting odor, and a tincture of its blossoms doubles as an insect repellant and balm for their bites.[3] It was once used as an antidote for overindulgence in opium.[2]

CHEMISTRY: The chemistry of feverfew is now well-defined. The plant is rich in sesquiterpene lactones, the principal one being parthenolide. [7] Parthenolide comprises up to 85% of the total sesquiterpene content.[1] Other active sesquiterpene lactones are canin, seco-tanapartholide A, artecanin, and 3-beta-hydroxyparthenolide.[8] Other members of this class have been isolated and have been shown to possess spasmolytic activity perhaps through an inhibition of the influx of extracellular calcium into vascular smooth muscle cells. The plant contains several flavonoid glycosides, the main ones being luteolin and apigenin. [9]

PHARMACOLOGY: Feverfew action does not appear to be limited to a single major mechanism; rather, plant extracts affect a wide variety of physiologic pathways.

In vitro: Feverfew appears to be an inhibitor of prostaglandin synthesis. Extracts of the above-ground portions of the plant suppress prostaglandin production by up to 88%; leaf extracts inhibit prostaglandin production to a lesser extent (58%). Neither the whole plant nor leaf extracts inhibit cyclooxygenation of arachidonic acid, the first step in prostaglandin synthesis.[10]

Aqueous extracts prevent the release of arachidonic acid and inhibit in vitro aggregation of platelets stimulated by ADP or thrombin. [11] Whether these extracts block the synthesis of thromboxane, a prostaglandin involved in platelet aggregation, is controversial. [12,13] Data suggest that feverfew's inhibition of prostaglandin synthesis differs in mechanism from that of the salicylates. Extracts may inhibit platelet behavior via effects on platelet sulfhydryl groups. [14,15]

Feverfew extracts are potent inhibitors of serotonin release from platelets and polymorphonuclear leucocyte granules, providing a possible connection between the claimed benefit of feverfew in migraines and arthritis. Feverfew may produce and antimigraine effect in a manner similar to methysergide maleate (*Sansert*), a known serotonin antagonist.[16,17] Extracts of the plant also inhibit the release of enzymes from white cells found in inflamed joints, a similar anti-inflammatory effect may occur in the skin, providing a rationale for the traditional use of feverfew in psoriasis.

In addition, feverfew extracts inhibit phagocytosis, inhibit the deposition of platelets on collagen surfaces, exhibit antithrombotic potential, have in vitro antibacterial activity, inhibit mast cell release of histamine. [18] and exhibit cytotoxic activity.[9] Monoterpenes in the plant may exert insecticidal activity, and alpha-pinene derivatives may possess sedative and mild tranquilizing effects.

Clinical Uses: Much interest has been focused on the activity of feverfew in the treatment and prevention of migraine headaches. [19] The first significant, modern, public account of its use as a preventative for migraine appeared in 1978. This story, reported in the British health magazine, *Prevention*, concerned a Mrs. Jenkins who had suffered from severe migraine since the age of 16. At the age of 68, she began using three leaves of feverfew daily, and after 10 months her headaches ceased altogether. This case prompted studies by Dr. E. Stewart Johnson.[6]

A study in eight feverfew-treated patients and nine placebo-controlled patients found that fewer headaches were reported by patients taking feverfew, for up to six months of treatment. Patients in both groups had self-medicated with feverfew for several years before enrolling in the study. The incidence of headaches remained constant in those patients taking feverfew but increased almost three-fold in those switched to placebo during the trial ($P < 0.02$).[20] The abrupt discontinuation of feverfew in patients switched to placebo caused incapacitating headaches in some patients. Nausea and vomiting were reduced in patients taking feverfew. The statistical analysis has been questioned but the results provide a unique insight into the activity of feverfew. [21] These results were confirmed in a more recent placebo-controlled study in 72 patients suffering from migraine. [22] On the basis of their research, Johnson, et al, predict that feverfew will be useful not only for the classical migraine and cluster headache, but for premenstrual, menstrual and other headaches, as well. [23]

However, studies at the London Migraine Clinic [24] found that the experimental observations may not be clinically relevant to migraine patients taking feverfew. Ten patients who had taken extracts of the plant for up to 8 years to control migraine headaches were evaluated for physiologic changes that may have been related to the plant. The platelets of all treated patients aggregated characteristically to ADP and thrombin and similarly to those of control patients. However, aggregation in response to serotonin was greatly attenuated in the feverfew users.

Feverfew has been investigated in the treatment of rheumatoid arthritis. In one major study, 41 female patients received feverfew (70 to 86 mg) or placebo once daily for 6 weeks under double-blind conditions. No significant differences were observed in more than 15 parameters between the test groups suggesting no apparent benefit from oral feverfew therapy.[25]

Canada's Health Protection Branch has granted a Drug Identification Number (DIN) for a British feverfew (*Tanacetum parthenium*) product. This allows the product's manufacturer, Herbal Laboratories, Ltd., to make the claim, as a nonprescription drug, for effectiveness in the prevention of migraine headache. Canada's Health Protection Branch recommends a daily dosage of 125 mg of a dried feverfew leaf preparation, from authenticated *Tanacetum parthenium* containing at least 0.2% parthenolide for the prevention of migraine.[26]

TOXICOLOGY: Much has been learned about the safety of feverfew over the last decade. In the study conducted by Johnson, et al, patients received 50 mg/day, roughly equivalent to two leaves. Adverse effects noted during 6 months of continued feverfew treatment were mild and did not result in discontinuation. Four of the eight patients taking the plant had no adverse effects. Heart rate increased dramatically (by up to 26 beats/min) in two treated patients. There were no differences between treatment groups in laboratory test results.

Patients who had been switched to placebo after taking feverfew for several years experienced a cluster of nervous system reactions (rebound of migraine symptoms, anxiety, poor sleep patterns) along with muscle and joint stiffness; Johnson refers to this as the "postfeverfew syndrome."

In a larger series of feverfew users, 18% reported adverse effects, the most troublesome being mouth ulceration (11%). Feverfew can induce more widespread inflammation of the oral mucosa and tongue, often with lip swelling and loss of taste. [20] Dermatitis has been associated with this plant.[18,27]

No studies of chronic toxicity have yet been performed on the plant and the safety of long-term use has not been established scientifically. The plant should not be used by pregnant women, as the leaves have been shown to possess potential emmenagogue activity and is not recommended for lactating mothers or children under the age of 2.[26] Although an interaction with anticoagulants is undocumented, this may be clinically important in sensitive patients.

One study has evaluated the potential genotoxic effects of chronic feverfew ingestion. Analysis of the frequency of chromosomal aberrations and sister chromatid exchanges in circulating lymphocytes from patients who ingested feverfew for 11 months found no unexpected aberrations suggesting that the plant does not induce chromosomal abnormalities.[29]

SUMMARY: Feverfew has been used for the treatment of disorders often controlled by aspirin, such as fever, rheumatic inflammations and headache. The chemistry and pharmacology of feverfew have been reasonable well defined. The ability of the plant to aid in the control of migraine has been under close study. To date, the studies comparing the plant to placebo have generally found a significant clinical benefit from the administration of feverfew. Preliminary safety data from clinical trials suggest that the plant is relatively safe, although the incidence of mouth ulcers has been disturbingly high in some trials. The plant does not appear to be mutagenic and should not be used by pregnant women.

PATIENT INFORMATION — Feverfew

Uses: Traditionally an antipyretic, feverfew has been used in recent times to avert migraines and relieve menstrual pain, asthma, dermatitis and arthritis.

Side Effects: Patients withdrawn from feverfew experienced a syndrome of ill effects. Most adverse effects of treatment with feverfew are mild, although some patients have experienced increased heart rate. Feverfew should not be used by pregnant or lactating women or children under age 2. Feverfew may possibly interact with anticoagulants.

Dosing: Feverfew generally is given for migraine at a daily dose of 50 to 150 mg of dried leaves. While some products have been standardized for parthenolide content (0.2 to 0.6 mg/dose), this compound has not been confirmed as a major active principle for migraine. [20,22,25,30]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FEVERFEW

FISH OILS

DATE OF ISSUE: APR 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Fish oils are predominantly comprised of the omega-3 fatty acids eicosopentaenoic acid (EPA) and docosahexaenoic acid (DHA); "fish oil" is a term frequently used interchangeably with, and in reference to, EPA and DHA.

COMMON NAME(S): Marine oils, marine oil fatty acids, n-3 fatty acids, omega-3 (?-3) fatty acids, omega-3 polyunsaturated fatty acids (PUFAs), long-chain PUFAs(LCPUFAs).

SOURCE: Marine sources containing the highest content of omega-3 fatty acids are fatty fish (eg, mackerel, halibut, salmon, bluefish, mullet, sablefish, menhaden, anchovy, herring, lake trout, coho, sardines) which provide = 1 g omega fatty acids/100 g (3.5 oz) of fish. Tuna, because of its common consumption, seal, and shellfish (eg, oysters) are additional sources. [1,2,3,4]

EPA and DHA are present in human milk and can be synthesized (albeit inefficiently) from the essential omega-3 fatty acid, alpha-linolenic acid (ALA). ALA cannot be synthesized by humans and must be consumed; it is found in fats and oils (eg, flaxseed, canola, soybean, walnut, and wheat germ), nuts, and seeds as well as in vegetables. Additionally, DHA can be synthesized from EPA. [1,2,3]

Dietary supplements (containing varying concentrations of EPA and DHA) are available commercially, usually as oil-filled capsules. However, daily allowance in otherwise healthy individuals is probably best achieved by consuming fish ˜ 2 times/week. [2,3]

HISTORY: Most uses of fish oils have been based on the beneficial effects of EPA and DHA, specifically those related to cardiovascular, inflammatory, neural, and hormonal support. Interest in possible health benefits followed observations that populations with a high dietary intake of fish, such as Eskimos, also had a low incidence of atherosclerotic and thrombotic disorders and inflammatory conditions. [5,6] Deficiencies historically were noted in infants fed nonfat or low-fat diets or in patients receiving long-term (eg, 2 to 3 weeks) parenteral nutritional formulations lacking PUFAs. [2,3]

CHEMISTRY: EPA and DHA are omega-3, long-chain (= 20 carbons) PUFAs. EPA consists of a 20 carbon chain with 5 double bonds (20:5) while DHA is a 22 carbon chain with 6 double bonds (20:6). As represented by the omega-3 nomenclature, the first double bond is located at the third carbon from the methyl group (omega) end of the chain. [2,3]

PHARMACOLOGY: Omega-3 fatty acids are metabolized into a class of biologically active, 20-carbon compounds called eicosanoids. Eicosanoids are hormone-like substances and include prostaglandins, prostacyclins, thromboxanes, and leukotrienes. These eicosanoids are potent regulators of blood pressure, blood clotting, childbirth, and gastric secretions, as well as immune and inflammatory responses. [2]

The actual location of the double bond significantly affects metabolism of the fatty acid, such that the structure and function of omega-3 derived eicosanoids differ from those derived from the omega-6 fatty acids (eg, arachidonic acid). [2] For example, omega-3 derived eicosanoids tend to decrease blood clotting and inflammatory responses. This contrasts significantly with the arachidonic acid (omega-6) derived eicosanoids, which increase clotting and inflammatory responses. [2,3]

Deficiency of omega-3 fatty acids has been associated with growth retardation, reproductive failure, skin lesions, renal and hepatic disorders, neurological disturbances (eg, behavioral, incoordination, learning disability, paresthesias, weakness), diarrhea, and visual problems. [2,3,7]

Cardiovascular: A potential role for fish oils in cardiovascular disease risk reduction first came from observations of Greenland Eskimos. [5,6] Despite ingesting up to 40% of calories as fat (mostly from marine sources), they exhibited a lower incidence of coronary heart disease (CAD) relative to individuals on a more conventional diet. [6]

Conflicting evidence has been reported on the cardiovascular protective effects of foods rich in marine n-3 fatty acids. [8,9,10,11] Despite the well-documented activity on eicosanoid metabolism, inflammation, tissue factor, beta-oxidation, endothelial dysfunction, cytokine growth factors, and gene expression of adhesion molecules, evidence has been lacking on the effects on atherosclerotic-thrombotic events. [12,13,14,15,16,17] However, a growing body of evidence strongly suggests protective effects.

Significant associations between fish intake and lower risk of CAD have been shown in a 30-year follow-up of the Western Electric study, an observational cohort of the Multiple Risk Factor Intervention Trial and the Honolulu Heart Program. [14] In 1989, the Diet and Reinfarction Trial (DART) found almost a 30% decrease over 2 years in overall mortality in men who ate fatty fish twice a week. [14,18] These results have been reproduced in 2 large-scale observational studies (the Health Professionals Study and the US Physicians' Health Study) and a multicenter, open-label, Italian trial that studied > 11,000 patients for 3.5 years. [14,18] This latter study, the GISSI-Prevenzione trial, determined that long-term dietary supplementation with 1 g n-3 PUFA (equivalent to ˜ 100 g fatty fish/day) significantly decreased the rate of death, nonfatal MI, and stroke. [14]

Documented inhibition on platelets and effects on smooth muscle cells highlighted the potential role of n-3 fatty acids in prevention of restenosis after percutaneous transluminal coronary angioplasty (PTCA). Results from clinical trials using various study designs, however, have been contradictory. [8,9,10,11] A well-designed double-blind, randomized, placebo-controlled trial using higher doses of EPA and DHA (4.5 g/day) implementing supplementation 3 weeks prior to PTCA reported a statistically significant reduction (P = 0.03) in restenosis frequency in the fish oil group (22% to 35.6%, depending on the definition of restenosis used) vs the olive oil control group (40% to 53.3%) at 6 months. [9] This reproduced the findings of an earlier study using the same dose. [10] However, 2 studies using 3 g/day doses found no reduction in the incidence of restenosis. [8,11]

People with type 2 diabetes mellitus are at increased risk for cardiovascular disease. [6] Dietary fish oil supplementation has been shown to improve hypertriglyceridemia in nondiabetic individuals, but in initial trials also had been associated with reduced glycemic control. [6] Recently, a systematic review of patients with type 2 diabetes mellitus revealed that 3 to 18 g/day of fish oil supplementation lowered triglycerides and had no statistically significant effect on glycemic control, total cholesterol, or HDL cholesterol. However, it did raise LDL cholesterol by 0.21 mmol/L (especially in hypertriglyceridemic patients on doses > 2 g of EPA). [6]

Hypercholesterolemia, elevated LDL and total cholesterol, as well as reduced HDL cholesterol, are well-established risk factors for the development of CAD. [19] A decrease in serum cholesterol in hypercholesterolemic patients is associated with a reduction in incidence and mortality of CAD. [20] Fish oil consumption consistently is reported to reduce triglycerides, but yields marginal if any effect on HDL or total cholesterol. [6,8,11,12,14,16,19,20,21,22,23,24,25] An increase in LDL cholesterol has been reported occasionally; however, evidence is not strong or consistent enough to suggest the risk to be greater than the health benefits related to increased fish oil consumption. [6,8,11,12,14,16,19,20,21,24,25]

Hypertension is a major risk factor for cardiovascular disease. The relationship between hypertension and atherosclerotic disease is fairly well established to be one of cause and effect. [26] A 1989 review concluded that some available evidence supported an influence of dietary marine oil on blood pressure (BP) but not of a substantial hypotensive nature. [26] Some studies in mild essential hypertensive patients have reported significant BP reductions in fish oil groups; another trial in

pharmacologically treated patients documented less of an increase in systolic BP when antihypertensive medication was stopped; and 1 randomized controlled trial in late pregnancy failed to show any effect on BP in 533 healthy women.[20,22,27,28] Evidence is still inconclusive.

Gynecological: Levels of PUFAs have been correlated with menstrual pain, with higher levels of omega-3 fatty acids associated with milder menstrual symptoms. A recent systematic review of herbal and dietary therapy for primary and secondary dysmenorrhea found 1 small, placebo-controlled trial of 42 women that reported a significant improvement in "use of additional medication" ($P < 0.001$) and in "menstrual pain" ($P = 0.004$) in the fish oil group compared with placebo after 2 months of supplementation. However, poor reporting of the "menstrual pain" data prevents an adequate assessment of efficacy related to this particular outcome. Adverse effects were significantly higher in the fish oil group, but they were not serious (eg, nausea, acne exacerbation, difficulty swallowing the capsules). [29]

Various outcomes in late pregnancy have been studied with an emphasis on prostaglandin metabolism and the potential effects of omega-fatty acids on preventing pre-eclampsia (characterized in the third trimester by hypertension, edema, and proteinuria).[30,31,32] Additionally, results in 533 pregnant women investigating the effects of fish oil on pregnancy duration and birth weight appear to be positive.[33] Data and study designs are variable and inconclusive to date.

Immunological/Inflammatory: EPA is a competitive substrate with arachidonic acid for generation of less active eicosanoid metabolites (eg, leukotrienes) and acts to reduce inflammation.[5] The most profound anti-inflammatory effects of n-3 fatty acids are on neutrophil function and mediator generation, providing a more likely benefit in neutrophilic inflammatory diseases like rheumatoid arthritis, psoriasis, cystic fibrosis, and inflammatory bowel disease.[5,34] Epidemiological studies support this, but results are often confounded by the potential beneficial effects ascribed to corn and olive oils, commonly used as placebos.[5,35,36,37,38] Eskimos, a population with a diet high in LCPUFAs (especially EPA and DHA from seal and fish oils), have been found to have a low incidence in rheumatoid arthritis and psoriasis.[4,5]

Evidence is accumulating to support clinical improvement in "number of tender joints," "morning stiffness," and "reduced antirheumatic medication dose" in rheumatoid arthritis patients receiving 3 to 6 g/day of n-3 fatty acids.[35,39,40,41] A minimum daily dose of 3 g EPA and DHA appears to be necessary to reduce the release of leukotriene B_4 from stimulated neutrophils and of interleukin-1 from monocytes.[35] It has been reported that doses of > 6 g/day do not appear to confer any additional benefit.[35]

Evidence is inconclusive to support clinical benefit of n-3 fatty acid supplementation in patients with psoriasis or atopic dermatitis.[4,36,38] Of theoretical interest, a review assessing effectiveness of treatments for guttate psoriasis found 1 small trial of hospitalized patients that reported apparent benefit with an IV infusion of an n-3 fatty acid rich lipid emulsion compared with a placebo emulsion with n-6 fatty acids.[42]

Malnutrition and malabsorption are often consequences of inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis (UC).[21] These conditions can lead to nutritional deficiencies, which in turn can be associated with reduced immunological competence.[21] Fish oil has been reported to improve host immune response in ICU patients with trauma, sepsis, or cancer, but results in patients with IBD have been contradictory.[21] It has, however, been shown that the fatty acid profile in IBD patients can be changed with oral supplements containing n-3 fatty acids.[21,37] These results indicate that oral immunomodulating formulations can be absorbed in these patients and thus may have a role to play in treatment.[21]

Preliminary data support a modest clinical benefit in patients with IBD, but such benefit may be favored in patients with UC more than in those with Crohn's disease.[25,43,44] In patients with active UC supplemented with 3 to 6 g of n-3 fatty acids a day for 4 months, 3 small studies noted a reduction in disease activity and in concomitant anti-inflammatory medication doses with limited to no change in histology index or colonic mucosal leukotriene B_4 levels.[25,43,44] One study also noted a significant weight gain of 1.74 kg.[44] Another small study reports no therapeutic effect of fish oils in UC despite changes exerted on cell membrane fatty acids.[37]

The ability of n-3 fatty acids to reduce eicosanoid production or action has led to the testing of dietary fish oil in patients with IgA nephropathy. In these patients, the initial immunological renal injury evokes cytokine and eicosanoid activity. Dietary fish oil has been tested in patients with several types of renal disease but with varying results. Results in patients with IgA nephropathy have been conflicting.[24]

To date, clinical benefit of fish oil in asthma is controversial.[5,45] n-3 Fatty acids do not have a significant effect on eosinophils and mast cells, which may explain a relative lack of efficacy in this particular inflammatory condition.[5] The role of other constituents in fish oil is unknown. It remains to be determined whether the benefit noted by 1 small study implementing dietary manipulation of fish oils, as opposed to supplementation, in asthmatic children can be duplicated.[5] A recent systematic review provided little evidence to recommend dietary supplementation with fish oil to improve asthma control, but also revealed no evidence of untoward risk.[5]

A potential for an enteral nutritional formula containing EPA plus gamma-linolenic acid as adjuvant therapy in the clinical management of acute respiratory distress syndrome also has been suggested.[46]

Neurological: Several studies have shown levels of certain essential fatty acids in patients with schizophrenia to often be lower than required for normal neuronal membrane metabolism. A systematic review indicates that dietary influences can affect the occurrence and course of schizophrenia. Early results from a few trials suggest a positive effect of EPA on mental state outcomes.[47]

One small study randomized previously unmedicated individuals experiencing a new schizophrenic episode to determine the effects of fish oil supplementation on the need for antipsychotic medication. After 12 weeks of supplementation, the need for antipsychotics was greater in the placebo (15/15) than the fish oil group (9/15). No pronounced adverse effects were noted for fish oil.[47]

Data are preliminary; results are encouraging but inconclusive. There appear to be few adverse effects and possibly some benefit of fish oil supplementation in patients suffering from schizophrenia. There is currently no reason to encourage or discourage use of essential fatty acids to supplement antipsychotic therapy.[47]

Postnatal growth and development: Dietary fat is fundamental for growth and development of infants. However, controversy exists whether LCPUFAs such as DHA are essential nutrients for infants born preterm or at term.[48,49] DHA is an important component of structural lipids of cell membranes and its perinatal availability has been related to visual acuity development, neurological development, behavior, and brain growth.[50,51] Its accretion occurs primarily during the last trimester of pregnancy and the infant's first year of life.[48,49]

Fetuses and preterm infants do not appear to synthesize sufficient amounts of DHA from the ALA precursor, indicating that DHA may be conditionally essential in the perinatal period.[49,52] During pregnancy, DHA crosses the placenta; postnatally it is supplied in breast milk.[48,49] The fatty acid composition of breast milk, however, is somewhat dependent on the maternal diet; DHA levels have been found to be much higher in the milk of women with high intakes of marine foods. Several supplementation studies with fish oil rich in omega-3 LCPUFAs or DHA have shown dose-dependent effects on breast milk EPA and DHA levels.[51]

While evidence does seem to indicate that the DHA and EPA composition of breast milk is affected by fish oil supplementation, evidence from 2 recent systematic reviews provide little support for benefit of supplementation to the infant.[48,49,50,51,52] Formula-fed infants have been shown to have significantly less DHA than infants fed breast milk. Reduced neural function and visual acuity have been documented in preterm infants fed formula relative to those who were breastfed. A review of LCPUFA supplementation studies demonstrated no benefit to visual or cognitive development in infants born at term receiving LCPUFA-supplemented formula.[48] However, some evidence did show that omega-3 LCPUFA supplementation of formula increases the early rate of visual maturation in preterm infants.[49] Malnourished infants, who may tend to have poor fat absorption, appear to also absorb fish oil supplement well and use this source of fatty acid for more than an energy source.[53]

Although formula supplemented with omega-3 fatty acids increases healthy as well as malnourished infant DHA and EPA levels, this may be at the expense of omega-6 derived fatty acids (eg, arachidonic acid). Because high levels of DHA and EPA appear to successfully compete for cyclo-oxygenase and other eicosanoid

enzymes, formula-fed infants should be supplemented with both omega-3 as well as omega-6 LCPUFAs if their fatty acid status is to be comparable with that of the breastfed infant.[50,51,54]

TOXICOLOGY: Fish oil at doses of 2 to 5.4 g/day EPA and DHA is well accepted and tolerable. Mild GI discomfort was the most serious adverse effect occasionally noted for any of the doses studied, which also was reported in some control groups.

An increase in LDL cholesterol has been reported occasionally; however, evidence does not suggest the risk to be greater than the health benefits related to increased fish oil consumption.[6,8,11,12,14,16,19,20,21,24,25]

SUMMARY: Fish oils have potential beneficial effects related to cardiovascular, inflammatory, neural, and hormonal actions. Evidence of clinical benefit is strongest for lowering risk of CAD, decreasing serum triglycerides, and improving symptoms of rheumatoid arthritis. Patients on fish oil supplementation often were reported to require lower doses of concomitant medications in these conditions.

Fish oils appear to be safe and well-tolerated. No serious adverse effects have been noted in studies using doses ranging from 2 to 5.4 g/day of EPA and DHA.

PATIENT INFORMATION — Fish Oils

Uses: Clinical benefit is strongest for lowering risk of CAD, decreasing serum triglycerides, and improving symptoms of rheumatoid arthritis.

Side Effects: Mild GI discomfort.

Dosing: Fish oils appear to be safe and well-tolerated in doses ranging from 2 to 5.4 g/day of EPA and DHA.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
  "F" MONOGRAPHS
  FISH OILS

FLAX

DATE OF ISSUE: AUG 2002

REPLACES MONOGRAPH DATED: JAN 1995

SCIENTIFIC NAME(S): *Linum usitatissimum* L. Family: Linaceae.

COMMON NAME(S): Flax, flaxseed, linseed, lint bells,[1] linum

BOTANY: The flax plant grows as a slender annual and reaches 0.3 to 0.9 m in height. It branches at the top and has small, pale-green alternating leaves that grow on the stems and branches. Flax was introduced to the North American continent from Europe, and it now grows widely in Canada and the northwestern US. Each branch is tipped with 1 or 2 delicate blue flowers that bloom from February through September.[2] Additional members of the genus *Linum* are used throughout the world for their fiber and oil content.

HISTORY: Flax has been used for more than 10,000 years as a source of fiber for producing linen.[2] It was one of the earliest plants used for purposes other than food. Flax is prepared from the fibers in the stem of the plant.[3] Linseed oil, derived from the flaxseed, has been used as a topical demulcent and emollient and as a laxative, particularly for animals. Linseed oil also is used in paints and varnishes and as a waterproofing agent. Flaxseed cakes have been used as cattle feed.

Traditional medicinal uses of the plant have been varied and, at times, bizarre; one text notes that the seeds have been used to remove foreign material from the eye. A moistened seed would be placed under the closed eyelid for a few moments to allow the material to adhere to the seed, thereby facilitating removal.[4] Other uses include the treatment of coughs and colds, constipation, and urinary tract infections.[2] The related *L. catharticum* yields a purgative decoction.[4]

CHEMISTRY: The medical properties of the plant are primarily associated with the seed. The oil contained within the seed, known as linseed oil, is a drying oil obtained by the expression (crushing and compressing the seeds to squeeze the oil out) of linseed. The seed contains many sugar compounds including the following: L-galactose; arabinose; L-rhamnose; D-xylose; D-galacturonic and mannuronic acids; fucose; glucuronic acid.[5,6] The oil component of the seed is composed mainly of unsaturated fatty acids, including linolenic, linoleic, and oleic acids.[7] Flaxseed and linseed oil are among the best natural sources of alpha-linolenic acid. Linoleic acid and alpha-linolenic acid are critical for the structural integrity of cell membranes. Flaxseed is a source of a soluble fiber mucilage, which also is obtained from other members of the *Linum*genus.

Flaxseed reportedly contains phenylpropanoids (eg, *p*-coumaric, *o*-coumaric, linusitamarin).[6,8] Flaxseed is also a rich source of lignans such as secoisolariciresinol and matairesionol. The former 2 lignans are believed to exert phytoestrogenic effects by acting as precursors of the following 2 active metabolites: Enterodiol and enterolactone.[6,9,10] Flax leaves and seed chaff contain the cyanogenic glycosides linamarin, linustatin, and neolinustatin; the action of the enzyme in the plant tissues release cyanide from these compounds when the tissues are crushed.[4,11]

PHARMACOLOGY: The German Commission E has approved the use of flaxseed for the treatment of chronic constipation, colons damaged by laxative abuse, irritable colon, and diverticulitis. It is also approved as a mucilage for gastritis and enteritis. When used externally, it is approved as a poultice for local inflammation.[12]

Significant interest has centered on the ability of diets rich in flax to improve the blood lipid profile. Preliminary work indicated that egg yolk was enriched with alpha-linolenic acid by feeding hens diets containing flax. Furthermore, the cholesterol content of the liver tissue of the chicks born to the flax-fed hens was lower ($P > 0.05$) than in chicks hatched from control hens.[13]

Evidence indicates that flax-supplemented diets reduce the atherogenic risk factors in humans. When 15 hypercholesterolemic subjects consumed 3 slices of bread containing flaxseed plus 15 g of ground flaxseed daily for 3 months, serum total and low-density lipoprotein cholesterol levels were reduced significantly ($P < 0.01$); however, high-density lipoprotein cholesterol levels did not change. In addition, thrombin-stimulated platelet aggregation decreased with the flax supplement. These changes suggest improvement in plasma lipid and related cardiovascular risk factors.[14]

A double-blind, crossover study was conducted comparing the effects of whole flaxseed and sunflower seed on serum LDL cholesterol levels of 38 postmenopausal women. Patients were randomized to consume 38 g of flaxseed or sunflower seed baked into muffins and bread daily for 6 weeks. The treatment consisted of a 6-week trial followed by a 2-week washout period and then another 6 weeks of treatment. Blood samples were collected at baseline and in the sixth, eighth, and fourteenth weeks. The flaxseed regimen significantly ($P < 0.001$) lowered LDL cholesterol (14.7%) as compared with baseline, but no statistical significant difference was obtained when compared with the sunflower seed regimen.[15]

In another study, when healthy female volunteers supplemented their diet with 50 g of ground flaxseed daily for 4 weeks, the diet raised alpha-linolenic acid levels in plasma and erythrocytes; serum total cholesterol decreased 9% and low density lipoprotein cholesterol was reduced 18%. Similar results were obtained when flaxseed oil or flour were used, suggesting high bioavailability of the alpha-linolenic acid from ground flaxseed. No cyanogenic glucosides were detected in baked flax muffins.[11]

Flax contains lignans that have antiestrogenic properties. When healthy women ingested flaxseed powder for 3 menstrual cycles, the ovulatory cycles consistently were associated with a longer luteal phase. There were no differences between control and flax cycles in estradiol or estrone levels, although the luteal phase progesterone/estradiol ratios were significantly higher during the flax cycles. These findings suggest a specific role for flax lignans in the relationship between diet and sex steroid action, and possibly between diet and the risk of breast and other hormone-dependent cancers.[16] The results of a randomized, crossover trial with 28 postmenopausal women further supports the influence of flax lignans on endogenous hormone metabolism.[17]

Preliminary evidence derived from a mouse model of lupus indicates that diets supplemented with 15% flaxseed for 14 weeks delayed the onset of proteinuria and significantly reduced overall mortality compared with controls.[18] Flaxseed contains high levels of the lignan precursor secoisolariciresinol diglucoside (SDG), which is associated with anti-inflammatory activity (eg, formation of less inflammatory classes of renal prostanoids),[19] thus offering a renoprotective[20] effect.

SDG is metabolized in the body to secoisolariciresinol and to the lignans enterodiol and enterolactone. The in vitro antioxidant activity of enterodiol and enterolactone is 3 times greater than SDG. The results from an in vitro study involving Zucker rats suggests that SDG may reduce oxidative stress in type 2 diabetes.[21] Pharmaceutical-grade flaxseed is advised for commercial products.

INTERACTIONS: Flaxseed contains mucilage; thus, absorption of drugs may be impaired when taken concomitantly. Flaxseed can decrease platelet aggregation; therefore, patients using anticoagulants or antiplatelet drugs in combination with flaxseed may increase their risk of bleeding.

TOXICOLOGY: Approximately 50% of workers exposed to flax at their jobs demonstrated immunologically positive antigen tests in 1 survey.[22] Thus, it is contraindicated in patients with known hypersensitivity to flaxseed.

There are no known restrictions regarding flaxseed use during pregnancy or lactation; however, because of the laxative effects of the whole powdered seed and because the fresh plant and seeds contain linamarin, which may be a source of small amounts of cyanide, caution is warranted.

The cyanogenic properties of some of the constituents of flax theoretically suggest that ingestion of large amounts of the plant may be harmful; however, this is primarily a veterinary problem encountered in grazing animals.

SUMMARY: Flax and its seed are economically important products that are used in medicine, in the paint and varnish industry, and in the manufacture of fibers for apparel and other weaving. Preliminary evidence suggests that diets supplemented with the ground seed can improve the lipid profile of hypercholesterolemic patients, reducing certain atherogenic risk factors.

PATIENT INFORMATION— Flax

Uses: Linseed oil, derived from flaxseed, has been used as a topical demulcent and emollient, as a laxative, and as a treatment for coughs, colds, and urinary tract infections. Dietary flaxseed has been used to improve the lipid profile in cardiovascular disease.

Interactions: Flaxseed contains mucilage and, thus, may impair absorption of other drugs. Flaxseed can decrease platelet aggregation; therefore, patients using anticoagulants or antiplatelet drugs in combination with flaxseed may increase their risk of bleeding.

Side Effects: Contraindicated in patients with known hypersensitivity to flaxseed. Flaxseed contains lignan compounds and thus is contraindicated during pregnancy and lactation. Theoretically, ingestion of large amounts may be harmful because of the cyanogenic glycosides.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FLAX

FO-TI

DATE OF ISSUE: MAY 1998

REPLACES MONOGRAPH DATED: APR 1992

SCIENTIFIC NAME(S): *Polygonum multiflorum Thunb.* (Polygonaceae)

COMMON NAME(S): He shou wu (Chinese), flowery knotweed, climbing knotweed, Chinese cornbind. This plant should not be confused with the commercial product Fo-ti Tieng, which does not contain fo-ti.

BOTANY: Fo-ti is native to central and southern China and is distributed in Japan and Taiwan. It is a perennial climbing herb, which can grow to 30 feet in height. The plant has red stems, heart-shaped leaves and white or pink flowers. The roots of 3- to 4-year-old plants are dried in autumn. The stems and leaves are used also.[1,2]

HISTORY: Fo-ti is a popular Chinese tonic herb, dating back to 713 A.D. [1] It is considered one of the country's great four herbal tonics (along with angelica, lycium and panax).[3] Regarded as a rejuvenating plant, fo-ti has been thought to prevent aging and to promote longevity. According to folklore, the older and larger roots have the most power.[1] One source quotes "...300-year-old (root) product makes one immortal." [3]

CHEMISTRY: Fo-ti contains chrysophanic acid, chrysophanic acid anthrone and chrysophanol. Anthraquinones emodin and rhein are also present. Lecithin has also been found in the plant.[1,3] A stilbene glucoside from fo-ti has been identified. [4] A spectrophotometric assay of stilbene glucoside in another report may be used for quality control in the plant's processing. [5] Qualitative analysis and content determination of phospholipids in fo-ti drug vs four processed products have been performed.[6] An alcoholic extract from fo-ti roots yielded three bioactive compounds: E-2,3,5,4´-tetrahydroxystilbene, 2-O-beta-D-glucopyranoside and cis- and trans-E-3-butylidene-4,5,6,7-tetrahydro-6,7-dihydroxy-1(3H)-isobenzofuranone. Two of these compounds were found to be calcium-ATPase inhibitors. [7]

PHARMACOLOGY: In China, millions take fo-ti regularly for its rejuvenating and toning properties. It is used to increase liver and kidney function and to cleanse the blood. The plant is also prescribed for symptoms of premature aging such as gray hair. [1] A Chinese-13-herb mixture ("shou xing bu zhi") that includes fo-ti has been studied for its antisenility effects in mice. Results showed this mixture was effective in slowing the aging process. [8] It is also indicated for insomnia, weak bones, constipation and atherosclerosis.[2] Lifespan and lipid studies of fo-ti in quails have been performed. [9] Fo-ti also has been shown to reduce blood cholesterol levels in animals.[1] The root portion of the plant has exhibited an inhibitory effect on triglyceride accumulation and has reduced enlargement of mice livers. [10] In a clinical trial in humans, fo-ti had similar cholesterol-lowering effects. [1]

Emodin exhibited vasodilation and immunosuppressive effects in rats, suggesting its usefulness against transplantation rejection and autoimmune disease. Extract of he shou wu significantly reduced tumor incidence in rats in another report. [12] The Chinese use the root of the plant for cancer as well. [3]

Stilbenes isolated from polygonium species have been evaluated on rat peritoneal polymorphonuclear leukocyte lipoxygenase and cyclooxygenase activity. [13] A mixture including fo-ti has been studied for its effects on glucocorticoid receptor in senile rat thymocyte. [14] The plant has also been shown to inhibit lipid peroxidation in isolated rat heart mitochondria.[15] Fo-ti also exhibits antimicrobial properties against tuberculosis bacillus and malaria. [1]

Other uses of the plant include: To increase fertility,[1] to increase blood sugar levels,[1] to treat anemia and to relieve muscle aches.[3]

TOXICOLOGY: There is little information in the area of toxicology from fo-ti. However, all plants that contain anthraquinone cathartic compounds should be used cautiously to prevent developing dependence on their laxative effects. One case report describes herb-induced hepatitis in a 31-year-old pregnant Chinese woman from medicine prepared from the plant.[16] The use of these compounds in pregnant women should be discouraged.

SUMMARY: Fo-ti is a widely used herb in ancient and current Chinese medicine. It is known for its rejuvenating and tonic properties, to increase liver and kidney function, to cleanse the blood and to slow down signs of premature aging. The plant also exhibits cholesterol-lowering effects and immunosuppressive actions and has antimicrobial properties. Little is known about the plant's toxicity as more studies are needed.

PATIENT INFORMATION — Fo-ti

Uses: Fo-ti has been used in China for its rejuvenating and toning properties, to increase liver and kidney function and to cleanse the blood. It is also used for insomnia, weak bones, constipation and atherosclerosis. It can increase fertility, increase blood sugar levels and relieve muscle aches and exhibits antimicrobial properties against tuberculosis bacillus and malaria.

Side Effects: Little information exists on fo-ti's side effects. Discourage use in pregnant women.

Dosing: Fo-ti is used at daily doses of 9 to 15 g of raw herb; however, there do not appear to be any clinical studies supporting this dosage.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FO-TI

FORSKOLIN

DATE OF ISSUE: NOV 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Coleus forskohlii* (Willd.) Briq., Lamiaceae (mint family)

COMMON NAME(S): Pashanabhedi, makandi, colforsin, HL-362, mao hou qiao rui hua. The plant is a component of *Asthma X-5* (Olympian Labs), *Ele-max* (Tyler), *Interex*, *Meta-Burn EF* (MRM), *Ripped Fuel Extreme* (Twinlab), *Fat Busters* (Nature's Plus), *GlucoLean* (Biochem), and *ForsLean* (Sabinsa).

BOTANY: *Coleus forskohlii* is a perennial herb in a large genus of mints. The plant is native to subtropical and tropical regions of India and east Africa. A synonym is *C. barbatus* (Andrews) Benth.

HISTORY: This species and other related species were used in Ayurvedic medicine under the name *pashanabhedi* for heart and lung diseases, intestinal spasms, insomnia, and convulsions.[1] It was studied for cardiovascular activity in 1974 by scientists from Hoechst India and the Central Drug Research Institute of India in screening programs that examined medicinal plants.[2]

CHEMISTRY: As a result of that screening program, the diterpene forskolin (coleonol) was isolated and elucidated as the major active hypotensive principle of the roots of the plant.[3] The absolute stereochemistry of forskolin was determined by x-ray crystallography.[4,5] The other most abundant diterpene, 1,9-dideoxy-forskolin, had no hypotensive activity.[6] Since that time, many closely related diterpenes have been isolated from the roots and aboveground portions of the plant.[6,7,8] Stigmasterol also was isolated.[9]

Because forskolin has been actively pursued as a drug development lead, there have been many analytical chemistry studies. A gas-liquid chromatography (GLC) method was developed for quantitation of forskolin in plant tissues and in dosage forms.[10] Both thin layer and high performance liquid chromatographic (HPLC) methods also have been published.[11] The GLC method was more sensitive but the HPLC method was found to be more rapid.[11] The HPLC method has been used to monitor variation in forskolin content in different germplasm. The content ranged from 0.01% to 0.27% for 38 samples.[12] A monoclonal antibody specific for forskolin has been developed for affinity isolation of forskolin.[13] The same antibody also has been used for extremely sensitive quantitation of forskolin in plant tissues at different stages of development.[14] Nuclear magnetic resonance data and a gas chromatography-mass spectral method also have been published for forskolin and its congeners.[15,16] Tissue culture methods for forskolin production also have been successfully explored because the relatively modest content of forskolin in the plant has limited its development as a drug.[17,18]

PHARMACOLOGY: The principle mechanism by which forskolin exerts its hypotensive activity is by stimulation of adenylate cyclase, thereby increasing cellular concentrations of the second messenger cyclic AMP (cAMP).[19] Radiolabeled forskolin was shown to bind to rat brain membranes in a saturable and specific manner.[20] Of the 9 types of adenylate cyclase in humans, forskolin can activate all but type IX, which is found in spermatozoa.[21] Photoaffinity derivatives of forskolin have been shown to irreversibly react with type I adenylate cyclase,[22] and the structure of forskolin bound to type II cyclase has been determined by x-ray crystallography.[23] Chemical modification of forskolin at the 6- and 7-positions has led to semisynthetic compounds with modest selectivity for particular cyclase isoforms, including the cardiac type V adenylate cyclase.[21,24,25] Stimulation of adenylate cyclase is thought to be the mechanism by which forskolin relaxes a variety of smooth muscles.

Forskolin also has been found to act through other mechanisms, however. Forskolin binds to the glucose transporter in adipocytes,[26] to the P-glycoprotein drug efflux pump,[27] alters potassium channel activity,[28] decreases GABA receptor chloride flux,[29] and modulates the nicotinic acetylcholine receptor.[30,31] The natural diterpene 1,9-dideoxy-forskolin, which has no activity on the cyclase enzyme, shows activity in most of these other systems. Because this compound is a major component of the plant, herbal preparations should be thought as acting through multiple pharmacologic mechanisms.

Forskolin exhibits hypotensive properties through vasodilation, relaxing vascular smooth muscle. In small doses it demonstrated positive inotropic effects in the cat, rat, and the spontaneously hypertensive rat.[1,32] In human heart tissues, forskolin activated adenylate cyclase and showed strong positive inotropic properties that were synergistic with isoproterenol.[33]

Forskolin also has been shown to inhibit platelet aggregation through adenylate cyclase stimulation, augmenting the effects of prostaglandins.[34,35] Its antithrombotic properties may be enhanced by cerebral vasodilation, which was observed in rabbits. This vasodilation was not potentiated by adenosine.[36] The use of crude *C. forskohlii* extract as a rational phytotherapeutic antithrombotic has been proposed.[2]

The smooth muscle relaxant properties of forskolin also have led to investigation of its use in asthma. In guinea pigs, forskolin blocked bronchospasm caused by histamine, leukotriene-4, or antigen.[37] In human basophils and mast cells, forskolin blocked the release of histamine and leukotriene C-4,[38] while stimulating gastric acid and pepsinogen secretion by isolated rabbit gastric glands.[39] A small human study found that inhaled forskolin powder formulations were capable of causing bronchodilation in asthma patients.[40]

Forskolin had no lasting effect, however, on intraocular pressure in monkeys with glaucoma.[41] It also showed no effect on humans in reducing aqueous flow when applied topically to the eye.[42] A further study found that forskolin induced lipolysis in intact rat fat cells without increasing cAMP, but had no effect in homogenized cells.[43] A patent claiming promotion of lean body mass and antidepressant activity of a forskolin-containing extract was granted to the supplement company Sabinsa in 1998.[44] Forskolin showed antidepressant activity in a rat forced swimming model.[45] Due to its vasodilating properties, forskolin and analogs have been proposed for intercavernosal treatment of erectile dysfunction, however, only small clinical studies have been reported.[46,47]

TOXICOLOGY: Avoid use with anticoagulants, antihypertensives, and vasodilators because of additive effects. Avoid use with ulcers because of stimulation of gastric acid and in diabetes due to stimulation of lipid release and gluconeogenesis.

SUMMARY: Forskolin causes vasodilation, inhibits platelet aggregation, and relaxes smooth muscle. The whole plant from which it is derived has other diterpenes with distinct activities. Because of the multiple sites of action, it should be used with caution. Typical dosage: 100 to 300 mg/day of an extract containing 10% to 20% forskolin.

PATIENT INFORMATION — Forskolin

Uses: Forskolin has been shown to dilate the blood vessels causing a decrease in blood pressure, increase the contractility of the heart, inhibit platelet aggregation, and relax contracted airways in asthma patients. Because of its multiple sites of action, it should be used with caution.

Drug Interactions: May have additive effects with anticoagulants, antihypertensives, and vasodilators.

Dosing: Typical dosage is 100 to 300 mg/day of an extract containing 10% to 20% forskolin.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FORSKOLIN

FORSYTHIA

DATE OF ISSUE: APR 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Forsythia suspensa* (Thunb.) Vahl. Family: Oleaceae (olives)

COMMON NAME(S): Forsythia, golden bells, lian qiao, weeping forsythia

BOTANY: *F. suspensa* is an attractive deciduous shrub native to China. It is often grown ornamentally in the US for its bright yellow flowers that appear in early spring. There are numerous horticultural varieties that are vegetatively propagated. The Chinese drug is obtained in the fall from the ripe fruits of the cultivated plant. The related species *F. viridissima* and *F. koreana* also are used medicinally.

HISTORY: Forsythia fruits are widely used in Chinese traditional medicine for antipyretic and anti-inflammatory activity in the treatment of bacterial infections and upper respiratory ailments. They are commonly combined with honeysuckle flower (*Lonicera*) and other ingredients. Forsythia fruits are also reputedly used as a diuretic and as a cardiovascular tonic.

CHEMISTRY: Lignans, such as phylligenin and pinoresinol, and their glucosides are major constituents of *F. suspensa* fruits, while the other species contain related compounds.[1] Caffeic acid glycosides with variation in the number of sugars include forsythiaside,[2] suspensaside,[3] and a number of forsythosides.[4] The reduced cyclohexylethane derivatives rengyol, rengyoxide, and rengyolone [5] and their glycosides (rengyosides A-C,[6] and forsythensides A and B[7]) have been reported. The distribution of various phenolics among 7 different species of forsythia in leaves and fruits has been studied. [8,9] Rutin is the major flavonoid of all 7 forsythia species.[9] Caffeic ester glycosides from related genera of the Oleaceae have been compared.[10] Several triterpenes have been isolated from the fruits as well.[11] An HPLC assay for major forsythia phenolics has been published.[12] The essential oil composition of the fruits has been studied.[13]

PHARMACOLOGY: The caffeic acid glycosides forsythoside A, C (=suspensaside), and D have been found to have antibiotic activity against *Staphylococcus aureus*,[3,4,14] although the activity was relatively weak. The anti-inflammatory activity of the extract in 1 study [15] was tracked to a dammarane triterpene;[11] however, other studies have found the caffeoyl glycosides to inhibit arachidonate metabolism in leukocytes. [16] Similarly, the structure-activity relations for the ability of caffeoyl glycosides to inhibit formyl-methionyl-leucyl-phenylalanine stimulated leukocytes in an antioxidant model have been delineated. [17] The ability of the butanol extract of *F. koreana* to inhibit nitric oxide production in a murine macrophage cell line also may be a related phenomenon.[18]

The bioactivity of the lignan constituents also may play an important role. Pinoresinol and its glucoside were shown to inhibit cyclic adenosine monophosphate phosphodiesterase, while phillyrin and phillygenin were inactive.[1] However, phillygenin was found in a separate study to inhibit platelet-activating factor binding at low micromolar concentrations.[19] Several tetrahydrofuran lignans from forsythia were recently shown to be active inhibitors of LDL oxidation.[20]

The flavonoid rutin was found to be the active anti-emetic constituent of forsythia fruits using an experimental chicken model of emesis.[21]

A clinical evaluation of a multiherbal mixture containing forsythia fruits in the treatment of respiratory infections was published. The herbal extract was administered IV in cases of severe disease, with the authors claiming efficacy equivalent to standard antibiotic treatment.[22]

TOXICOLOGY: *F. suspensa* extracts were not mutagenic in Ames tests; however, the incidence of chromosomal aberrations and micronucleated polychromatic erythrocytes in bone marrow of treated mice were somewhat elevated.[23]

Use during pregnancy is strictly contraindicated because of its emmenagogue/uterine stimulant properties.

SUMMARY: Forsythia fruits are official in the Chinese Pharmacopeia. Forsythia fruits are a well-known Chinese traditional medicine used primarily for respiratory infections. There is evidence supporting its use, although clinical data are limited. The potential for toxicity appears to be minimal.

PATIENT INFORMATION — Forsythia

Uses: Forsythia has been used for treatment of bacterial infections and upper respiratory tract infections, although the clinical evidence supporting its use is limited.

Side Effects: Forsythia has minimal potential for toxicity.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FORSYTHIA

FRUIT ACIDS

DATE OF ISSUE: APR 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Alpha hydroxy acids, malic acid, lactic acid, gluconolactone

COMMON NAME(S): Fruit acids

SOURCE: As the name indicates, these acidic organic compounds are derived primarily from fruit sources. Juices and fruit pulps may be rich in malic and lactic acids, although other sources may be used for commercial production of these acids (ie, starch, glucose or other sugars).

HISTORY: Organic acids such as lactic acid have long been used in dermatologic preparations as humectants to improve the moisturization of the top skin layers. Organic acids have also been used to de-hair and to tan animal hides. [1]

Most organic acids can be caustic in sufficiently high concentrations. As agents that modify the keratinization process (see Pharmacology), alpha hydroxy acids may be useful for the treatment of acne and other skin disorders. [2] Since they help debride dead cells from the skin, they have been added to a variety of skin cleansers.

A number of cosmetic companies are marketing products that contain alpha hydroxy acids for their anti-aging effects on the skin. While the fruit acids have the ability to promote the sloughing of outer skin layers, there is no evidence that the use of these products, particularly over a long period of time, can "rejuvenate" the skin or alter the basic aging-related changes of the skin. It is possible, however, that removal of top skin layers may enhance the appearance of the skin.

CHEMISTRY: The "fruit acids" are a group of organic acids that share a common chemical structure consisting of a hydroxyl group positioned at the alpha-carbon position. Consequently, these compounds are often referred to as "alpha hydroxy acids." Common fruit acids include lactic and malic acids. Because of the structural configuration of these acids, they are optically active and only certain forms of the isomers are obtained from natural sources. For example, only (-)malic acid is obtained from fruit juices.[3]

PHARMACOLOGY: Lactic acid (in concentrations of approximately 1% to 2% in creams or lotions) has been reported to be an effective naturally occurring skin humectant, having beneficial effects on dry skin and also in severe hyperkeratotic conditions.

Hyperkeratinization appears to play a role in the development of acne and is often the result of decreases in the rate of skin cell sloughing, which itself is due to an increase in the cohesion of cells known as corneocytes. [4] Alpha hydroxy acids may decrease the cohesiveness of corneocytes by weakening intracellular bonding, [5] thereby freeing skin cells and permitting more efficient cell removal and skin cleansing. [6]

One fruit acid component, gluconolactone, has been found to be as effective as benzoyl peroxide in the treatment of acne. [4] In a double-blind trial of 150 patients, a 14% solution of gluconolactone was compared with benzoyl peroxide 5% lotion and to a placebo vehicle.

Both active treatments significantly reduced the number of inflamed lesions (compared to baseline) during the 12-week study. While there was no significant difference between active treatments during the first 4 weeks, the benzoyl peroxide was significantly better in reducing the number of inflamed lesions by weeks 8 and 12 than was the alpha hydroxy acid. Both groups were similarly effective in reducing the total number of inflamed and noninflamed lesions, but dryness was reported by significantly more patients treated with benzoyl peroxide.

Overall, 50% of the benzoyl peroxide-treated patients reported adverse events, compared to 24% of those treated with gluconolactone and 10% of the placebo-treated patients. Dryness, scaling and burning were the most commonly reported events.

TOXICOLOGY: Depending on the concentrations used, alpha hydroxy acids can cause severe skin irritation, burning and sloughing. Hypersensitive individuals and those with irritated skin should use alpha hydroxy acids with caution.

SUMMARY: The fruit acids are growing in popularity for their topical use as skin cleansers and for the management of disorders such as acne. While natural in their composition, they must be used cautiously because of their potential to irritate skin. Preparations containing lactic acid are available both over-the-counter and by prescription. Many of the consumer-oriented products, however, do not define the composition of the fruit acids used, thereby eliminating the method by which consumers could recognize the presence of potentially irritating substances in the product.

PATIENT INFORMATION— Fruit Acids

Uses: Fruit acids are used for cleansing, moisturizing the top layers of skin and for treating acne.

Side Effects: Dryness, scaling, burning and similar effects may occur in sensitive individuals or with prolonged use.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FRUIT ACIDS

FUMITORY

DATE OF ISSUE: AUG 2003

REPLACES MONOGRAPH DATED: NOV 2002

SCIENTIFIC NAME(S): *Fumaria officinalis* L. Family: Fumariaceae

COMMON NAME(S): Fumitory, common fumitory, earth smoke

BOTANY: Fumitory is an annual plant of somewhat variable characteristics, often resembling a bush but also appearing as a low, trailing shrub. It has gray, pointed leaves that, at a distance, give the plant a wispy appearance of smoke (hence the common name).[1] The pink-purple flower blooms in spring. The plant is widely dispersed and can be found in gardens, on slopes, and in wastelands. The flowering plant (aerial parts) has traditionally been used in herbal medicine.

HISTORY: Fumitory has been known since antiquity and was described in herbals from the Middle Ages. Fumitory is a predominantly Mediterranean genus that was once used medicinally. The climbing fumitory, or Allegheny vine, is a North American plant of another genus (Adlumia). Several genera of the family are native to South Africa.[2] Traditional preparation involved expressing the juice and evaporating it. In traditional medicine, the plant has been used to treat eczema and other dermatologic conditions. It has been used as a laxative and diuretic. *Fumaria* species are used in Turkish folk medicine as a blood purifier and an anti-allergic agent. [3] *Fumaria* extracts may be useful in the management of disorders of the cardiovascular system and hepatobiliary tract. Work has focused on extracts from other *Fumaria* species, noting their antihepatotoxic activity and their potential as antipsoriatic agents.

CHEMISTRY: The chemical composition of active compounds in *F. officinalis* is not well documented. A number of flavone heterosides[4] have been identified. The alkaloid content is approximately 0.87% to 1.27%, with protopine comprising 0.18% to 0.25% and fumoficinaline ranging from 0.16% to 0.2%. [5] An alkaloidal fraction is likely responsible for the cardiovascular activity of the plant. [6] Pharmacologically active substances have been isolated from other species (*F. indica*, *F. parvifolia*) and are therefore the focus of research. In 1998, monomethyl fumarate was isolated from *F. indica*. This compound has important antihepatotoxic activity in vitro and in vivo.[7]

PHARMACOLOGY: Investigations in animals and humans have identified several pharmacologic actions of fumitory extracts. IV injection of 1 to 2 mg/kg in dogs reduced ischemia caused by experimental ligation of the circumflex artery. A dose of 5.2 mg/kg prevented ischemic-induced arrhythmias for up to 87 minutes. [6]

In addition, another study examined the effect of fumitory on diabetic rats. Diabetes mellitus was induced in 20 out of 25 adult male albino rats. The diabetic rats were divided into 4 groups, 3 of which were fed a diet containing 6.25% body weight (fumitory) and coriander seed for 15 days. The fourth group received a normal diet, whereas the remaining nondiabetic rats received neither alloxan nor the mentioned plants. Comparison between 3 experimental groups showed that fumitory may have profound effects on levels of serum glucose, cholesterol, creatinine, and activity in various liver tests. [8]

In addition, fumitory extracts have been shown to ameliorate bile duct blockage in animals and assist in the management of similar disorders in humans. *Fumaria* extract typically has been administered by nebulizer and has been investigated in gallbladder calculi in mice and rats. [9,10,11] When investigated in 85 patients with cholecystopathies, a *Fumaria*-containing preparation improved patient status in 70% of the cases overall and in more than 80% of the cases of biliary dyskinesia. Optimum results were obtained following 10 days of therapy and the difference was statistically greater than observed with placebo. [11] *F. officinalis* is approved in Germany for the colicky pain affecting the gallbladder and biliary system, together with the gastrointestinal tract. [12]

The antihepatotoxic activity of several *Fumaria* species warrants further investigation.[13] Monomethyl fumarate, found in *F. indica*, demonstrated antihepatotoxic activity against thioacetamide in vitro and carbon tetrachloride, acetaminophen, and rifampin in vivo. This activity is comparable with silymarin, a known antihepatotoxic agent.[7] In another study, an aqueous-methanolic extract of *F. parvifolia* administered prophylactically protected against acetaminophen-induced liver injuries by reducing the toxin-induced rise in serum enzymes.[14]

Furmaric acid esters have been used as a treatment for psoriasis for nearly 30 years. This treatment is regaining interest by dermatologists as more active compounds and derivatives are being developed. Monomethyl fumarate is the most active metabolite in a German antipsoriasis drug, *Fumaderm*.[15] Its action is attributed to the stimulation of an anti-inflammatory mediator profile in human leukocytes and inhibition of the proliferation of keratinocytes. Although several studies document the efficacy of fumaric acid ester therapy, a large percentage of patients experience side effects. [17,18,19] Adverse effects have occurred in as many as 69% of patients, with GI complaints (56%) and flushing (31%) being the most common symptoms.[15]

The efficacy of the alkaloids of common fumitory in disorders of coronary blood flow (in the circumflex artery) was studied in 8 dogs. Occlusion of the vessel was caused by means of a remote controlled loop implanted in the thoracic wall. The arrest of circulation in the artery was increased by the appearance of pathological signs on the ECG in the form of tachycardia, growth of the T-wave amplitude, and displacement of the RS-T interval. [6]

Futhermore, fumitory alkaloids inhibited exudative phase of dextran inflammation at 100 mg/kg and that of serotonin inflammation at 50 mg/kg, but had no effect against agar inflammation even at the higher dose. Both alkaloids decreased vascular permeability to the same extent at 50 mg/kg doses. [15]

TOXICOLOGY: Fumitory has not been associated with clinically important toxicity. In 1 clinical study, no adverse events were reported. Monomethyl fumarate was found to be nonhepatocytotoxic in doses up to 1 mg/mL in vitro and up to 50 mg/kg in in vivo studies in albino rats. Alkaloids found in other members of the Fumariaceae family (eg, protopine), have caused trembling, convulsions, and death when consumed in large quantities. [20] Many patients experience side effects with fumaric acid ester therapy, with GI complaints and flushing the most common symptoms.

SUMMARY: Fumitory monographs are in the *British Herbal Pharmacopoeia* and in the German Commission E. It has a long history of use in traditional medicine and has been investigated for its therapeutic potential in the management of cardiovascular and hepatobiliary disorders, and psoriasis. Other work shows important pharmacological activity in several species, suggesting the need for further isolation of active constituents. Fumitory has not been associated with clinically important toxicity, although adverse events may be common.

PATIENT INFORMATION— Fumitory

Uses: Fumitory has been traditionally used as a laxative, diuretic, and as a treatment for dermatologic conditions such as eczema. Limited evidence suggests that it benefits those with cardiovascular and hepatobiliary disorders. There are limited studies to support these uses.

Side Effects: Fumitory is not associated with clinically important toxicity, but large quantities of other members of the family have caused fatal outcomes. Many patients experience side effects with fumaric acid ester therapy, with GI complaints and flushing the most common symptoms.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "F" MONOGRAPHS
    FUMITORY

"G" MONOGRAPHS

GAMMA LINOLENIC ACID

DATE OF ISSUE: OCT 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Gamma linolenic acid

COMMON NAME(S): GLA, gamolenic acid[1]

SOURCE: GLA is found in the seeds and oils of a range of plants including *Onagraceae* (evening primrose), *Saxifragaceae* (borage), and *Rubaceae*(blackcurrant). The richest source of GLA is borage (*Borago officinalis*).[1]

HISTORY: The evening primrose plant is native to North America and was introduced into Europe in the 17th century. Native Americans consumed the leaves, roots, and seedpods as food and prepared extracts of the oil for use as a painkiller and asthma treatment. Some of these early therapeutic effects are thought to be because of GLA, which is found in high quantities in the oil. [2]

In the 1930s and 1940s, several investigators found dietary supplementation with essential fatty acids such as GLA to be of therapeutic value in atopic dermatitis (AD).[3] In 1947, the first study was published that suggested a relationship between disturbances in linoleic acid metabolism and the pathogenesis of AD. [4] The advent of topical glucocorticoids brought an end to this form of treatment. However, by the early 1980s, there was a return to using these agents because of the unwanted side effects of glucocorticoids, and they have regained scientific interest. [3] Over the last 2 decades, numerous other indications have been proposed for GLA.

CHEMISTRY: Fatty acids are the basic building blocks for all lipids. They consist of chains of carbon and hydrogen with an end acid group. Fatty acids vary in length and degree of saturation and are generally up to 26 carbons long.

The polyunsaturated fatty acids contain more than 1 double bond.[1] The double bonds (counted from the methyl end) are at carbon 3 (n-3) or 6 (n-6). GLA falls into the latter family, known as omega-6 fatty acids.[5]

PHARMACOLOGY: Unsaturated fatty acids are essential components of cell membranes and can influence receptors, enzymes, ion channels, and signal transduction pathways. Dihydro-?-linolenic, arachidonic, and eicosapentaenoic acids are precursors of eicosanoids, which can influence numerous inflammatory and immunological processes. After intake, n-3 unsaturated fatty acids are rapidly incorporated into the cell membranes of immune and inflammatory cells, where they compete with n-6 unsaturated fatty acids as substrates for the cyclooxygenase and lipoxygenase pathways. This results in a diminished production of biologically active leukotrienes and prostaglandins.[5] GLA has been extensively studied, with many reports in the literature demonstrating benefit in a number of diseases. This review provides a summary of those clinically relevant indications for GLA with the most substantial supporting evidence.

Atopic dermatitis (AD): AD usually becomes evident during the first 2 to 3 months of life.[6] It is generally accepted that patients show an increased IgE production. Increased levels of linoleic acid and deficiencies in GLA have been observed in the plasma and epidermis of patients with AD. [7] This is proposed to be because of a defect in the function of the enzyme delta-6-desaturase, which is responsible for conversion of linoleic acid to GLA; GLA is a precursor of eicosanoids. [3]

Supplementation of AD patients with GLA appears to be rational therapy. The beneficial effect of GLA-rich plant oils has been demonstrated in several placebo-controlled studies. Oral GLA therapy has been demonstrated to reduce pruritus, the degree of erythema, and roughness of atopic skin, [6,7] as well as reduce inflammation and overall disease severity.[3] This improvement in severity appears to be dose-related (maximum dose, 7.5 g/day).[8]

A study in 10 children with AD evaluated GLA 3 g/day for 28 days. A gradual improvement in erythema, excoriations, and lichenification was seen. [9] No side effects were recorded.[6,8,9] It should be noted that the placebo effect is remarkably strong in practically all studies, underlying the importance of robust study designs.

Atopic bronchial asthma: Atopic disease in children is often characterized by a change in the clinical picture from dermatitis in early childhood to a later presentation of bronchial asthma. However, there appears to be no biochemical evidence for a defect in the enzyme delta-6-desaturase (see Atopic dermatitis) in children with atopic bronchial asthma and, therefore, there is no rationale for GLA supplementation in atopic patients. [4]

Prevention of atopic diseases: Breastfeeding has been shown to protect against the development of atopic diseases, although infants may develop atopic diseases during exclusive breastfeeding.[10] Breast milk of allergic mothers has been shown to contain less GLA than that of healthy mothers. Similarly, infants with atopic diseases have less GLA than healthy infants. Reduced dietary proportions of GLA may be a risk factor for the development of atopic disease. [10] After maternal supplementation, increased levels of GLA can be present in breast milk.[11] Results support the theory that a defect in the conversion of linoleic acid into its long-chain polyunsaturated metabolites occurs in infants predisposed to atopic dermatitis. [12]

Psoriasis: Although psoriasis does not have an atopic component, use of GLA has been investigated. In a small study (n = 17), patients with psoriasis were fed a low-fat diet supplemented with a combination of n-3 (linoleic acid) and n-6 (GLA) fatty acids or placebo. Some improvement was noted in patients after 4 months of treatment. It was not possible to predict which patients would respond to dietary therapy as the effects were variable and 18% of the patients showed no improvement.[13] Therefore, use of GLA in the treatment of psoriasis is questionable.

Rheumatoid arthritis (RA): Rheumatologic conditions such as arthritis are common, progressive, and disabling disease processes. Although conventional treatment of these conditions generally is considered to have improved in terms of effectiveness, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), second-line therapies, and corticosteroids all have been associated with adverse reactions. For this reason, patients suffering chronic musculoskeletal disorders are likely to seek alternative methods of symptomatic relief, and studies have shown rheumatology patients to be among the highest users of complementary and alternative medicine. The Cochrane Collaboration, an international health care review organization, performed an extensive search of the literature to evaluate which herbal therapies could be used for RA. Seven studies compared GLA with placebo (n = 286). Sources of GLA included evening primrose oil, borage seed oil, and blackcurrant seed oil. These sources provided between 525 mg/day and 2.8 g/day of GLA and were administered for 6 weeks to 12 months. All of the GLA studies found some improvement in clinical outcomes but methodology and study quality were variable. However, other studies suggest potential relief of pain, morning stiffness, and joint tenderness. Benefits appeared to be increased when dosages were greater than 1.4 g/day and were administered for at least 6 months, although it appears that maximum benefit may not be achieved within this time period. The authors suggest that further studies are required to establish optimum dosage and duration of therapy.[14]

Cancer: It has been proposed that linoleic acid and GLA may play important roles in cancer treatment. Oxidation of linoleic acid by lipoxidase increases tumor cell death and GLA inhibits urokinase-type plasminogen activator (uPA) activity. Increased uPA activity is responsible for cancer invasion and metastases and for proteolysis of lipoxidase, which promotes a decrease in cancer cell death. Hence, it has been proposed that the addition of linoleic acid and GLA to available therapeutic regimens may be worth consideration in cancer treatment.[15]

Several in vitro and limited in vivo studies have shown that GLA has selective tumoricidal actions. [16] These effects are produced by augmentation of free radical generation and lipid peroxidation in tumor cells but not in normal cells. Also, lymphokines such as interferon and tumor necrosis factor seem to produce their antitumor effects by inducing the release of unsaturated fatty acids from the cell membrane lipid pool and free radical generation. Several anticancer agents, especially doxorubicin and vincristine, have the capacity to augment free radical generation and promote lipid peroxidation. Tumor cells are known to contain low levels of

unsaturated fatty acids, have decreased capacity to generate free radicals and lipid peroxides, and to be highly susceptible to free radical-induced cytotoxicity compared with normal cells. This evidence, coupled with the observation that there is a low cancer incidence in Eskimos, who traditionally have high unsaturated fatty acid diets, suggests that GLA may be employed as a possible anticancer agent. [16]

Investigations in this area primarily are performed on transformed cell lines. Such studies have shown GLA to have tumoricidal activity in bladder cancer [17] and to reduce estrogen receptor expression in breast cancer. [18]

A number of in vivo studies have shown improvement in immunologic status. Patients (n = 18) with unresectable pancreatic cancer received a 10-day continuous infusion of GLA at a mean dose of 5.7 g/day, followed by oral GLA at a mean dose of 3 g/day. T-cell function increased 50% after 1 month of therapy. [19] In a phase 2 trial, patients (n = 38) with estrogen-sensitive breast cancer took 2.8 g GLA in addition to 20 mg/day of tamoxifen. These were compared with 47 patients who received tamoxifen alone. There was a significant reduction in estrogen receptor expression in both treatment arms, but those taking combination therapy sustained a greater response. Patients on combination therapy also achieved a clinically significant faster response. [20]

A further area of interest is that of gliomas. Intratumoral injection of 1 mg/day of GLA caused regression of cerebral gliomas as evaluated by computerized tomography and improved survival by 1.5 to 2 years. [21]

It should be noted that all of the studies cited were relatively small and it would be beneficial if the proposed effects were investigated further.

Immune system: Lymphocytes are key components of the regulation, amplification, and memory of the cell-mediated immune response. A study was performed with 48 healthy subjects, 55 to 75 years of age, who were randomly allocated to treatment or placebo. The treatment group consumed capsules rich in unsaturated fatty acids (4 g) including GLA. The study found that GLA reduced lymphocyte production by up to 65%. This decrease was partially reversed 4 weeks after stopping the medication. [22]

Cardiovascular protection: The apparent low death rate from coronary heart disease among Eskimos has focused interest on the potential benefits of the n-3 polyunsaturated fatty acids. Several epidemiological studies indicate that populations consuming large amounts of n-3 polyunsaturated fatty acids have relatively low incidences of atherosclerotic cardiovascular disease. In a small study, 12 hyperlipidemic males were randomly allocated to evening primrose oil capsules (containing 240 mg GLA) or placebo. GLA supplementation decreased plasma triglyceride levels by 48% and increased HDL cholesterol concentration by 22%. Total cholesterol and LDL cholesterol were significantly decreased. Additionally, platelet aggregation decreased. These effects suggest that GLA may contribute to cardiovascular protection. [23] However, this is still an area of controversy.

Diabetes mellitus: There are multiple abnormalities of essential fatty acid metabolism in diabetes. Diabetic subjects require higher amounts of these fats than nondiabetic patients. Conversion of linoleic acid to GLA is impaired. There have been several successful attempts to manage diabetic complications by the provision of very high levels of linoleic acid intake. These studies have shown that the development of cataracts, retinopathy, and cardiovascular damage can all be slowed by the administration of large daily doses of essential fatty acids. However, outcomes have been disappointing, largely because most patients are unable to maintain this diet. Therefore, administration of GLA as an alternative to this strict diet has been studied. [24] Diabetic neuropathy is the most common complication of diabetes mellitus. A small study showed possible benefits of GLA for diabetic peripheral neuropathy. [25] This was followed by a multicenter, randomized study of 100 patients where the effect of administration of GLA (480 mg/day) on neuropathies was investigated. The GLA group demonstrated consistent and progressive improvement while the placebo group showed deterioration. [26]

Breast pain and premenstrual syndrome (PMS): PMS involves a wide range of psychological and physical symptoms. Breast pain is one of the common symptoms of PMS. Breast pain and PMS appear to be common when the intake of fat, especially saturated fat, is high. A drastic reduction in fat intake has been shown to relieve breast pain. Experimental investigations have demonstrated that hormone receptors in membranes richer than normal in saturated fats and poorer than normal in essential fatty acids have increased affinity for their ligands. Therefore, normal levels of hormones will produce an exaggerated peripheral response. In support of these findings, clinical studies have shown that GLA is more effective than placebo at relieving PMS symptoms. [24]

Lower-limb atherosclerosis: The Cochrane Collaboration reviewed the literature on the use of lipid-lowering therapy in patients with lower-limb arterial disease. Nine eligible randomized, controlled trials were located. The reviewers concluded that lipid-lowering therapy may be useful in preventing deterioration of underlying disease and in alleviating symptoms. However, their results could not be used to determine whether one lipid-lowering regimen was superior to another. [27]

TOXICOLOGY: There have been no reports of serious adverse events in those taking GLA supplements. GLA is usually very well tolerated, with no significant adverse effects. GLA should not be used by pregnant women and nursing mothers unless recommended by a physician. Because of possible antithrombotic activity, hemophiliac patients and patients who take warfarin should exercise caution. GLA should not be used before surgery. [1]

SUMMARY: GLA has been successful in the treatment and prevention of atopic diseases in which a disorder in fatty acid metabolism has been demonstrated. Most convincing evidence supports its use in the treatment of AD. Good evidence also exists to support use in RA. GLA may contribute to cardiovascular protection; however, this is an area of controversy. Beneficial effects in diabetic patients with peripheral neuropathy have been shown in a number of studies.

PATIENT INFORMATION— Gamma Linolenic Acid

Uses: A few small clinical studies have found GLA to be of benefit for the treatment and prevention of AD and atopic asthma, adjunctive treatment of RA, management of lipid lowering in cardiovascular diseases, and treatment of diabetic neuropathies.

Side Effects: No serious adverse effects have been noted. Pregnant women, hemophiliac patients, and patients taking warfarin should avoid its use.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GAMMA LINOLENIC ACID

GAMMA ORYZANOL

DATE OF ISSUE: SEP 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): "*Oz*,"*gamma-orizanol*, *caclate*, *gammajust 50*, *gamma-oz*,*gammariza*, *gammatsul*, *guntrin, hi-z*, *maspiron*, *oliver*, *oryvita*, *oryzaal*, *thiaminogen*

COMMON NAME(S): Rice bran oil

SOURCE: Gamma oryzanol, a sterol-like structure, is a mixture of ferulic acid esters of sterols and triterpene alcohols, extracted from rice bran oil and other grain oils such as corn and barley.[1] Ferulic acid compounds are also present in many foods, including oats, berries, citrus fruits, tomatoes, olives, and vegetables. Gamma oryzanol serves as an important antioxidant within plant cells. [2]

HISTORY: Early reports are available from the mid-1950s discussing isolation, extraction, and purification methods of gamma oryzanol. [1] However, the Japanese have been using it as a medicine since 1962. It was first used to treat anxiety. In the 1970s it was found to be an effective treatment for menopause. Gamma oryzanol therapy was approved to treat elevated cholesterol and triglyceride levels in the late 1980s. [2]

CHEMISTRY: This mixture of esters of sterols (such as campestrol, stigmasterol, and beta-sitosterol) and triterpene alcohols (such as cycloartanol, cycloartenol, 24-methylenecycloartanol, and cyclobranol) known as gamma oryzanol. Extraction from rice bran, corn, and barley oils has been performed. [1] The Japanese process approximately 7500 tons of gamma oryzanol from rice bran each year.[2] Separation of three major components of gamma oryzanol has yielded "oryzanol A" ($C_{40}H_{58}O_4$), "oryzanol C" ($C_{41}H_{60}O_4$), and "oryzanol B," which has been found to be a mixture of oryzanols A and C.[1] Gamma oryzanol has been laboratory-synthesized.[3] Mass fragmentographic determination of ferulic acid in plasma has been performed. [4] A review is available concerning constituents of rice bran oils as functional foods.[5]

PHARMACOLOGY: The pharmacokinetics of gamma oryzanol have been reported in animals. [6,7]

Gamma oryzanol possesses many therapeutic effects including menopausal, hypolipidemic, gastrointestinal, central nervous system (CNS), endocrine, and "bodybuilding."

Menopausal: Gamma oryzanol has been proven effective to treat symptoms of menopause such as hot flashes.[2] In 40 patients experiencing aging syndromes, gamma oryzanol administration lessened menopausal complaints.[8] A report in oophorectomy patients, given 300 mg of gamma oryzanol daily, found a 50% reduction in menopausal symptoms in about 70% of patients. A later study reported 85% improvement in symptoms with the same 300 mg dosage.[2] The proposed mechanisms of gamma oryzanol are the reduction in secretion of leutinizing hormone by the pituitary gland and promotion of endorphin release by the hypothalamus. [2]

Hypolipidemic: Several studies indicate gamma oryzanol and its related constituents (eg, tocotrienols) in rice bran oil exert marked hypocholesterolemic effects.[9,10,11,12] Positive effects of gamma oryzanol on lipid metabolism in animals have also been extensively reported, [13,14,15] including IV administration of gamma oryzanol increasing excretion of lipids in rat blood, [16] reducing of liver lipids and increasing of HDL cholesterol in rats, [17] and an increase fecal excretion of cholesterol, which lowers the level by 20% in rats.[18] Oryzanol has cholesterol-lowering actions, reducing aortic fatty streak formation in hamsters. [19] However, in another report gamma oryzanol had little or no preventative effects on atherosclerosis in rabbits. [20] Another study concludes that rats fed oryzanol along with a 1% cholesterol diet, inhibited platelet aggregation. [21]

Human studies are also promising. Reduced total cholesterol and triglyceride levels, and increased HDL levels were noted in hyperlipidemic patients given gamma oryzanol.[1,8] Total cholesterol and LDL levels were decreased in 20 schizophrenic dyslipidemic patients with no side effects observed. [22] Another clinical trial involving 67 hyperlipidemic patients given 300 mg of gamma oryzanol for 4 weeks, found cholesterol levels to decrease by approximately 10%, mean triglyceride levels to decrease from 222 mg/dl average to 190 mg/dl average, and HDL levels to slightly elevate. [2] The mechanism of action of gamma oryzanol involves the increase of cholesterol conversion to bile acids, the increase in bile acid excretion and inhibition of cholesterol absorption. [16,18]

Gastrointestinal: In Japan, at least 23 clinical studies have been conducted regarding gamma oryzanol and its effectiveness in treating gastrointestinal disorders. [2] Animal studies include its anti-ulcer effect in rats. [23,24,25] inhibition of gastric secretion in rats, [26] improvement in gastric lesion and suppression of intestinal propulsion in mice,[28] and its effects on stomach and ileum movement in dogs.[29]

An endocrinological study is available evaluating gastrointestinal symptoms in gastritis patients. [30] The mechanisms by which gamma oryzanol seems to exert its effects appear to be the normalizaton of nervous system control of digestive secretions. [2]

CNS/Endocrine: Gamma oryzanol's effects on the CNS and endocrine systems have been sporadically reported. The results primarily concern mechanisms more than specific beneficial therapeutic actions. More human clinical trials are needed. The overall importance of these effects has not been fully determined.

Gamma oryzanol component, "cycloartenol ferulic acid ester," has suppressant effects on the CNS, different from existing tranquilizers. However, it may serve to be a cerebral activator because of its efficacy in models of cerebral dysfunction. [31] Gamma oryzanol has also been found to increase brain norepinephrine content in rats by inhibiting degradation or release of this neurotransmitter. [32] Gamma oryzanol's endocrine effects include a rat pituitary study, [33] suppression of growth hormone synthesis and prolactin release, [34] potent inhibition of LH release and weak inhibition of prolactin in rats, [35,36,37] and in humans, its inhibition of serum TSH levels in patients with primary hypothyroidism, possibly by a direct action at the hypothalmus. [38] From these studies, one can conclude that gamma oryzanol's actions are mainly on the hypothalmus and pituitary gland. It produces certain effects on these control hormones, but does not appear to alter the level of hormones they control. [2]

Bodybuilding: Gamma oryzanol supplementation in bodybuilding has been addressed. [39] Some studies suggest that gamma oryzanol is poorly absorbed, the majority being excreted in the feces. Endocrinological studies in animals, as previously mentioned, indicate that gamma oryzanol suppresses leutinizing hormone release, reduces growth hormone and increases of neurotransmitters in the brain. Gamma oryzanol may even reduce testosterone production. [40]

Few well controlled human trials exist. However, in one well controlled study, weight lifters taking ferulic acid esters (vs placebo) for 8 weeks, experienced increases both in body weight and strength (as measured by repetitious weight lifting). Another double-blinded study found increases in beta endorphin levels after ferulic acid supplementation, indicative of gamma oryzanol's actions on the hypothalmus.[2] In a later study, however, 9 weeks of 500 mg/day of gamma oryzanol supplementation did not influence performance during resistance exercise training. [41]

Other: At least two reports are available on gamma oryzanol's role as an antioxidant.[3]

TOXICOLOGY: Gamma oryzanol has been shown to be very safe. No side effects have been reported in either animal or human studies. [2] In one report, gamma oryzanol was not damaging to DNA nor mutagenic nor clastogenic.[44] In addition, it was not carcinogenic in mice [45] or rats.[46]

SUMMARY: Gamma oryzanol is a mixture of ferulic acid esterols of sterols and triterpene alcohols. It is a natural product extracted from rice bran oil and other grains. Therapeutic benefits, although unproven, include treatment of menopausal symptoms, hyperlipidemias, and gastrointestinal problems. Gamma oryzanol has been demonstrated to be safe in both animal and human studies.

PATIENT INFORMATION — Gamma Oryzanol

Uses: Gamma oryzanol has been used to treat menopausal symptoms, hyperlipidemias, and GI problems. It is being studied for effects on the CNS and endocrine systems and also as a supplementation in bodybuilding.

Side Effects: No known side effects.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GAMMA ORYZANOL

GARLIC

DATE OF ISSUE: OCT 2001

REPLACES MONOGRAPH DATED: APR 1994

SCIENTIFIC NAME(S): *Allium sativum* L. Family: Liliaceae (lilies)

COMMON NAME(S): Garlic, allium, stinking rose, rustic treacle, nectar of the gods, camphor of the poor, poor man's treacle [1]

BOTANY: A perennial bulb with a tall, erect flowering stem that grows to 2 to 3 feet. The plant produces pink to purple flowers that bloom from July to September. The bulb is odiferous.

HISTORY: The name *Allium* comes from the Celtic word all meaning burning or smarting. Garlic was valued as an exchange medium in ancient Egypt; its virtues were described in inscriptions on the Great Pyramid of Cheops. The folk uses of garlic have ranged from the treatment of leprosy in humans to managing clotting disorders in horses. Physicians prescribed the herb during the Middle Ages to cure deafness and the American Indians used garlic as a remedy for earaches, flatulence, and scurvy.

CHEMISTRY: Fresh garlic is a source of numerous vitamins, minerals, and trace elements, although most are found in only minute quantities. Garlic contains the highest sulfur content of any member of the Allium genus. Two trace elements, germanium and selenium, are found in detectable quantities and have been postulated to play a role in the herb's antitumor effect.

Garlic contains about 0.5% of a volatile oil composed of sulfur-containing compounds (diallyldisulfide, diallyltrisulfide, methylallyltrisulfide). [2] The bulbs contain an odorless, colorless, sulfur-containing amino acid called alliin (S-allyl-L-cysteine sulfoxide), which has no pharmacologic activity. [3] When the bulb is ground, the enzyme allinase is released, resulting in the conversion of alliin to 2-propenesulfenic acid, which dimerizes to form allicin. Allicin gives the pungent characteristic odor to crushed garlic and is believed to be responsible for some of the pharmacologic activity of the plant.

PHARMACOLOGY: A number of trials have examined the effects of garlic on lipoproteins and hypercholesterolemia. The exact mechanism for this action is uncertain, but it is thought that the organic disulfides present in garlic oil can reduce the activity of the thiol group found in many enzymes and can oxidize nicotinamide adenine dinucleotide phosphate (NADPH). These compounds can inactivate thiol enzymes such as coenzyme A and HMG-CoA reductase, and can oxidize NADPH, all of which are factors normally required for lipid synthesis.

Individual randomized controlled trials comparing garlic to placebo have provided disparate results. Some studies have suggested that garlic has no effect in adults with mild to moderate hypercholesterolemia.[4,5,6,7,8] Evidence has shown that garlic has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.[9] However, other studies looking specifically at moderate hypercholesterolemia in males have demonstrated that garlic has beneficial effects on lipid profiles (reduction in total cholesterol and LDL cholesterol). [10,11] Other data have shown that there may be a role for garlic as add-on therapy to traditional medicines (eg, reducing the dose of HMG-CoA reductase inhibitors). [12] Additional trials have demonstrated that allicin (the presumed active ingredient of garlic) may reduce total cholesterol and LDL cholesterol in adults with moderate hypercholesterolemia. [13]

One meta-analysis report on the use of garlic for hypercholesterolemia specifically examined randomized, controlled trials comparing garlic with placebo. [14] The inclusion criteria were patients with a mean total cholesterol level of 5.17 mmol/L (200 mg/dL). Pooling data from 13 trials (including 796 patients) suggested that garlic is superior to placebo in reducing cholesterol levels. However the effect is modest (6% reduction in total cholesterol).

Another meta-analysis of 16 randomized, controlled trials (including 1365 patients) also showed a modest reduction in serum lipids. [15] Overall, a 12% greater reduction was observed with garlic therapy compared with placebo. This meta-analysis, however, consisted of small randomized studies of poor quality and not all patients recruited had hyperlipidemia.[15]

Overall, these effects are generally short-term and whether they are sustainable beyond 3 months is unclear. The evidence for lowering LDL and total cholesterol is still questionable and may not be clinically meaningful.

Researchers demonstrated that allicin increased the levels of 2 important antioxidant enzymes in the blood: catalase and glutathione peroxidase. This discovery confirmed the antioxidant and free-radical scavenging potential of allicin. The clinical utility of antioxidant activity is not clear to researchers. Other researchers studied the sulfur compounds in aged garlic extract (a popular deodorized form of garlic) and found 5 sulfur compounds that inhibited lipid peroxidation in the liver, preventing a reaction that is considered to be one of the main features of aging in liver cells. According to the findings, the sulfur compounds "appear to be approximately 1000 times more potent in antioxidant activity than the crude, aged garlic extract." [16]

Studies on the effects of platelet aggregation have produced inconsistent results, possibly related to variations in study design and in the garlic preparation used. The proposed mechanism for garlic oil inhibition of platelet function is by interfering with thromboxane synthesis. [17] Researchers isolated a component of garlic oil that inhibits platelet aggregation and identified it as methylallyltrisulphide (MATS). MATS is present in natural oil in a concentration of 4% to 10%. The purified compound inhibits ADP-induced platelet aggregation at a concentration of < 10 mcmol/L in plasma. [2]

Further studies indicated that the most potent antithrombotic compound in garlic is 4,5,9, trithiadodeca-1,6,11-triene 9-oxide, also known as ajoene. This compound is formed by an acid-catalyzed reaction of 2 allicin molecules followed by rearrangement; the compound can be synthesized commercially. Unlike other antithrombotics now under investigation, ajoene appears to inhibit platelet aggregation regardless of the mechanism of induction. [18]

Scientists demonstrated the effect of ajoene in preventing clot formation caused by vascular damage. The experiment was designed to mimic the conditions of blood flow in small- and medium-sized arteries by varying the velocity of the blood; the compound proved to be effective in both conditions. The authors suggested that the compound may be useful in situations where emergency treatment is needed to prevent clot formation produced by vascular damage. [16] Clinical studies have demonstrated that inhibition of platelet aggregation is also observed in vivo after ingestion of fresh garlic. In 1 study, the platelets from healthy subjects who had eaten garlic cloves (100 to 150 mg/kg) showed complete inhibition to aggregation induced by 5-hydroxytryptamine. [19] Other studies have shown that ingestion of "aged" garlic extract can produce an inhibition of some of the platelet functions important for initiating thromboembolic events in the arterial circulation. [20] The effects of garlic on platelet aggregation may be dependent on the garlic preparation used. Differences appear to be mostly dependent on their content of organo-sulfur compounds, many of which are unstable or capable of interconversion during processing. [21]

Strong evidence for the effect of garlic on blood pressure is lacking. The results of a meta-analysis suggest that garlic supplements of 600 to 900 mg/day for 1 to 3 months are associated with a clinically important reduction in blood pressure. [22] Their meta-analysis included 8 trials consisting of 415 patients. However, the trials were of generally moderate to poor quality and not all patients were hypertensive. A review of the literature suggested that the effects of garlic on blood pressure were insignificant.[23] No firm conclusions should be drawn from these trials.
BR>The effect of garlic on the GI system has been the topic of some debate. Oral administration of the oil (0.1 mL/10 g) in mice reduced the gastric transit time of a charcoal meal by 75% and prevented castor oil-induced diarrhea for up to 3 hours. [24] The investigators concluded that garlic oil can be investigated for its effectiveness in the management of hypermotile intestinal disorders.

An additional role proposed in the literature is that garlic may be used in the treatment of *Helicobacter pylori* infection; however, the evidence does not support this. [25]

The protective effect of garlic against colorectal and stomach cancers was addressed in meta-analyses of 18 studies. [26] It was concluded that high intake of garlic may

offer protection. These results should be interpreted with caution because of the heterogeneity of the trials included in the meta-analyses.

Garlic has been suggested to reduce blood glucose levels, [3] increase serum insulin, and improve liver glycogen storage. [27] A review of the literature [28] demonstrated that glucose levels decreased from 89 to 9 mg/dL in healthy volunteers given garlic (800 mg dried powder for 35 days) as compared with placebo group. However, other reviews have shown that, in fact, garlic has no effect on glucose levels. [23] Garlic administration should not be recommended for this indication because of the lack of randomized controlled trials.

The antiseptic and antibacterial properties of garlic have been known for centuries. As recently as World War II, garlic extracts were used to disinfect wounds. During the 1800s, physicians routinely prescribed garlic inhalation for the treatment of tuberculosis. Garlic extracts inhibit the growth of numerous strains of *Mycobacterium*, but at concentrations that may be difficult to achieve in human tissues. [27] Preparations containing garlic extracts are used widely in Russia and Japan. Both gram-positive and gram-negative organisms are inhibited in vitro by garlic extracts. The potency of garlic is such that 1 mg is equivalent to 15 Oxford units of penicillin, making garlic about 1% as active as penicillin. [27]

Garlic extracts have shown antifungal activity when tested in vitro [27] and their use has been suggested in the treatment of oral and vaginal candidiasis. In an attempt to quantitate the in vivo activity of garlic extracts, researchers administered 25 mL of fresh garlic extract orally to volunteers. [29] Serum and urine samples were tested for antifungal activity against 15 species of fungal pathogens. While serum exhibited anticandidal and anticryptococcal activity within 30 minutes after ingestion, no biological activity was found in urine. The findings suggest that while garlic extracts may exhibit some antifungal activity in vivo, they are probably of limited use in the treatment of systemic infections.

Oncology: The antineoplastic activity of garlic has been studied in mice injected with cancer cells that had been pretreated with a garlic extract. No deaths occurred in this treatment group for up to 6 months, while mice injected with untreated cancer cells died within 16 days. [27] It is believed that the reaction of allicin with sulfhydryl groups (the concentration of which increases rapidly in dividing cells) may contribute to this inhibitory effect. Scant data, primarily from case-control studies, suggest that dietary garlic consumption is associated with decreased odds of laryngeal, gastric, colorectal, and endometrial cancer and adenomatous colorectal polyps. [30]

Immunology: Garlic contains the trace elements germanium and selenium, which have been thought to play a role in improving host immunity. One study found that 2 oil-soluble compounds from garlic, diallyl sulfide and diallyl disulfide, when applied topically succeeded in protecting mice against carcinogen-induced skin tumors and increased survival rate. [16]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Although garlic is used extensively for culinary purposes with essentially no ill effects, the safety of the long-term use of concentrated extracts is unclear. Ingestion of a single 25 mL dose of fresh garlic extract has caused burning of the mouth, esophagus, and stomach, nausea, sweating, and lightheadedness; safety of repeated doses of this amount has not been defined. Rarely, ingestion may also cause anaphylaxis. [31]

Topical exposure to crushed, uncooked garlic cloves for 3 to 5 minutes has resulted in toxic contact dermatitis. [32] Additionally, repeated exposure to garlic dust can induce asthmatic reactions. [17] Garlic dust allergy, presenting as coughing, wheezing, chest tightness, difficulty breathing, blocked or runny nose, sneezing, and running or itching eyes is relatively rare. However, an IgE-mediated hypersensitivity reaction has been reported to affect mainly young atopic subjects. Cross-sensitivity to other members of the Liliaceae family may be observed. [33] The degree of cross-reactivity appears to vary among individuals. [34]

There are no studies that evaluate the effect of garlic and its extracts in people who require stringent blood glucose control or in patients being treated with anticoagulants (coumarins), salicylates, or antiplatelet drugs, but the potential for serious interactions should be kept in mind.

SUMMARY: Garlic is a common herb used in cooking throughout the world. Garlic and its extracts have a long history of folk use and recent research has indicated that the herb has pharmacologic activity when administered even in small doses. There are insufficient data to draw conclusions regarding garlic's effects on clinical cardiovascular outcomes such as claudication and MI. Garlic preparations may have small, positive, short-term effects on lipids. A consistent reduction in blood pressure with garlic has not been demonstrated and no definitive effects on glucose or insulin sensitivity have been found. Some promising antithrombotic effects have been reported.

PATIENT INFORMATION — Garlic

Uses: Evidence suggests that garlic may beneficially affect cholesterol and lipids. Among its traditional uses, it has been employed for its antiseptic and antibacterial properties.

Side Effects: Garlic may affect patients being treated with anticoagulants. It may also cause allergic reactions.

Dosing: Garlic dosage is complicated by the volatility and instability of important constituents and by such products as "deodorized garlic," "aged" extracts, and distilled oils. Doses of fresh bulbs studied in clinical trials for hyperlipidemia or atherosclerosis range from 2 to 4 g/day and a daily intake of 2 to 12 mg allicin has been proposed. Because garlic is a widely consumed foodstuff, dosage will remain a matter of personal tolerance. [9,14,35,36]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GARLIC

GELSEMIUM

DATE OF ISSUE: FEB 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Gelsemium sempervirens* (L.) Ait. Synonymous with *G. nitidum*Michx. and *Bignonia sempervirens* L. Family: Loganiaceaea or Spigeliaceae. Not to be confused with true jasmine (*Jasminum grandiflorum* L.)

COMMON NAME(S): Gelsemium, yellow or Carolina jasmine, wild, yellow or Carolina jessamine, woodbine, evening trumpet flower

BOTANY: Gelsemium is a climbing, woody evergreen vine characterized by very fragrant, bright yellow flowers. Although native to the southwest United States, it also grows in Mexico and parts of Central America where it is widely cultivated as an ornamental. [1]

HISTORY: Gelsemium has been used as an ingredient in some analgesic and homeopathic products, but its use has been limited due to its toxicity. At the turn of the century, it was a popular ingredient in asthma and respiratory remedies. [2] Related species have been used in traditional Chinese medicine to treat neuralgia and various painful conditions. It is the state flower of South Carolina.

CHEMISTRY: The active components of gelsemium are the alkaloids, which are present in a concentration of about 0.5%. These consist primarily of gelsemine, with lesser amounts of related compounds (gelsemicine, gelsedine, etc). [1] Other compounds found in the plant include scopoletin (also called gelsemic acid), a small amount of volatile oil, fatty acid and tannins. [1]

PHARMACOLOGY: Gelsemium and its principle alkaloid gelsemine have been reported to exert central stimulant and analgesic effects, being able to potentiate the effects of aspirin and phenacetin. [1] The plant has been investigated for its anticancer properties.

TOXICOLOGY: All parts of the plant contain toxic alkaloids that can cause paralysis and death, and should never be ingested. Gelsemium alkaloids are highly toxic. Ingestion of as little as 4 ml of a fluid extract has been reported to be fatal. Toxic symptoms include giddiness, weakness, ptosis, dilated pupils and respiratory depression. Gelsemicine is more toxic than gelsemine. [3]

Toxicity has been reported in animals that have grazed on gelsemium, and bees that pollinate the plant have been poisoned. [2] Honey derived from the plant nectar has been reported to be toxic.[2]

SUMMARY: Gelsemium is a beautiful yet highly toxic plant. Although it has been used in traditional medicine, its narrow safety margin limits its use. Today, the plant is widely cultivated for its ornamental flowers.

PATIENT INFORMATION — Gelsemium

Uses: Gelsemium has been traditionally used to treat pain and respiratory ailments.

Side Effects: All parts of the gelsemium are toxic and can cause death when ingested.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GELSEMIUM

GENTIAN

DATE OF ISSUE: APR 1993

REPLACES MONOGRAPH DATED: FEB 1990

SCIENTIFIC NAME(S): *Gentiana lutea* L. Stemless gentian is derived from *G. acaulis* L. Family: Gentianaceae

COMMON NAME(S): Gentian, stemless gentian, yellow gentian, bitter root, pale gentian, gall weed

BOTANY: Native to Europe and western Asia, *G. lutea*is a perennial herb with erect stems and oval leaves, which grows to 1.8 meters in height. The plant produces a cluster of fragrant orange-yellow flowers. *G. acaulis* is a small herb with a basal rosette of lance-shaped leaves and generally grows to only 10 cm in height. It is native to the European Alps at 3000 to 5000 feet above sea level. The roots and rhizomes are nearly cylindrical, sometimes branched, varying in thickness from 5 to 40 mm. The root and rhizome portions are longitudinally wrinkled. The color of the rhizomes, ranging from dark brown to light tan, appears to be related to its bitter principal content, the darker roots having more of a persistent bitter taste. [1] The roots and rhizome of *G. lutea*are used medicinally, whereas the entire plant of *G. acaulis* is used.

HISTORY: The gentians have been used for centuries as bitters to stimulate the appetite, improve digestion and to treat a variety of gastrointestinal complaints (eg, heartburn, vomiting, stomach ache, diarrhea).[2,3] Both gentian and stemless gentian are approved for food use. Stemless gentian usually is consumed as a tea or alcoholic extract such as *Angostura Bitters*. The extracts are used in a variety of foods, cosmetics and some antismoking products. The plant has been used externally to treat wounds and internally to treat sore throat, arthritic inflammations and jaundice.

CHEMISTRY: The most characteristic aspect of gentian is its bitter taste. This is imparted by a number of bitter compounds, primarily amarogentin, gentiopicrin (about 1.5% in fresh roots),[4] gentiopicroside and swertiamarin. Amarogentin is one of the most strongly bitter compounds known. The speed of drying of the roots affects its use as a medicinal bitter. Slow drying permits enzymatic hydrolysis of gentiopicrin into gentiogenin and glucose, thus reducing the bitter nature of the product.[5] Gentian extract is used in concentrations of about 0.02% in nonalcoholic beverages. In addition, the plant contains numerous alkaloids (gentianine and gentialutine), xanthones, triterpenes, common sugars and a small amount of a volatile oil. [6] Stemless gentian also contains the xanthone glycoside gentiacauloside. It should be noted that the dye, gentian violet, is not derived from this plant.

PHARMACOLOGY: Bitter substances ingested before eating are reputed to improve the appetite and aid digestion by stimulating the flow of gastric juices and bile. However, since gentian is most often consumed as an alcoholic beverage, it is difficult to distinguish the effects of gentian from those of alcohol, which are quite similar when alcohol is consumed in moderate amounts.[7]

Gentianine has been shown to exert a measurable anti-inflammatory effect in animals.

TOXICOLOGY: Although the extract usually is taken in very small doses that do not appear to cause adverse effects, at least one author has suggested that gentian may not be well tolerated by persons with hypertension or by women who are pregnant. [6] The extract may cause gastric irritation, resulting in nausea and vomiting.

The highly toxic white hellebore (*Veratrum album*L.) often grows in close proximity to gentian. At least five cases of acute veratrum alkaloid poisoning have been reported in persons who prepared homemade gentian wine that had been accidentally contaminated by veratrum. [8]

SUMMARY: Gentian is a widely recognized plant that has been used as a bitter tonic for centuries. It is believed that a small amount of the extract (usually mixed with alcohol) can stimulate appetite and improve digestion. Aside from this, none of the other professed effects is well documented in humans.

PATIENT INFORMATION— Gentian

Uses: Gentian is used in bitters to stimulate appetite, improve digestion and treat GI complaints. It has also been used to treat wounds, sore throat, arthritic inflammations and jaundice.

Side Effects: The extract may cause gastric irritation and may not be tolerated by pregnant women or hypertensive patients.

Dosing: Gentian root has been used as a bitter digestive tonic in doses from 1 to 4 g/day. There are no clinical studies to substantiate this dose recommendation.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GENTIAN

GINGER

DATE OF ISSUE: MAY 2000

REPLACES MONOGRAPH DATED: NOV 1991

SCIENTIFIC NAME(S): *Zingiber officinale* Roscoe; occasionally *Z. capitatum* Smith.[1] Family: Zingiberaceae

COMMON NAME(S): Ginger, ginger root, black ginger, zingiberis rhizoma

BOTANY: A native of tropical Asia, this perennial is cultivated in tropical climates such as Australia, Brazil, China, India, Jamaica, West Africa, and parts of the US. [1] The term "root" is actually a misnomer because it is the rhizome that is used medicinally and as a culinary spice. Cultivation with natural manuring is thought to increase the spiciness of the rhizome and is therefore preferred to wild crafting. [1] The rhizome is harvested between 6 and 20 months; taste and pungency increase with maturity.[1] The plant carries a green-purple flower in terminal spikes; the flowers are similar to orchids. [1,2]

HISTORY: Medicinal use of ginger dates back to ancient China and India; references to its use are found in Chinese pharmacopoeias, the Sesruta scriptures of Ayurvedic medicine as well as Sanskrit writings.[1] Once its culinary properties were discovered in the 13th century, use of this herb became widespread throughout Europe. In the Middle Ages, it held a firm place in apothecaries for travel sickness, nausea, hangovers, and flatulence. [1]

Ginger and its constituents are stated to have antiemetic, cardiotonic, antithrombotic, antibacterial, antioxidant, antitussive, antihepatotoxic, anti-inflammatory, antimutagenic, stimulant, diaphoretic, diuretic, spasmolytic, immunostimulant, carminative, and cholagogue actions as well as to promote gastric secretions, increase intestinal peristalsis, lower cholesterol levels, raise blood glucose, and stimulate peripheral circulation. [1,3,4] Traditionally, ginger is used as an acrid bitter to strengthen and stimulate digestion.[1] Modern uses include prophylaxis for nausea and vomiting (associated with motion sickness, hyperemesis gravidarum and surgical anesthesia), dyspepsia, lack of appetite, anorexia, colic, bronchitis, and rheumatic complaints. [1,3,4,5] The food industry uses ginger oil as a spice and ginger extract in the manufacturing of ginger ale.[1,5] In China, ginger root and stem are used as pesticides against aphids and fungal spores. [6]

Ginger is in the official pharmacopoeias of Austria, China, Egypt, Great Britain, India, Japan, the Netherlands, and Switzerland. [1,4,5] It is approved as a nonprescription drug in Germany and as a dietary supplement in the US.[4] Only scraped or unscraped, unbleached ginger is accepted as a medicinal-grade drug, containing greater than or equal to 1.5% volatile oil. [1] Langner et al consider Jamaican and Cochin ginger to be the best varieties, and report the Japanese plant to be of inferior quality and do not recommend it for medicinal use. [1] Standards of quality for ginger can be found in *The United States Pharmacopeia National Formulary*.

Powder, alcoholic solutions, and freshly pressed juice and oil are found in pharmaceutical preparations. Ginger as a spice, seasoning, flavoring, oil, extract, and oleoresin is considered "Generally Recognized As Safe" (GRAS) by the FDA. [7,8] Deliberate or accidental adulterants include exhausted (overprocessed) ginger, Japanese ginger, *Z. cassummunar*, *Z. zerumbet*, and other foreign substances.[1]

CHEMISTRY: It had long been believed that the "pungent principles" of ginger were also responsible for its pharmacologic activity, and this has been found to be accurate. The characteristic aroma of ginger is due mainly to the presence of a zingiberol volatile oil. [1,9]

The major constituents in ginger rhizomes are carbohydrates (50 to 70%), which are present as starch. The concentration of lipids is 3 to 8% and includes free fatty acids (eg, palmitic, oleic, linoleic, linolenic, capric, lauric, myristic), triglycerides, and lecithins. Oleoresin provides 4 to 7.5% of pungent substances as gingerol homologues, shogaol homologues, zingerone, and volatile oils. [1] Volatile oils are present in 1 to 3% concentrations and consist mainly of the sesquiterpenes beta-besabolene and zingiberene; other sesquiterpenes include zingiberol and zingiberenol; numerous monoterpenes are also found. Amino acids, raw fiber, ash, protein, phytosterols, vitamins (ie, nicotinic acid and vitamin A), and minerals are among the other constituents. [1,6]

Analyses of the oleoresins have resulted in the identification of a class of structurally related cardiotonic compounds called gingerols, which upon dehydration, form shogaols and degrade further to zingerone.[1,6] [6]-gingerol and [6]-shogaol are the main components however, the pharmacologically active compounds [6]- and [10]-dehydrogingerdione, and [6]- and [10]-gingerdione have also been identified. [1,10,11]

PHARMACOLOGY: The gingerols and the related compound shogaol have been found to possess cardiotonic activity. Crude methanol extracts of ginger were known to have a strong positive inotropic effect on animal hearts. The gingerols have been found to exert a dose-dependent positive inotropic action at doses as low as 10^{-4} g/ml when applied to isolated atrial tissue.[12] Cardiac workload is further decreased by dilation of blood vessels via stimulation of prostacyclin biosynthesis. [1]

Administration of [6]-gingerol and [6]-shogaol (1.75 to 3.5 mg/kg IV and 70 to 140 mg/kg orally) inhibited spontaneous motor activity, produced antipyretic and analgesic effects, and prolonged hexobarbital-induced sleeping time in laboratory animals. [6]-shogaol was generally more potent than [6]-gingerol and showed an intense antitussive effect when compared with dihydrocodeine phosphate. Interestingly, [6]-shogaol inhibited intestinal motility when given IV, but facilitated GI motility after oral administration. Both compounds were cardiodepressant at low doses and cardiotonic at higher doses. [10]

[6]-gingerol, the dehydrogingerdiones, and the gingerdiones are potent inhibitors of prostaglandin biosynthesis through the inhibition of prostaglandin synthetase (cyclo-oxygenase).[11] Inhibition of thromboxane synthesis results in inhibition of platelet aggregation, but evidence indicates this is dose dependent or may only occur with fresh ginger.[1,13] The only 2 in vivo reports of impaired platelet function involved consumption of large quantities of raw ginger; 1 subject consumed large quantities of marmalade containing 15% ginger, and 1 study administered 5 g raw fresh ginger daily for 1 week. [13] One study was unable to detect measurable changes in bleeding time, platelet count, or platelet aggregation following a single 2 g dose of dried ginger in 8 healthy males. [13]

Ginger has been reported to have weak fungicidal, strong antibacterial, and anthelmintic properties. Active constituents have been shown to inhibit reproduction of *Escherichia coli*, *Proteus* species, staphylococci, streptococci, and *Salmonella* but to stimulate lactobacilli growth.[1] In vitro anthelmintic activity has been documented for the volatile oil of *Z. purpureum* Roxb against *Ascaridia galli* Schrank.[5] Activity has also been reported against parasites, such as *Schistosoma* and *Anisakis*.[1]

The cytotoxic compound zerumbone and its epoxide have been isolated from the rhizomes of *Z. zerumbet*. This plant, also a member of the family Zingiberaceae, has been used traditionally in China as an antineoplastic. The isolates inhibited the growth of a hepatoma tissue culture. [14] In addition, juice prepared from ginger root has been found to inactivate the mutagenicity of tryptophan pyrolysis products in vitro. [15]

Human clinical trials have examined ginger's antiemetic effects related to kinetosis (motion sickness), perioperative anesthesia, and hyperemesis gravidarum. However, little is still known regarding its human pharmacology in these settings. Animal studies have described enhanced GI transport as well as anti-5-hydroxytryptamine ($5HT_3$) and possible CNS antiemetic effects.[17]

One clinical trial (n = 12) employed gastroduodenal manometry to evaluate prokinetic effects of ginger in fasting and postprandial healthy subjects. A significant increase in antral motility and in corpus motor response with a trend toward increased motor response in all regions was found. [18] However, no effect of ginger on gastric motility using an acetaminophen absorption technique was found in 16 healthy volunteers. [19]

Kinetosis: One double-blind study (n = 36) compared the effect of 940 mg powdered ginger root, 100 mg dimenhydrinate, and placebo (chickweed herb) in the prevention of motion sickness. Preparations were administered 20-25 minutes prior to placing blindfolded subjects in a rotating chair. Those receiving ginger root

remained in the chair longer (average of 5.5 minutes, compared with 3.5 and 1.5 minutes for the dimenhydrinate and placebo groups, respectively), and 50% remained in the chair for the full 6 minutes of the test; none of the subjects in the other groups completed the test. In general, it took longer for the ginger group to begin feeling sick, but once the vomiting center was activated, sensations of nausea and vomiting progressed at the same rate in all groups. [20]

A double-blind, placebo-controlled study in seasick marine cadets (n = 79) reported significant reductions in symptoms (vomiting and cold sweats) and noticeably suppressed dizziness following administration of 1 g ginger rhizome. Nystagmus was reported as unchanged. [1] A study involving 1741 participants on an ocean sailing tour described the administration of 250 mg ginger prior to departure to be as effective as cinnarizine, scopolamine, dimenhydrinate, meclizine, and cyclizine. [1] Ginger (500 mg every 4 hours) and dimenhydrinate (100 mg every 4 hours) were compared in another double-blind study with similar protective effects, however those receiving ginger reported no side effects. [1]

Other trials have shown no significant differences among ginger, antiemetics, and placebo with regard to gastric as well as nongastric symptoms. Two separate investigations showed no effect of ginger on the CNS impairment caused by kinetosis as subjects retained the ability to perform certain head and eye movements. A scopolamine/*d*-amphetamine combination proved most effective but resulted in definite side effects. [1]

Another placebo-controlled study evaluated participants' ability to tolerate head movements in a rotating chair while blindfolded. [21] Ginger was compared against scopolamine (0.6 mg orally) in several small groups of test subjects. It was concluded that ginger administered as 500 to 1000 mg powdered root or 1000 mg fresh root provided no protection against motion sickness under various test conditions, while the scopolamine group was able to tolerate a significant increase in number of head movements. In this same study, gastric emptying and gastric electrical activity (via electrogastrogram [EGG]) were evaluated in 2 more small groups of subjects. Ginger partially inhibited and stabilized tachygastria but did not affect EGG amplitude. The authors concluded that symptoms of motion sickness can be dissociated from gastric electrical activity and that the partial tachygastric effects of ginger offer little to relieve the onset or severity of these symptoms. [21]

It has been proposed that, unlike antihistamines which act on the CNS, the aromatic, carminative, and possibly absorbent properties of ginger ameliorate the effects of motion sickness in the GI tract directly. [1,6,20] It may increase gastric motility and block GI reactions and subsequent nausea feedback. [20]

Postoperative nausea and vomiting (PONV): The anti-emetic effects of ginger have been compared with metoclopramide and droperidol in prevention of PONV. [22,23] One prospective, randomized, double-blind trial (n = 120) evaluated 1 g powdered ginger root and 10 mg metoclopramide administered 1 hour prior to anesthesia in women undergoing gynecological laparoscopy; anesthesia was induced with propofol, fentanyl, and atracurium. Findings supported those of previous studies; ginger and metoclopramide were equally effective and were more effective than placebo in reducing the incidence of PONV (21%, 27%, and 41%, respectively). The need for postoperative antiemetics was significantly reduced in those receiving ginger over the placebo group (15% vs 38%, $P = 0.006$). [22]

In a placebo-controlled comparison against droperidol, no statistically significant difference was found with ginger root or ginger root plus droperidol in the incidence of PONV in 120 women undergoing outpatient gynecological laparoscopy; anesthesia was induced with thiopental, fentanyl, and succinylcholine. Patients were given droperidol (1.25 mg IV), oral ginger root (1 g given 1 hour prior to induction of anesthesia and 1 g given 30 minutes prior to discharge), ginger plus droperidol or placebo. While incidences of postoperative nausea (20%, 22%, 33%, and 32%) and vomiting (13%, 25%, 25%, and 35%) did not reach statistical significance, the figures do appear to have potential clinical importance. [23]

A dosage study (randomized, double-blind, placebo-controlled) concluded that 0.5 g and 1 g powdered ginger root were ineffective in reducing the incidence of PONV in 108 patients. However, study methods in this particular trial could be questioned. To allow the identifying aroma of the ginger capsules to dissipate, capsules were removed from their original container and stored in pairs for 2 days in plastic bags until the odor disappeared. It has already been noted that the pungent principles (including the sesquiterpenes lending ginger its characteristic aroma) are responsible for ginger's pharmacological activity. [24]

Hyperemesis gravidarum: Pregnant women suffering from hyperemesis gravidarum received ginger (250 mg 4 times daily) or placebo for 4 days. About 70% of women subjectively preferred ginger treatment, with greater symptomatic relief being observed compared with placebo. [25]

Selective serotonin reuptake inhibitor discontinuation syndrome: One case report describes the successful use of ginger in one female patient with subsequent beneficial use in over 20 additional patients for the amelioration of symptoms (eg, disequilibrium, nausea) associated with abrupt discontinuation or intermittent noncompliance of selective serotonin reuptake inhibitors. Administration of 1100 mg ginger root 3 times daily at the onset of discontinuation-induced symptoms resulted in partial to complete relief of symptoms within 24 to 48 hours; ginger therapy was continued for approximately 2 weeks, the time required for symptoms to usually abate. [26]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: There are no reports of severe toxicity in humans from the ingestion of ginger root. In culinary quantities, the root is generally devoid of activity. Large overdoses carry the potential for causing CNS depression. Inhibition of platelet aggregation has been reported after consumption of large (clinically impractical) amounts of ginger but returned to normal within one week of discontinuation. [13] Cardiotonic and cardiodepressant activity have been demonstrated in animals. Reports that ginger extracts may be mutagenic or antimutagenic in experimental test models require confirmation. [1,25]

There is no convincing evidence regarding the safety of ingesting large amounts of ginger by pregnant women. The German Commission E contraindicates ginger for the use of morning sickness, however, data are lacking to support toxic effects in pregnant women. [1,3,4] The FDA considers ginger as a food supplement as generally recognized as safe (GRAS). [7,8]

SUMMARY: Ginger root is an ancient spice that has had a role in herbal medicine for thousands of years. Evidence appears to support its usefulness in symptoms of motion sickness, postoperative nausea and vomiting, and GI disturbances. These effects seem to be associated with direct actions of ginger on the GI tract and less, if at all, on the CNS. Studies have been conducted in pregnant women with benefit shown over placebo for symptoms of morning sickness. Ginger has extremely low toxicity and is devoid of side effects at normal doses.

PATIENT INFORMATION— Ginger

Uses: Ginger and its constituents have antiemetic, cardiotonic, antithrombotic, antibacterial, antioxidant, antitussive, antihepatotoxic, anti-inflammatory, antimutagenic, stimulant, diaphoretic, diuretic, spasmolytic, immunostimulant, carminative, and cholagogue actions. Ginger is used to promote gastric secretions, increase intestinal peristalsis, lower cholesterol levels, raise blood glucose, and stimulate peripheral circulation. Traditionally used to stimulate digestion, its modern uses include prophylaxis for nausea and vomiting (associated with motion sickness, hypermesis gravidarum, and anesthesia), dyspepsia, lack of appetite, anorexia, colic, bronchitis, and rheumatic complaints. Ginger can be used as a flavoring or spice as well as a fungicide and pesticide.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Excessive amounts may cause CNS depression and may interfere with cardiac function or anticoagulant activity.

Dosing: Ginger root has been given for nausea in clinical trials in 1 g doses, repeated as necessary. [27,28]

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Document Bibliographic Information:
- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
      GINGER

GINKGO

DATE OF ISSUE: MAR 1998

REPLACES MONOGRAPH DATED: FEB 1994

SCIENTIFIC NAME(S): *Ginkgo biloba* L. Family: Ginkgoaceae

COMMON NAME(S): Ginkgo, maidenhair tree, kew tree, ginkyo, yinhsing (Silver Apricot-Japanese)

BOTANY: The ginkgo is the world's oldest living tree species, and it can be traced back more than 200 million years to the fossils of the Permian period. It is the sole survivor of the family Ginkgoaceae. Individual trees may live as long as 1000 years. They grow to a height of about 125 feet and have fan-shaped leaves. The species is dioecious; male trees more than 20 years old blossom in the spring. Adult female trees produce a plum-like gray-tan fruit that falls in late autumn. Its fleshy pulp has a foul, offensive odor and causes contact dermatitis. The edible inner seed resembles an almond and is sold in oriental markets. [1]

HISTORY: The ginkgo species was almost destroyed during the ice age. The species survived in China, where it was cultivated as a sacred tree, and is still found decorating Buddhist temples throughout Asia. Preparations have been used for medicinal purposes for more than a thousand years. Traditional Chinese physicians used ginkgo leaves to treat asthma and chillblains, which is the swelling of the hands and feet from exposure to damp cold. The ancient Chinese and Japanese ate roasted ginkgo seeds, and considered them a digestive aid and preventive for drunkenness. [2] In the Western world, ginkgo has been used since the 1960s when technology made it possible to isolate its essential compounds. The flavonoids act as free radical scavengers, and the terpenes (ginkgolides) inhibit platelet activating factor.[3] Currently, oral and intravenous forms are available in Europe, where it is one of the most widely prescribed medications. Neither form has been approved for medical use in the United States, although ginkgo is sold as a nutritional supplement.

CHEMISTRY: There is a seasonal variation in the content of active compounds in leaves, with the highest amounts present in autumn. [4] Leaf constituents include amino acid 6-hydroxykynurenic acid, flavonoids (dimeric bioflavones) such as bilobetin, ginkgetin, isoginkgetin, sciadopitysin, and flavonols quercetin, kaempferol and their glycosides.[4,5] About 40 different flavonoids have been indentified so far. Some of these flavonoids are catechins, dehydrocatechins (proanthocyanidins), and flavones (eg, ginkgetin, amentoflavune, bilobetin, sciadopitysin). [6] Also present in ginkgo leaves are terpenoids (diterpenes), such as bilobalide, and gingolides A, B, C, J and M.[5,6] Other leaf components include steroids (sitosterol, stigmasterol), polyprenols, organic acids (shikimic, vanillic, ascorbic, p-coumaric), benzoic acid derivatives, carbohydrates, straight chain hydrocarbons, alcohol, ketones and 2 hexenol. [6]

The seed portion of ginkgo contains carbohydate (38%), protein (4%) and fat (< 2%). Alkaloids such as ginkgotoxin, amino acids, cyanogenetic glycosides and phenols (long-chain, including anacaric acid, bilobol and cardanol) are also present. [5] Ginkgolic acid and related alkylphenols from lipid fraction of the fruit pods has been reviewed.[7] The foul-smelling odor of the fleshy portion of the seeds is caused by high concentrations of butanoic and hexanoic acids. 4-O-methylpyridoxine has also been isolated from the seeds.[6]

Biological standardization of ginkgo extracts has been reported. [8]

PHARMACOLOGY: Pharmacokinetic parameter testing of ginkgo has been performed in animals,[6,9] and also in humans evaluating three ginkgo forms (capsules, drops and tablets).[10] Behavior of ginkgo after IV and oral administration in humans has been documented. [11]

Numerous studies on the pharmacological actions of ginkgo have been reported, including treatments for cerebral insufficiency, dementia, circulatory disorders and asthma. The plant is also known for its antioxidant and neuroprotective effects.

Cerebral insufficiency: Cerebral insufficiency may cause anxiety and stress, memory, concentration and mood impairment, and hearing disorders, all of which may benefit from ginkgo therapy.

In man, intravenous injection of ginkgo biloba extract (GBE) increased cerebral blood flow in about 70% of the patients evaluated. This increase was age-related: Patients between the ages of 30 and 50 years had a 20% increase from baseline, compared with 70% in those 50 to 70 years old. Further, the time to reach peak blood flow was shorter in the elderly.[12] Ginkgo leaf improves cerebral metabolism and protects against hypoxic damage in animals with cerebral ischemia.[5] Cerebral insufficiency in 112 patients (average age 70.5 years) treated with ginkgo leaf extract (120 mg) for 1 year, resulted in reduced symptoms such as headache, dizziness, short-term memory, vigilance and disturbance.[5] Electroencephalographic effects of different preparations of GBE have been performed. [13] A review of 40 clinical trials was performed, most evaluating 120 mg GBE per day for 4 to 6 weeks, reporting positive results in treating cerebral insufficiency. Only eight studies did not have major methodological flaws; the results from these studies were, nevertheless, difficult to interpret. They suggested that long-term treatment (greater than 6 weeks) is required and that any effect is similar to that observed following treatment with ergoloids. [14] A meta-analysis of 11 placebo controlled, randomized, double-blinded studies, concluded GBE (150 mg/day) to be superior to placebo in patients with cerebrovascular insufficiency. [15]

Ginkgo's role as a psychotropic drug is under review.[16]

Anti-anxiety/stress: MAO inhibition in rats produced by extracts of ginkgo (dried and fresh leaves) has been performed, suggesting a mechanism by which the plant exerts its anti-stress actions.[17] Glucocorticoid synthesis, regulated by ACTH (adrenocorticotropic hormone), which accelerates cholesterol transport, can lead to neurotoxicity. Ginkgolides A and B, through a series of events, decrease cholesterol transport, resulting in decreased corticosteroid synthesis. The anti-stress and neuroprotective effects of GBE may also be caused by this mechanism of action.[18]

GBE in combination with *Zingiber officinale*, was compared to diazepam to study anxiolytic effects in animals. Results showed these effects to be comparable to those of diazepam, but in high doses, the combination may have anxiolytic properties. [19] Social behavior in animals has been evaluated using GBE, diazepam and ethyl beta-carboline-3-carboxylate.[20]

Memory improvement: Oral administration of GBE (alone and in combination with panax ginseng) improved retention of learned behavior using conditioned-reflex methods (punishment or positive reinforcement) in young and old rats.[21] GBE can help improve behavioral adaptation despite adverse environmental events, as shown in rats taught reward vs punishment (stress) testing to obtain drinking water. This supports clinical use of the plant to treat cognitive impairment in the elderly population.[22]

In elderly men with slight age-related memory loss, ginkgo supplementation reduced the time required to process visual information. [23] Effects of GBE on event-related potentials in 48 patients with age-associated memory impairment has been performed. [24] Significant improvement in memory (as measured by a series of psychological testing), in 8 patients (average age, 32 years) was found one hour after administration of 600 mg GBE vs placebo, again confirming the plant's usefulness in this area.[5]

Tinnitus hearing disorder therapy: Because of the diverse etiology of tinnitus, and lack of objective method to measure its symptoms, results using GBE for treatment of this disease are contradictory. GBE may have positive effects in some individuals. [25] In animals with salicylate-induced tinnitus, GBE resulted in a statistically significant decrease of behavioral manifestations of tinnitus. [26]

In patients with hearing disorders secondary to vascular insufficiency of the ear, about 40% of those treated orally with a leaf extract for 2 to 6 months showed improvement in auditory measurements. The extract also was extremely effective in relieving vertigo associated with vestibular dysfunction. [27]

Dementias: Clinical application of ginkgo biloba in dementia syndromes has been reported, and therapeutic effectiveness of the plant in this area has been demonstrated.[28,29] One report recommends early GBE therapy in dementias, especially because there are not side effects associated with other dementia drugs. [30]

Effects of 240 mg/day GBE in approximately 200 patients with dementia of Alzheimer type and multi-infarct dementia, have been investigated in a randomized, double-blinded, placebo controlled, multi-center study. Parameters such as psychopathological assessment, attention, memory and behavior were monitored, resulting in clinical efficacy of the extract in dementias of both types. [31] In another set of patients with moderate dementias (of Alzheimer, vascular or mixed type), short-term IV infusion therapy with GBE also had positive results, improving psychopathology and cognitive performance. [32] In a 52-week, randomized, double-blinded, placebo controlled, multi-center study, mild to severe Alzheimer or multi-infarct dementia patients received 120 mg/day GBE vs placebo. Results of this report again confirm improved cognitive performance and social functioning in a number of cases. [33]

Circulatory disorders/asthma: Ginkgolides competively inhibit the binding of platelet-activating factor (PAF) to its membrane receptor. [5,6] Effects of this mechanism are useful in the treatment of allergic reaction and inflammation (asthma and bronchospasm) and also in circulatory diseases.

Ginkgolides have been proven effective in both early and late phases of airway hyperactivity in one double-blinded, randomized, crossover study in asthma patients. [5]

A meta-analysis evaluating GBE in peripheral arterial disease, concludes a highly significant therapeutic effect of the plant in this area. [34] Numerous studies are available concerning GBE and circulatory disorders including its ability to protect against cardiac ischemia reperfusion injury, [35] to adjust fibrinolytic activity[36] and, in combination with aspirin, to treat thrombosis.[37] It also appears useful in management of peripheral vascular disorders such as Raynaud's disease, acrocyanosis and post-phlebitis syndrome.[27] In man, IV injection of 50 to 200 mg of ginkgo extract caused a dose-dependent increase in microcirculation and blood viscoelasticity in patients with pathologic blood flow disorders.[38]

A 6-month, double-blind trial suggested some efficacy in treating obliterative arterial disease of the lower limbs. Patients who received extract showed a clinically and statistically significant improvement in pain-free walking distance, maximum walking distance and plethysmorgraphic recordings of peripheral blood flow. [39] GBE improves walking performance in 60 patients with intermittent claudication, with good tolerance to the drug. [40] However, another report concludes GBE (120 mg/day) to have no effect on walking distance or leg pain in intermittent claudication patients (but finds other cognitive functions to be improved). [41] A review of 10 controlled trials evaluating treatment of the plant for this condition, found poor methodological quality, but did note all the studies to show clinical effectiveness of GBE in treating intermittent claudication.[42]

Antioxidant/neuroprotective effects: GBE is known to improve diseases associated with free radical generation. The ginkgolides may contribute to neuroprotective effects. The flavonoid fraction contains free radical scavengers, both of which are important in areas such as hypoxia, seizure activity and peripheral nerve damage. [43]

GBE exerts a restorative effect in aged rats caused by its protective action on neuronal membrane. [44] It was also shown to protect rat cerebellar neurons suffering from oxidative stress induced by hydrogen peroxide.[45] GBE may be a potent inhibitor of nitric oxide production under tissue-damaging inflammatory conditions in murine macrophage cell lines.[46] GBE was found to be more effective than water-soluble antioxidants and as effective as lipid-soluble antioxidants, in an in vitro model using human erythrocyte suspensions.[47]

Other numerous reports exist concerning this topic, including GBE's effect against lipid peroxidation and cell necrosis in rat hepatocytes, [48] its effect as an oxygen radical scavenger and antioxidant,[49] and its powerful effects on copper-mediated LDL oxidative modification.[50] In Chernobyl accident recovery workers, GBE's antioxidant effects were also studied. Clastogenic factors (risk factors for development of late effects of irradiation) were successfully reduced by the plant. [51]

A number of other potentially beneficial pharmacologic effects have been observed for ginkgo, including its ability to prevent the deterioration of lipid profiles when subjects were challenged with high-cholesterol meals over an extended holiday season, [52] improvement in the symptoms of PMS, particularly breast-related symptoms.[53] GBE's use in eye problems[6] and its scavenging abilities to reduce functional and morphological retina impairments. [54] In addition, GBE has in vitro and in vivo activity against *Pneumocystis carinii*[55] and has been studied in animals with diabetes[56,57] and in human diabetic patients. When GBE extract was given, peripheral blood flow increased by 40% to 45%, compared with an increase of 35% after administration of nicotinic acid. [58] Other reports suggest GBE to be effective in arresting fibrosis development (in 86 chronic hepatitis patients), [59] promoting hair regrowth in mice[60] and relaxing both animal and human penile tissue, suggesting a possible use as a drug for impotence.[61] Long-chain phenols from ginkgo biloba seeds are active against sarcoma 180 ascites in mice. [5] Seed extracts of the plant possess antibacterial and antifungal activity. [6]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Ingestion of the extract has not been associated with severe side effects. Adverse events from clinical trials of up to 160 mg/day for 4 to 6 weeks did not differ from placebo group. German literature lists ginkgo's possible side effects as headache, dizziness, heart palpitations and GI and dermatologic reactions. Injectable forms of ginkgo may cause circulatory disturbances, skin allergy or phlebitis. Willmar Schwabe Co. has withdrawn its parenteral ginkgo product *Tebonin* from the market because of the possible severity of side effects from this form.[6]

A toxic syndrome, ("Gin-nan" food poisoning) has been recognized in the Orient in children who have ingested ginkgo seeds. Approximately 50 seeds produce tonic/clonic seizures and loss of consciousness.[62] Seventy reports (between 1930 and 1960) found 27% lethality, with infants being most vulnerable. Ginkgotoxin (4-O-methylpyridoxine), found only in the seeds, was considered responsible for this toxicity. [5,6]

Contact with the fleshy fruit pulp has been known since ancient times to be a skin irritant. Constituents alkylbenzoic acid, alkylphenol and their derivatives cause reactions of this type. Allergic dermatitis such as erythema, edema, blisters and itching have all been reported. [6] A cross-allergenicity exists between ginkgo fruit pulp and poison ivy. Ginkgolic acid and bilobin are structurally similar to the allergens of poison ivy, mango rind and cashew nut shell oil. Contact with the fruit pulp causes erythema and edema, with the rapid formation of vesicles accompanied by severe itching. The symptoms last 7 to 10 days. Ingestion of as little as two pieces of pulp has been reported to cause perioral erythema, rectal burning and tenesmus (painful spasms of the anal sphincter). [1]

Allergans ginkgols and ginkgolic acids can also cause contact reactions of mucous membranes, resulting in cheilitis and GI irritation. Oral ingestion of ginkgo preparations, however, do not have this ability. [5,6] Ginkgo pollen can also be strongly allergenic.[63]

In one report, spontaneous bilateral subdural hematomas have, in addition, been associated with ingestion of the plant. [64]

In animal experimentation, no mutagenic or teratogenic effects were found. Oral administration of up to 1600 mg/kg/day of GBE to rats did not produce teratogenic effects. Other animal toxicity data is available including lethal dosing and other studies performed in mice, rats, guinea pigs, rabbits and dogs. [6]

No human data is yet available concerning pregnancy and lactation, so ginkgo should be avoided by this population. [5,6]

SUMMARY: The ginkgo is the oldest known living tree species. An extract of the leaves has been shown to have pharmacologic activity in the areas of cerebral insufficiency, dementias, circulatory disorders and bronchoconstriction. The plant also is known for its antioxidant and neuroprotective effects. Ingestion of ginkgo extract has not been associated with severe side effects, but contact with the fleshy fruit pulp causes allergic dermatitis, similar to poison ivy. In animals, ginkgo does not produce teratogenicity, but limited human data is available on this subject, suggesting avoidance of use during pregnancy and lactation.

PATIENT INFORMATION— Ginkgo

Uses: Ginkgo has been used in treating Raynaud's disease, cerebral insufficiency, anxiety/stress, tinnitus, dementias, circulatory disorders/asthma. It has positive effects on memory and diseases associated with free radical generation.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Severe side effects are rare; possible effects include headache, dizziness, heart palpitations and GI and dermatologic reactions. Ginkgo pollen can be strongly allergenic. Contact with the fleshy fruit pulp causes allergic dermatitis, similar to poison ivy.

Dosing: Standardized gingko leaf extracts such as EGb761 (*Tebonin forte*, Schwabe) have been used in clinical trials for dementia, memory, and circulatory disorders at daily doses of 120 to 720 mg of extract. Extracts usually are standardized to 24% flavones and 6% terpene lactones. [40,65,66,67,68,69,70,71]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GINKGO

GINSENG, PANAX

DATE OF ISSUE: FEB 2001

REPLACES MONOGRAPH DATED: SEP 1990

BOTANY: Ginseng commonly refers to *Panax quinquefolius* L. or *Panax ginseng* C.A. Meyer, two members of the family Araliaceae. The ginsengs were classified as members of the genus Aralia in older texts.

Scientific name	Synonyms	Common name	Distribution
P. ginseng	P. pseudoginseng Wallich; P. schinseng Nees	Asian, Chinese, Korean, or Oriental ginseng;[1,2] red ginseng (steamed)	NE China, Korea, Eastern Siberia
P. japonicus			China var bipinnatifidus [2]
P. japonicus (Will.) subsp. Japonicus	P. pseudoginseng C.A. Meyer[2]	Japanese ginseng[1,2] or zhu je ginseng[4]	India, Southern Chikusetsu ginseng,[3] China, Japan
P. japonicus			China var. major [2]
P. notoginseng	P. pseudoginseng Wallich var. notoginseng (Burkhill) Hoo & Tseng;[2] Five-fingers; ([Buck] F.H.Chen)	Western ginseng; Tien-chan[1] or tienqi[4] ginseng	Asia
P. pseudoginseng		Himalayan ginseng	Nepal subsp. himalaicus
P. pseudoginseng		Zhuzishen	China var. major
P. quinquefolius L.		American or Canadian ginseng[1,6]	Eastern and Central USA and Canada
P. vietnamensis Ha et Grushv.		Vietnamese ginseng[1,5]	Vietnam

In the eastern and central United States and Canada,[3] ginseng is found in rich, cool woods; a significant crop is also grown commercially. The short plant grows from 3 to 7 compound leaves that drop in the fall. It bears a cluster of red or yellowish fruits from June to July. The shape of the root can vary between species and has been used to distinguish types of ginseng. Medicinally, it is the root that is considered most valuable in providing the pharmacologically active ginsenosides. Ginsenoside content varies with the age of the root, season of harvest, and preservation method. While at least 4 ginsenosides are detectable in most young roots, this number more than doubles after 6 years of growth. High quality ginseng is generally collected in the fall after 5 to 6 years of growth. [3]

HISTORY: Ginseng is perhaps the most widely recognized plant used in traditional medicine and now plays a major role in the herbal health care market. For more than 2000 years, various forms have been used in medicine. The name *Panax* derives from the Greek word for "all healing" and its properties have been no less touted. Ginseng root's man-shaped figure (shen-seng means "man-root") led proponents of the "Doctrine of Signatures" to believe that the root could strengthen any part of the body. Through the ages, the root has been used in the treatment of asthenia, atherosclerosis, blood and bleeding disorders, colitis, and to relieve the symptoms of aging, cancer, and senility.

Evidence that the root possesses a general strengthening effect, raises mental and physical capacity, and exerts a protectant effect against experimental diabetes, neurosis, radiation sickness, and some cancers has been reported. Today, its popularity is because of the proposed "adaptogenic effect" (stress-protective) of the saponin content.

CHEMISTRY: The first study of the plant was reported in 1854 when a saponin called panaquilon was isolated from *P. quinquefolium*.[7] The analysis of ginseng has focused on this group of compounds, which has several naming conventions and may be referred to as ginsenosides, panaxosides, chikusetsu-saponins, or dammarane derivatives.[2,3] Saponins, or triterpenoid glycosides, are steroid-like compounds linked to sugars. [3,4,8,9] About 12 major ginsenosides have been isolated.[3,10] Several dozen minor glycosides also have been identified.

The saponin content varies among *Panax* species based on the species, age of the root, location, season, and curing method. [11] Of the 13 major saponins (ginsenosides) isolated from *P. ginseng*, only 2 are common to Japanese, Chinese, Korean, and American ginseng (R_{g2} and R_o).[3] Saponins are difficult to purify on a large scale. Therefore, the whole root is used in herbal preparations.

Many other minor components have been isolated and may contribute to the pharmacologic effects. These include volatile oils, beta-elemine, sterols, acetylenes, polysaccharides, starch, flavonoids, peptides, vitamins (eg, B_1, B_2, B_{12}, pantothenic acid, biotin) minerals, enzymes, and choline.[2,12]

A wide range of ginseng products are available over the counter as food flavorings and as herbal medicines. These range from fresh and dried roots to extracts, solutions, capsules, tablets, sodas, and teas.[1,13,14] However, the taste of ginseng is disagreeable to many.

A study analyzing various commercial ginseng products from 11 different countries revealed that among the 14 purest preparations, ginsenoside content varied between 1.9% to 8.1% (wt/wt); and among 20 extract preparations, the concentration varied from 4.9% to 13.3%.[3] Of 17 different products analyzed from Sweden, total ginsenoside content per capsule or tablet was 2.1 to 13.3 mg.[3] These variations, as do other comparative studies, emphasize the need for quality control. [3,15,16]

The German Commission E defines ginseng root (*ginseng radix*) as containing at least 1.5% ginsenosides, calculated as ginsenoside R_{g1}.[13,14]

In addition to ginsenoside content variation, methylxanthines are produced by the ginseng plant and can also be contained within commercial ginseng preparations. The type and concentration of xanthines (eg, caffeine, theophylline, theobromine) also varies with the variety of ginseng and may contribute to some of the reported physiological effects. Levels of xanthines have been reported to range from 0.1 mg/dose in American ginseng products to 200 mg/dose in Asian ginseng products. [3]

Physical and chemical analyses have shown that while some commercial products closely resemble the whole root in composition, many contain little or no detectable ginsenoside concentrations.[11,17] Some preparations have been adulterated with phenylbutazone, aminopyrine, or mandrake root, while others have been contaminated with pesticides and fungicides.[3,18,19] Other preparations labeled "native American ginseng" were found not to contain any species of *Panax*. The root of Siberian ginseng (*Acanthopanax senticosus* Harms. or *Eleutherococcus senticosus* Maxim) is sometimes used in herbal medicine for the same purposes as traditional ginseng. This is an entirely different plant and is described in more detail in a separate monograph (see eleutherococcus monograph).

Variances in cultivation and processing methods as well as individual genetics of each plant source result in varying chemical compositions among commercial products. The variance in products may be a contributing factor to the lack of consensus among studies on the pharmacology and efficacy of ginseng and need to be considered when interpreting and conducting research.

PHARMACOLOGY: Over the past 40 years, in vitro and animal studies have identified a diverse array of pharmacologic effects of ginseng. These effects vary with dose, duration of treatment, and animal species, and include CNS depression or stimulation, variable effects on systemic blood pressure, a papaverine-like action on smooth muscle, and analgesic and anti-inflammatory activity.[20] Because most studies have used whole root preparations, there likely has been considerable variation

among these preparations (uncertain species identification, age of the roots, curing process used, etc). Variations in saponins among the various species also may contribute to the lack of consensus among researchers on ginseng's pharmacology.

Adaptogenic effects: From the earliest times, it has been claimed that ginseng exerts a strengthening effect while also raising physical and mental capacity for work. These properties have been defined as an "adaptogenic effect" or a nonspecific increase in resistance to the noxious effects of physical, chemical, or biological stress.[8] Animal studies have shown that ginseng extracts can prolong swimming time, prevent stress-induced ulcers, stimulate the proliferation of hepatic ribosomes, increase natural killer cell activity, and may enhance the production of interferons. [21] Huong, et al (1998), described antistress effects in rats of a saponin in Vietnamese ginseng (MR2); evidence from this study suggested that modulation of opioid, GABA, corticotropin-releasing factor, or interactions thereof were responsible for the effects of MR2.[5] However, a study in mice found no adaptogenic effects.[22]

Antineoplastic/Immunomodulatory effects: Ginsenosides have been shown to exert anticarcinogenic effects in vitro, including direct cytotoxic and growth inhibitory effects as well as inducing differentiation and inhibiting metastasis. High concentrations of M1, an active metabolite of R_{b1}, R_{b2}, and R_c induced cell death of mouse melanoma cells by regulating proteins involved in apoptosis. R_{h2} and R_{h3}-induced differentiation of promyelocytic leukemia cells into granulocytes; R_{g3} inhibited adhesion and invasion of melanoma cells and decreased pulmonary metastasis.[23] Animal studies have supported these immunomodulatory effects. R_{g1}has been shown to increase cell-mediated and humoral immune responses; ginsenosides and polysaccharides found in ginseng root have been found to stimulate antibody production and phagocytosis of the reticuloendothelial system.[23,24] However, two studies in healthy volunteers measuring T-lymphocyte immunomodulation yielded equivocal results.[1,23]

Cardiovascular effects: Ginseng saponins have been reported to act as selective calcium antagonists as well as enhance the release of nitric oxide (NO) from endothelial and neuronal cells. In vitro studies have shown that total ginseng saponins extracted from *P. notoginseng* and *P. quinquefolius* inhibited calcium entry through receptor-operated calcium channels without affecting calcium entry through voltage channels or intracellular calcium release. [25] In studies involving rabbits and dogs, ginsenosides R_o and R_b from *P. ginseng* offered a protective effect in myocardial ischemia and reperfusion injuries. [26] It is postulated that this effect is partly mediated by increased release of prostacyclin and by activation of NO synthase and subsequent release of NO. This is supported by evidence from studies in the corpus cavernosum in which ginsenosides not only induced relaxation but also enhanced both acetylcholine- and transmural nerve stimulation-induced relaxation of the corpus cavernosum (actions mediated by NO).[26] These actions may contribute to the historical use of ginseng in China for cardiovascular diseases and as an aphrodisiac.

CNS effects: R_{b1} and R_{g1} appear to play a major role in CNS stimulatory and inhibitory effects and may modulate neurotransmitters. Cholinergic activity implicated in mediating learning and memory processes has been shown to be affected by certain ginsenosides. Animal studies show that R_{b1}, R_{g1}, and R_e prevent scopolamine-induced memory deficits, and that R_{b1} and R_{g1} appear to increase central choline uptake and facilitate the release of acetylcholine from hippocampal tissues. Results from a study in aged rats suggest that daily oral administration of *P. ginseng* extract at 8 g/kg/day for 12 days improved learning performance.[3] In animal tissues, ginseng extract also has been shown to inhibit GABA, glutamine, dopamine, noradrenalin, and serotonin uptake in a concentration-dependent manner. An in vivo study suggested possible CNS depressant effects of ginsenosides when a mixture of R_{b1}, R_{b2}, and R_c prolonged hexobarbital sleeping time in mice. Ginseng saponins also have been shown to prevent dopamine receptor supersensitivity and physical dependence induced by chronic morphine, methamphetamine, and cocaine administration; while the total extract and R_f were reported to inhibit sensory neuron calcium channels in a manner equal to that of opioids. [23,24] However, while ginseng exhibits anti-opioidergic actions, it is not affected by the opioid receptor antagonist naloxone. [23] It has been observed in mice that administration of opioids and psychostimulants (eg, cocaine) can suppress certain immune responses (eg, macrophage activity, tumor necrosis factor levels), and that administration of ginsenosides and ginseng polysaccharides that block opioid behavioral dependence also markedly stimulates these and other immune responses. [23,24] Some researchers have postulated that these processes may be related and that ginseng's immune-activating effects may play a role in inhibiting opioid and psychostimulant behavioral dependence.[23]

In humans, two randomized double-blind, placebo-controlled studies (n = 32 and n = 127) using *P. ginseng* (200 to 400 mg/day for 8 to 12 weeks) were reported to have shown improvements in cognitive functioning, specifically mental arithmetic and abstraction. [1] However, another evaluation of one of these same studies claimed the improvements were not significant.[3] A third study of 50 elderly patients (65 to 80 years of age) comparing *P. ginseng* (dose not reported) to a neurotrophic amino acid/vitamin B_{12} combination reported significant improvements for the ginseng group over baseline however, these results were inferior compared with those of the neurotrophic combination group.[3]

Endocrine effects: Randomized, placebo-controlled human trials have confirmed the hypoglycemic effects of ginseng reported in earlier animal studies. [27,28,29] One study noted statistically significant ($P < 0.01$) improvements in fasting blood glucose and reductions in $HbA1_c$ in subjects with type 2 diabetes mellitus treated 8 weeks with 100 and 200 mg ginseng, respectively (manufacturer listed but species not noted). However, all patients studied also lost weight, which may be touted as equivocal overall results. Two studies have shown that 3 g ground root of *P. quinquefolius* exerts a glucose-lowering effect only postprandially or when stimulated by glucose ingestion.[28,29] Evidence appears to support modulation of insulin sensitization and secretion based on the fact that the cholinergic, dopaminergic, adrenergic, and NO actions found with ginsenosides also have been noted to affect glucose metabolism in animal studies. [28,29]

Ergogenic effects: Strong evidence supporting the efficacy of ginseng in improving physical performance seems to be lacking. Physical performance in young, active volunteers was found unimproved in 4 studies; however, other studies reported a decrease in heart rate and an increase in maximal oxygen uptake. [1] One comprehensive literature search evaluated data from human studies on *P. ginseng* preparations. Properly controlled studies using higher doses (standardized to 2 g/day of dried root), administered for at least 8 weeks and in larger subject numbers, more often exhibited statistically significant improvements in physical or psychomotor performance. Benefit was most likely to be seen in untrained subjects or those over 40 years of age.[4]

INTERACTIONS: A possible interaction with warfarin has been noted in a case report of a 47-year-old man stabilized on warfarin for 5 years. Four weeks prior to taking ginseng, as *Ginsana* (a commercial product) 3 times daily, his international normalized ratio (INR) was 3.1 and had ranged from 3 to 4 over the previous 9 months; 2 weeks after starting *Ginsana*, his INR decreased to 1.5, but returned to 3.3 within 2 weeks after discontinuing the ginseng. Changes in drug regimens, dietary consumption of vitamin K, or other nutritional supplements were ruled out as a possible cause of his subtherapeutic INR. No thrombotic episodes occurred during *Ginsana* administration; however, risk of thrombosis prevented rechallenge to confirm this interaction. The mechanism of this interaction is unknown; whether this is a drug interaction or assay interference has yet to be determined. [30]

Refractoriness to the loop diuretic furosemide has been reported in a 63-year-old man approximately 10 days after he started taking 10 to 12 ginseng tablets daily. [31] The patient was hospitalized for edema and hypertension. While in the hospital, he did not receive any nutritional products and responded to IV furosemide. He was discharged from the hospital on oral furosemide. Following discharge, the patient started taking his nutritional supplements and once again developed worsening edema and hypertension.

Two case reports describe hyperstimulation symptoms (eg, insomnia, headache, tremulousness, irritability, and visual hallucinations) when ginseng was taken concomitantly with phenelzine.[32]

For other potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: It is estimated that more than 6 million people ingest ginseng regularly in the United States. There have been few reports of severe reactions.

Several reports have implicated ginseng as having an estrogen-like effect in women. [33] One case of diffuse mammary nodularity has been reported,[34] as well as a case of vaginal bleeding in a 72-year-old woman.[35]

Neonatal death has been reported; avoid use during pregnancy and lactation.

The most commonly reported side effects of ginseng are nervousness and excitation, which usually diminish after the first few days of use or with dosage reduction. It has been suggested that methylxanthine constituents of ginseng root (eg, caffeine, theophylline) may contribute to these physiological effects. [3] Inability to concentrate has also been reported following long-term use. [36]

The hypoglycemic effect of the whole root and individual panaxosides has been reported by many investigators. Although no cases of serious reactions in diabetic patients have been reported, people who must control their blood glucose levels should take ginseng with caution.

Ginseng also should not be used by those with high blood pressure.

SUMMARY: Ginseng is one of the oldest and most widely recognized herbal products. At least 6 species and varieties of *Panax* have been used in traditional medicine. Today, ginseng is one of the most popular herbal supplements sold over-the-counter. It is available in a variety of dosage forms and is promoted for its "anti-stress" effects. Numerous animal studies have confirmed this "adaptogenic effect." However, establishing the proper dose and duration of use remains poorly defined. As a result of controlled studies, the German Commission E recommends 1 to 2 g daily dose of root or equivalent preparations (20 to 30 mg ginsenosides). [13,37] Ginseng is not usually associated with serious adverse reactions, although a potential "ginseng abuse syndrome" has been reported.

PATIENT INFORMATION — Ginseng, Panax

Uses: Ginseng is popular for a variety of uses, including adaptogenic, antineoplastic, immunomodulatory, cardiovascular, CNS, endocrine, and ergogenic effects, but these uses have not been confirmed by clinical trials.

Interactions: Possible interactions with warfarin, loop diuretics, and phenelzine have been reported.

Side Effects: The most commonly reported side effects with ginseng are nervousness and excitation. However, there have been reports of diffuse mammary nodularity and vaginal bleeding. A hypoglycemic effect has also been reported; use with caution in those who must control their blood glucose levels.

Dosing: Ginseng root is standardized on content of ginsenosides, which should be greater than 1.5%. Extracts typically contain from 4% to 7% ginsenosides. Note that the profile of particular ginsenosides differs between American and Asian ginseng; however, the total ginsenoside content is similar. In numerous clinical trials, dosage of crude root has been from 0.5 to 3 g/day and dosage of extracts generally from 100 to 400 mg. [1,27,38,39]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GINSENG, PANAX

GLUCOMANNAN

DATE OF ISSUE: AUG 1995

REPLACES MONOGRAPH DATED: JUL 1986

SCIENTIFIC NAME(S): *Amorphophallus konjac*Koch. Family: Araceae

COMMON NAME(S): Konjac, Konjac mannan, glucomannan

SOURCE: Konjac mannan is a polysaccharide derived from the tubers of konjac. It is purified from konjac flour by repeated treatment with cupric hydroxide and subsequent washings with ethanol[1] or by dialysis against water (US patents 3, 973,008 [Aug 3, 1976] and 3, 856, 945 [Dec 24, 1974]).

CHEMISTRY: Glucomannan is composed of glucose and mannose combined by beta-1,4 glucosidic linkages in a molecular ratio of 1:1.6 and is often referred to as glucomannan. The polysaccharide is easily "denatured" through enzymatic cleavage or treatment with weak alkaline solutions, becoming irreversibly water insoluble. In Japan, this coagulated product is called "konnyaku" and is commonly used as a foodstuff.

PHARMACOLOGY: Polysaccharides such as guar gum (composed of galactose and mannose; galactomannan), tragacanth, cellulose, methylcellulose, pectin, and wheat bran have found use as foodstuffs and, more recently, as dietary and therapeutic agents. Their ability to swell by the absorption of water has made them useful as laxatives. Konjac mannan has been reported to alleviate moderate constipation in 1 to 2 days and reduces fecal flora by a factor of 1000 in 10 days. Research on microflora in mice and rats suggests that a diet that includes konjac mannan alters the microbial metabolism in the intestine. [2] The study noted that in animals bearing human microflora, the differences in microbial composition were only slight despite the metabolic differences observed.

By increasing the viscosity of the intestinal contents, slowing gastric emptying time, and acting as a barrier to diffusion, agents such as guar gum have been shown to delay the absorption of glucose from the intestines.[3] Several small studies have shown that diabetics fed a diet consisting largely of raw vegetables, uncooked seeds, fruits and goat's milk, were able to reduce or discontinue their insulin requirements. [4] Similarly, konjac mannan has been reported to reduce the need for hypoglycemic agents. When 13 diabetic patients received 3.6 or 7.2 g of konjac mannan daily for 90 days, their mean fasting glucose levels fell by 29% and insulin or hypoglycemic agent doses were reduced in most patients.[5] Five healthy men enrolled in the same study underwent a glucose tolerance test with or without a single dose of 2.6 g konjac mannan. The polysaccharide reduced mean blood glucose levels by 7.3% at 30 minutes with a concomitant decrease in serum insulin concentration. Another study of 72 type II diabetic patients showed a significant reduction in fasting blood glucose and postprandial blood glucose after consuming konjac food 30 and 65 days.[6]

Konjac mannan is gaining popularity as a weight-reducing agent and is often included in "grapefruit diet" tablets. One U.S. patent claims that its use resulted in weight loss without appetite changes; however, no weights were reported. Some research has indicated that patients treated with oral glucomannan have decreased body weight compared with control groups. In one study involving an 8-week cardiac rehabilitation program, patients were given 1.5 grams of glucomannan twice daily. [7] Body weight among treated patients decreased by 1.5 kg at the end of 4 weeks and by 2.2 kg at the end of 8 weeks. These losses were significant when compared with the placebo group. In contrast, other research conducted with overweight children has found no significant difference in weight loss between children treated with 1 g glucomannan twice daily and those given a placebo.[8]

Hydrophilic gums have found some use as diet aids based on the theory that the feeling of fullness provided by their swelling leads to a decrease in appetite. Such agents are generally considered to be only marginally effective.

Konjac mannan has been shown to reduce plasma cholesterol levels in rats.[9] Interestingly, only water-soluble konjac mannan retains this effect. The hypocholesteremic effect is completely eliminated when the mannan is coagulated to a water-insoluble form. Rats fed high cholesterol diets containing 3% crude konjac mannan for 7 days exhibited plasma cholesterol levels 16% lower than control rats fed only the high cholesterol diet. Rats fed highly purified konjac mannan had plasma cholesterol levels 23% lower than the controls. Rats treated with konjac mannan that had been coagulated with cellulase had mean cholesterol levels greater than the controls. The implication is that the foodstuff konnyaku (coagulated water-insoluble product) most likely has no cholesterol-reducing activity.

In a study of 10 overweight patients, the daily administration of 100 ml of 1% solution of konjac mannan for 11 weeks resulted in decreases in serum cholesterol levels of 0% to 39% (mean, 18%) (US patent 3,973,008). In a separate double-blind crossover trial involving 63 men, total cholesterol was reduced by 10% among subjects given a daily dose of 3.9 g of konjac glucomannan for a 4-week period.[10] Interestingly, no significant change in high-density lipoprotein (HDL) cholesterol was observed as a result of the treatment. The diabetic patients treated in another study [5] showed a reduction in mean serum cholesterol levels of 11% after 20 days of konjac mannan treatment. Several other studies confirm the effects of konjac mannan on lipid metabolism.[11,12,13]

The activity of this polysaccharide cannot be explained by a simple interaction with bile acids since konjac mannan shows no in vitro or in vivo bile-binding activity. Rather, it appears to inhibit the active transport of cholesterol in the jejunum and the absorption of bile acids in the ileum. [14] A study on bile output in rats fed a diet of 5% konjac mannan showed an increase in the volume of bile juice secreted and the release of bile acids, protease and amylase compared to animals fed a control diet without fiber.[15] This effect was only observed for prolonged feeding of the experimental diet with konjac mannan and could not be produced with a single dose.

A Chinese study has investigated the ability of konjac powder to inhibit lung cancers in mice. [16] Mice fed a diet of 8% Konjaku powder, mixed in with a common diet, showed a reduction in cancer rate from 70.87% in the positive control group to 19.38% in the group fed with konjac powder. Lung tumors were induced with MNNG. The study reported no adverse reactions to the konjaku powder.[16]

TOXICOLOGY: Four cases of severe esophageal obstruction due to glucomannan diet tablets have been reported. [17,18] Seven additional cases were noted during 1984/85 by the Australian Adverse Drug Reactions Advisory Committee.[19] Glucomannan-containing tablets have been banned in Australia since May 1985 because these also carry the potential for inducing lower gastrointestinal obstruction. Encapsulated and powder forms remain available.

Glucomannan use is associated with a reduction in the need for hypoglycemic agents, and the product may result in a loss of glycemic control in diabetic patients. It should be used with great care by diabetic patients.

SUMMARY: Konjac mannan (glucomannan) has been shown to possess many of the pharmacologic characteristics of other polysaccharides. In large doses it has laxative activity and may alter the metabolism of microflora in the intestine. It should be used with care by diabetics, in whom its use may result in altered insulin or hypoglycemic requirements. Konjac mannan may be effective in reducing serum cholesterol levels in man and animals. There is conflicting evidence regarding its use as a weight-reduction aid though it does appear to alter lipid metabolism.

PATIENT INFORMATION— Glucomannan

Uses: Glucomannan reportedly alleviates constipation, reduces intestinal flora, lowers blood sugar and cholesterol and may possibly promote weight loss and inhibit cancer.

Side Effects: Severe esophageal and GI obstruction have been reported due to glucomannan tablets. The hypoglycemic effects are potentially dangerous to diabetics.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GLUCOMANNAN

GLUCOSAMINE

DATE OF ISSUE: SEP 2002

REPLACES MONOGRAPH DATED: NOV 1996

SCIENTIFIC NAME(S): 2-Amino-2-deoxyglucose

COMMON NAME(S): Chitosamine

BIOLOGY: Glucosamine is found in mucopolysaccharides, mucoproteins, and chitin. Chitin is found in yeasts, fungi, arthropods, and various marine invertebrates as a major component of the exoskeleton. It also occurs in other lower animals and members of the plant kingdom.[1]

CHEMISTRY: Chemically, chitin is a biopolymer that is cellulose-like but differs in that it is made up of predominantly unbranched chains of beta (1-4)-2-acetamido-2-deoxy-D-glucose or N-acetyl-D-glucosamine residues. Basically, it can be perceived as a cellulose derivative where the C-2 hydroxyl groups of the polymer have been replaced by acetamido moieties. Chitin is a normal component of shellfish such as crab, shrimp, and lobster.[2] Glucosamine is isolated from chitin and is chemically 2-amino-2-deoxyglucose.[3] It also can be prepared synthetically. Glucosamine sulfate is the preferred form. N-acetyl-D-glucosamine (NAG) also is sold but has no advantages over glucosamine, nor has the potential of NAG in a sustained-release formulation shown any greater benefit.[2,4,5]

PHARMACOLOGY: Chitin has been described as a vulnerary or wound-healing polymer,[3] while glucosamine has been referred to as a pharmaceutical aid, chondroprotective, antireactive,[6] and antiarthritic.[1] In osteoarthritis (the most common form of arthritis), there is a progressive degeneration of cartilage glycosaminoglycans (GAG). The idea of using glucosamine orally is to provide a "building block" for its regeneration. Glucosamine is the rate-limiting step in GAG biosynthesis. It is biochemically formed from the glycolytic intermediate fructose-6-phosphate by way of amination of glutamine as the donor, ultimately yielding glucosamine-6-phosphate. This is subsequently converted or acetylated to galactosamine before being incorporated into growing GAG. This will stimulate the production of cartilage components and bring about improvement of the articular conditions, thus leading to joint repair.[4,6] Glucosamine also has been reported to protect the articular cartilage from the damages exerted by some nonsteroidal anti-inflammatory agents (NSAIDs).[7]

Several double-blind studies indicate that glucosamine sulfate may be better than some NSAIDs and placebos in relieving pain and inflammation caused by osteoarthritis.[4,8,9,10,11] The efficacy and safety of IM glucosamine sulfate in osteoarthritis of the knee were studied in a randomized, placebo-controlled, double-blind study and revealed that the treatment was well tolerated and effective.[8] Two clinical studies of intra-articular glucosamine were conducted and resulted in reduced pain, increased angle of joint flexion, increased walking speed, and restored articular function compared with placebo.[9,12] The relative efficacy of ibuprofen and glucosamine sulfate was compared in the management of osteoarthritis of the knee.[13,14,15] This included 3 studies, 2 at 4 weeks and 1 at 8 weeks, that showed glucosamine (1.5 g/day orally) was more effective in reducing pain when compared with ibuprofen. Oral glucosamine sulfate therapy vs placebo in osteoarthritis was studied (80 patients, 1.5 g/day orally) and researchers found decreased symptoms and improved autonomous motility with glucosamine.[16] These investigators also employed electron microscopy studies on cartilage and found that patients who received placebo showed a typical picture of established osteoarthrosis while those given glucosamine showed a picture similar to healthy cartilage. They concluded that glucosamine tends to rebuild damaged cartilage, thus restoring articular function in most chronic arthrosic patients.[16]

Other studies on glucosamine show its pharmacokinetics in dogs and man (radiolabeled glucosamine was quickly and completely absorbed orally or by IV);[17] attempt to synthesize derivatives of glucosamine that have immunomodulating activity;[18] demonstrate the ability of glucosamine to inhibit the development of viral cytopathic effects and the production of infective viral particles,[19] and show the inhibitory effects of D-glucosamine on a carcinoma and protein, RNA, and DNA synthesis.[20]

The majority of these early studies were completed outside of North America. Two other studies, one in Canada and one in the United States, did not show any significant difference when glucosamine was compared with placebo in reducing pain in knee osteoarthritis.[21,22]

A Cochrane Systematic Review identified 16 randomized, controlled trials that demonstrated efficacy and safety of glucosamine in osteoarthritis. The formulation of glucosamine used was questioned as most trials used a formulation available in Europe.[23]

A meta-analysis compared 6 glucosamine trials that also concluded that glucosamine has a moderate effect on osteoarthritis. The formulation of glucosamine used was also questioned, along with the short duration of the trials, and potential publication bias.[24,25]

Glucosamine also can be found in combination with chondroitin sulfate with or without manganese. Two randomized, placebo-controlled trials have demonstrated these combinations' ability to relieve symptoms of knee osteoarthritis.[26,27]

A 3-year randomized, double-blind, placebo-controlled trial involving 139 patients over 50 years of age with primary, mild to moderate knee osteoarthritis compared 1500 mg/day of glucosamine to placebo. Symptom improvement was reported, as well as mild adverse events. There was no significant joint-space narrowing in patients who received glucosamine, demonstrating slowing of progression of osteoarthritis. This study excluded obese patients (in whom osteoarthritis is prevalent) and was conducted in Europe where glucosamine is a standardized prescription product. Extrapolation to products available in the United States cannot be made.[28,29]

Deficiencies of studies include short duration (4 to 8 weeks), exclusion of the severe forms of osteoarthritis, sponsorship by the glucosamine manufacturer, use of different formulations of glucosamine and different dosages, use of analgesics in some trials, and use of different outcome assessments of arthritis pain and mobility (ie, Lequesne Index and Western Ontario and McMaster Universities [WOMAC] questionnaire). Different patient populations were studied in various countries, making generalization to individual patients difficult.[11,14,21,22,23,25,28,30]

Controversy about glucosamine arose with the publication in 1997 of *The Arthritis Cure*. Subsequent response by *The Medical Letter on Drugs and Therapeutics* stated, "glucosamine appears to be safe and might be effective."[31]

A randomized, double-blind, placebo-controlled clinical efficacy study called the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) is recruiting patients (as of June 10, 2002) with osteoarthritis of the knee in the United States to determine effect on joint space and to definitively determine the efficacy and safety of glucosamine and chondroitin (alone and in combination) with a 2-year follow-up period. Additional information along with inclusion and exclusion criteria can be found at the clinical trials Web site, http://www.clinicaltrials.gov.[32]

TOXICOLOGY: No direct toxic effects of glucosamine could be found in the scientific literature; however, 1 report describes potential bronchopulmonary complications of antirheumatic drugs including glucosamine.[33]

The majority of side effects have been mild, including gastric discomfort (eg, heartburn, diarrhea, nausea, vomiting) and itching.[11,14,15,26] Occult blood in feces has been reported in patients taking glucosamine.[13]

Concern that glucosamine may increase blood glucose levels in patients with diabetes is the result of several animal and human studies.[34,35,36] Variability in results was reported because of different glucosamine doses used, from a significant 17% reduction to a marginal effect.[34,37] A study in 10 healthy patients found that an

infusion of glucosamine sulfate reduced glucose tolerance.[38] The exact mechanism of the effect of glucosamine on glucose levels has not been elucidated.[39] Until a definitive conclusion has been made, patients with diabetes and osteoarthritis are advised to inform their health care provider prior to starting glucosamine.[40,41]

SUMMARY: Glucosamine appears to be a safe and effective approach to the management of osteoarthritis.

The effective dosage has not been established.[42] From the results in clinical trials, symptom relief may not be evident until 2 weeks after starting glucosamine.[14]

Patients with diabetes and osteoarthritis are advised to inform their health care provider prior to starting glucosamine because of potential detrimental effects (eg, increase in blood glucose levels) of glucosamine on blood glucose control.

Glucosamine is sold as a dietary supplement. Quality and consistency may vary between brands. As alternative products are not regulated by the Food and Drug Administration (FDA), there is no guarantee the label is accurate. Patients should purchase glucosamine only from reputable sources.[5]

PATIENT INFORMATION— Glucosamine

Uses: Glucosamine is being investigated extensively as an antiarthritic in osteoarthritis.

Side effects: Well tolerated. No serious side effects have been associated directly with glucosamine. The potential of glucosamine to alter blood glucose levels warrants caution of use in diabetic patients. The majority of side effects have been mild, including gastric discomfort (eg, heartburn, diarrhea, nausea, vomiting) and itching.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GLUCOSAMINE

GOAT'S RUE

DATE OF ISSUE: DEC 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Galega officinalis* Fam: Leguminosae

COMMON NAME(S): Goat's rue, French lilac, Italian fitch

BOTANY: Originating in Europe and Asia, goat's rue thrives in temperate regions. The plant prefers damp, low-lying areas and sandy soil. Goat's rue is a perennial herb, growing to > 1 m in height. Its leaves are compound with lance-shaped ends, and the fruit consists of a round, indented pod containing many seeds. The flowers are white, lilac, light blue, or pinkish in color and grow on terminal spikes. These dried, above-ground parts, harvested during flowering season (summer), are the parts of the plant used medicinally. The plant has no scent unless bruised, when it emits a disagreeable odor, perhaps how the name "goat's rue" originated. Goat's rue should not be confused with "rue" (Ruta graveolens). [1,2,3,4,5,6]

HISTORY: Goat's rue has been employed as a vermifuge, to treat snakebites, and to aid in treating the plague. It was believed to have been used as a diuretic and tonic in typhoid conditions and also as a nervous system stimulant. [2,5,6] Culpepper suggested goat's rue as a soak for tired feet and for cheese making. [5] Hill's *Universal Herbal* (1832) mentions the dried flowers of goat's rue being added to boiling water as an infusion and then taken to induce sweating and aid in fevers. [5] The plant is widely cultivated as cattle feed. [2] Today, use of goat's rue is solely reserved for folk medicinal practices. [1]

CHEMISTRY: Guanidine derivatives are present in all parts of goat's rue and include galegine (isoamyl-eneguanidine) and hydroxygalegine. [1,2] Several older reports confirm the presence of galegine and related compounds. [7,8,9,10,11,12] A later study discusses the presence of several guanidine derivatives, including galegine and 4-hydroxygalegine flavones, and flavone glycosides. [13] Flavonol triglycosides kaempferol and quercetin derivatives have been found in the plant, [14] as have norterpenoid and sesquiterpenoid glycosides, including a rare dearabinosyl pneumonanthoside. [15] Vasicine and other quinazoline alkaloids have been confirmed in Galega species. [16] Other constituents, including peganine, various flavonoids, saponins, and tannins, are also present in goat's rue. [1,2,17,18]

PHARMACOLOGY: Galegine in goat's rue has been associated with marked reductions in blood sugar levels. Studies in the 1970s demonstrated galegine and other guanidine derivatives to reduce blood sugar levels. [2] Alcoholic extracts of goat's rue were shown to exhibit hypoglycemic effects in diabetic rabbits. [19] A report found galegin lowers blood sugar by 32% in diabetic rats. [20] Another study investigated a probable mechanism as to how fractions of the plant exert its hypoglycemic effects. It was concluded that inhibition of transport of glucose across monolayers of human intestinal cells takes place in a dose-dependent manner. [21] Another report compared the hypoglycemic actions of G. officinalis to others. [22] The chromium salt content may also possess antidiabetic effects. [1] A review evaluating several alternative therapies for diabetes found all reports encouraging as new possibilities in treatment but advises further examinations in this area before establishment of use. [23] Therefore, goat rue's role may be of some value as supportive treatment or in early stages of adult onset diabetes with a physician's guidance, but it may not be completely justified because of the severity of the disease and the availability of better alternatives. [2,3]

A reversible, marked weight-reducing effect of Galega was demonstrated in mice, regardless of food intake. Post-mortem examinations revealed a striking absence of body fat related to the plant. [24,25]

Goat's rue is also a well-known, useful diuretic. [2,3] Also, refer to the Herbal Diuretics monograph in the Appendix. Because of this characteristic, goat's rue may be considered useful for disturbances related to secretion of fluids, such as GI ailments (eg, fermentive dyspepsia, gastrocardiac syndrome, diarrhea). Goat's rue is said to stimulate the adrenal glands and pancreas and to aid in "glandular disturbances." None of these claims, however, are clinically documented. [3]

Goat's rue increases breast milk production. [2] Reports of the lactogenic effects of the plant exist. [26] Goat's rue given to cows would increase milk secretion from 35% to 50%. [5] Goat's rue is recommended in veterinary medicine to stimulate milk secretion. [1]

Goat's rue also is used as a tonic, liver-protectant, [3] and an inhibitor of platelet aggregation. [27,28]

INTERACTIONS: Possible interactions may exist with other hypoglycemic medications. [21]

Goat's rue may interfere with absorption of iron and other minerals. [29]

TOXICOLOGY: In humans, danger of intoxication has been observed with other guanidine derivatives. Most biguanidine preparations developed in the 1950s have been withdrawn from the market. [1] Use of goat's rue to treat diabetes should only proceed under professional supervision, as there is still uncertainty to its effectiveness. [2,3]

One text advises discontinuation of goat's rue preparation if symptoms such as headache, jitteriness, or weakness occur. The safety of the plant has not yet been proven in pregnancy or breastfeeding; therefore, caution is warranted with its use during these times. [29]

SUMMARY: The dried, above-ground parts of goat's rue have been used medicinally as far back as the 1800s to treat plague and typhoid, aid in sweating, and reduce fever. Animal studies demonstrate the plant as having hypoglycemic effects. Humans may receive some benefits in certain diabetic conditions, but further study is needed in this area to justify its use. Goat's rue is also a known diuretic and may benefit those affected by disturbances related to fluid secretion. The plant also possesses lactogenic effects and inhibits platelet aggregation.

PATIENT INFORMATION — Goat's Rue

Uses: Goat's rue derivatives have been associated with reductions in blood sugar levels, but more study is needed. Goat's rue is also a well-known diuretic and increases breast milk production. Other effects include use as a tonic, liver-protectant, and as a platelet aggregation inhibitor.

Interactions: Possible interactions may exist with other hypoglycemic medications. Goat's rue may interfere with absorption of iron and other minerals.

Side Effects: Discontinue use if symptoms such as headache, jitteriness, or weakness occur. The safety of the plant has not been proven in pregnancy or breastfeeding. Goat's rue may interfere with the absorption of iron and other minerals.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GOAT'S RUE

GOLDENSEAL

DATE OF ISSUE: FEB 2000

REPLACES MONOGRAPH DATED: MAY 1994

SCIENTIFIC NAME(S): *Hydrastis canadensis* L. Family: Ranunculaceae

COMMON NAME(S): Goldenseal, yellowroot, orangeroot, eyebalm, eyeroot, goldenroot, ground raspberry, Indian turmeric, yellow puccoon, jaundice root, sceau d'or

BOTANY: Goldenseal is a perennial herb found in the rich woods of the Ohio River valley and other locations in the northeastern US. The single, green-white flower, which has no petals, appears in the spring on a hairy stem above a basal leaf and 2 palmate, wrinkled leaves. The flower develops into a red seeded berry. The plant grows from horizontal, bright yellow rhizomes, which have a twisted, knotty appearance.

HISTORY: Goldenseal root was used medicinally by American Indians of the Cherokee, Catawba, Iroquois, and Kickapoo tribes as an insect repellent, a diuretic, a stimulant, and a wash for sore or inflamed eyes.[1] It was used to treat arrow wounds and ulcers,[2] as well as to produce a yellow dye. Early settlers learned of these uses from the Indians and the root found its way into most 19th century pharmacopeias. The Eclectic medical movement was particularly enthusiastic in its adoption of goldenseal for gonorrhea and urinary tract infections. The widespread harvesting of *Hydrastis* in the 19th century, coupled with loss of habitat, resulted in depletion of wild populations. In 1997, *Hydrastis* was listed under Appendix ?? of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), which controls exports of the root to other countries. The final listing included roots or live plants but excluded finished products. As an alternative to wild harvesting, goldenseal was cultivated in the Skagit Valley of Washington state and is being promoted as a cash crop in New York, North Carolina, [3] and Canada. Because of its high price, goldenseal, like other expensive herbs, has often been adulterated. Common adulterants include species of *Coptis* and *Xanthorrhiza*,[4] both of which also contain large amounts of the yellow alkaloid berberine. The popular notion that goldenseal can be used to affect the outcome of urinalysis for illicit drugs evolved from the novel *Stringtown on the Pike*by pharmacist John Uri Lloyd, in which goldenseal bitters are mistaken for strychnine in a simple alkaloid test by an expert witness in a murder trial.[5] Goldenseal can be variously ingested prior to testing or added to the urine sample after collection. It is one of several adulterants commonly detected in urinalysis samples.[6]

CHEMISTRY: The isoquinoline alkaloids hydrastine (4%), berberine (up to 6%), and canadine are present in goldenseal root and are viewed as the principle bioactive components.[7] Other minor alkaloids such as canadaline.[8] and canadinic acid[9] have been isolated. Quinic acid esters were elucidated.[10] Quantitation of the alkaloids has been accomplished in a variety of ways including spectrophotometry,[11] thin-layer chromatography,[12] ion-pair dye colorimetry,[13] high-performance liquid chromatography (HPLC),[14] capillary electrophoresis,[15] and CE-mass spectrometry.[16]

PHARMACOLOGY: While berberine is widely distributed in plants, hydrastine is characteristic of goldenseal root and is considered to be the most important bioactive alkaloid. There is extensive pharmacologic literature on hydrastine and berberine. The alkaloids are poorly absorbed when taken orally, so studies of parenterally administered goldenseal alkaloids must be interpreted with care. Goldenseal alkaloids have modest antimicrobial activity, which may be relevant when applied topically. Berberine, canadine, and canadaline had disinfectant activity against 6 strains of bacteria, while hydrastine was inactive. [17] Berberine sulfate was bactericidal against *Vibrio cholerae*but bacteriostatic to *Staphylococcus aureus*.[18] Berberine sulfate has been shown to block adherence of *Streptococcus pyogenes* to epithelial cells, which may be a reasonable mode of action for topical antimicrobial use. [19] Berberine has been identified as the active component of Hydrastis in an antitubercular assay,[10] while hydrastine and other isolated compounds had no activity. Berberine has been reported to inhibit uptake of glucose by cancer cells, [20] and to inhibit tumor promotion by phorbol esters in a mouse skin carcinogenesis model. [21] Berberine showed weak activity in an antioxidant model.[22] Palmery investigated the inhibitory activity of *Hydrastis* alkaloids on isolated rabbit aorta stimulated by epinephrine, finding a weak synergistic effect for berberine, canadine, and canadaline, but no activity in hydrastine.[23] In isolated guinea pig ileum preparations, the same group found that berberine, canadine, and canadaline evoked contractions, while hydrastine again was inactive.[24] A third study found a relaxant effect of berberine on rabbit prostate strips stimulated by norepinephrine or phenylephrine;[25] however, an adrenergic mechanism was considered unlikely. While hydrastine is closely related to the convulsant isoquinoline alkaloid bicuculline, hydrastine had no activity in a GABA-receptor binding assay at high concentrations. [26]

Very high doses of goldenseal may rarely induce nausea, anxiety, depression, seizures, or paralysis. Hydrastine was once used as a uterine hemostatic, [7] but was found inferior to ergot in the treatment of postpartum hemorrhage. Goldenseal is generally contraindicated for use in pregnancy. Because of hypertensive actions of the alkaloids, it is also contraindicated in cardiovascular patients.

SUMMARY: A *Hydrastis* monograph is under preparation by the American Herbal Pharmacopeia. *Hydrastis*was official in the US Pharmacopeia from 1860 to 1926, and in the National Formulary from 1936 to 1955.

Goldenseal's popularity is out of proportion to its scientifically documented worth. It may be of use in topical infections and is still used as an eyewash. While contraindicated in pregnancy and hypertension, adverse effects to usual doses are rare.

PATIENT INFORMATION— Goldenseal

Uses: Goldenseal may be of use in topical infections and is used as an eyewash. Goldenseal has been included in cold and flu preparations for its anticatarrhal effects but little evidence supports this use and its effects are debatable.

Side Effects: Goldenseal is contraindicated in pregnancy and hypertension; adverse effects to usual doses are rare.

Dosing: Goldenseal has not been the subject of any formal clinical trials for external antiseptic or antiherpes properties. Extracts standardized to 5% hydrastine are available; however, the berberine content may be more important for goldenseal's medicinal uses. Doses of 100 mg hydrastine and 2 g crude root have been proposed.[27]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GOLDENSEAL

GOSSYPOL

DATE OF ISSUE: NOV 1994

REPLACES MONOGRAPH DATED: DEC 1989

SCIENTIFIC NAME(S): Gossypol is commonly derived from members of the family Malvaceae. Cotton (*Gossypium* spp.) represents the most common source.

HISTORY: Gossypol was first identified as an antifertility agent as a result of epidemiologic studies conducted in China during the 1950s. Investigators had been puzzled by the extremely low birth rates in a particular geographic region. The men had very low sperm counts and many women had amenorrhea. Eventually the phenomenon was related to the exclusive use of crude cottonseed oil for cooking. Further investigation revealed that the antifertility component was gossypol, a potentially toxic phenolic pigment found in the seed, stem and root of the cotton plant. [1]

CHEMISTRY: Gossypol is a natural product that can be made synthetically [2] or produced inexpensively on a very large scale by the extraction of cottonseed. Estimates have placed US gossypol production at more than 50,000 tons per year, all as a by-product of cottonseed oil production. [3] Cotton represents perhaps the most well-known source of this compound. The seeds of species of *Gossypium* vary widely in their gossypol content with levels ranging from 0.13% to 6.6%. [2]

PHARMACOLOGY: Gossypol has been shown to be an active antifertility agent in male hamsters and rats. [4] Large-scale clinical trials in men by Chinese investigators have found gossypol to be orally active and relatively safe and effective. Gossypol is a nonsteroidal compound that acts by inhibiting sperm production and motility in a variety of male animal species and humans. It does not affect sex hormone levels or libido, and its mechanism is somewhat distinct from that of steroidal oral contraceptives used by women.

Gossypol exerts its contraceptive action by inhibiting an enzyme that plays a crucial role in energy metabolism in sperm and spermatogenic cells. The target enzyme, lactate dehydrogenase X, is found only in sperm and male gonadal cells. It is involved in glycolysis and plays a role in inducing mitochondria to produce energy. A variety of lactate dehydrogenases are found throughout the body and gossypol exerts a degree of inhibition on many of these. However, the drug exhibits its greatest inhibitory effect on lactate dehydrogenase X.

Sperm recovered from the epididymis of rats and hamsters treated with gossypol for as little as 6 weeks were immotile with detached heads or tails. [5] Gossypol does not demonstrate estrogenic or androgenic activity but does potentiate the androgenicity of methyltestosterone. [6]

Male contraception: The clinical testing of gossypol began in the early 1970s in China, and to date the drug has been studied extensively in thousands of men. The usual daily dose is 20 mg until the sperm count is reduced below 4 million/ml; this usually requires 2 to 3 months of treatment. Maintenance doses of 75 to 100 mg are subsequently taken twice a month. A proposed contraceptive dose is 3 g/man/year.

Wu[7] published a comprehensive review of the clinical trials of gossypol. Clinical trials have found the drug's antifertility effect to be more than 99%. Sperm counts usually return to normal within 3 months after termination of therapy, and men treated with gossypol have fathered normal children. However, long-term follow-up studies indicate that inhibition of spermatogenesis may continue following discontinuation in up to 20% of men after 2 years. Spermatogenesis does not return to normal in some men. Concerns regarding the lack of predictable reversible effects have delayed the further clinical development of gossypol in western countries.

Female contraception: Although gossypol is generally considered to be a male antifertility agent, it is effective when given to female animals. The intramuscular injection of gossypol to female rats inhibited implantation and the maintenance of normal pregnancy, most likely by affecting luteinizing hormone levels. [8] Gossypol is also an inhibitor of platelet activating factor and leukotrienes. [9]

Gossypol has also shown effects that suggest some inhibition of ovarian function and cytotoxicity in endometrial cells. [10]

Gossypol has been evaluated as a topical spermicide. Solutions of gossypol or gossypol acetate do not decrease sperm motility. However, a solution of gossypol-PVP coprecipitate completely immobilized all spermatozoa within 3 minutes at a concentration of 5 mg/ml and within 20 seconds at 40 mg/ml. The spermicidal activity of gossypol was found to be equal to or greater than that of the commercially available creams *Delfin*and *Preceptin* and *Encare Oval*vaginal suppositories.[11] A gelatin coprecipitate of gossypol is an effective spermicide in monkeys. [12] A gossypol-containing gel decreased the number and rapidly immobilized sperm when tested in healthy women.[13] The topical use of gossypol has been recommended because it has low systemic toxicity, it acts in micromolar concentrations and is effective in the presence of cervical mucus.[14]

Other clinical uses: Gossypol has been investigated for the treatment of uterine myoma, endometriosis and dysfunctional uterine bleeding. Gossypol and its derivatives are active against the HIV virus [15] and the herpes simplex virus type 2.[16] A trial is now under way to evaluate the therapeutic efficacy of gossypol for the treatment of metastatic carcinoma of the endometrium or ovary, and as an antiviral and interferon inducer in patients with AIDS. [7]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Commercial cotton seed oil is processed in order to remove its gossypol content.

A low incidence of side effects was originally reported in men treated with gossypol. Some men develop a transient weakness during the first days of administration and this appears to be related to hypokalemia induced by gossypol. This may be caused by renal loss of potassium during therapy and can be managed effectively with oral potassium supplementation. Some men notice changes in appetite. Gossypol also inhibits malate dehydrogenase in animals and glutathione-S-transferase in both animals and man. This latter enzyme is involved in the detoxification of potentially toxic and carcinogenic compounds. At high doses (100 to 700 times the contraceptive dose) gossypol may cause diarrhea, hair discoloration, malnutrition, circulatory problems and heart failure. The compound has not been found to be mutagenic when tested in the Ames salmonella microsome test,[17] but questions still remain about is genotoxic characteristics. [18]

The results of more recent well-controlled studies found that the incidence of adverse events was significantly high as to warrant abandoning the development of gossypol as a male contraceptive.[19]

Gossypol is found in two isomeric forms. Only (-) gossypol shows antispermatogenic effects in animals; the (+) form appears to be associated with hypokalemia. Therefore, administration of a purified (-) form may provide efficacy while reducing certain side effects.

Gossypol toxicity is a potential veterinary problem and as little as 200 ppm of free gossypol could kill a calf. [18] Non-ruminant animals are more sensitive to the toxic effects of gossypol than ruminants.[21]

SUMMARY: Gossypol is a toxic component contained in cottonseed. This compound has been shown to be an orally effective male contraceptive. Although it has been used widely in China, its development has not been pursued in the West primarily because its inhibitory effects on spermatogenesis are not predictably reversible. A reduction in dosage may be associated with a lower incidence of permanent sterility. The drug is effective when used as a topical spermicidal cream or gel.

PATIENT INFORMATION — Gossypol

Uses: Gossypol acts as a male and female contraceptive. It may be a treatment for certain gynecological problems and viral infections.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: It is potentially toxic. Contraceptive effects may not be reversible.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GOSSYPOL

GOTU KOLA

DATE OF ISSUE: AUG 1996

REPLACES MONOGRAPH DATED: DEC 1988

SCIENTIFIC NAME(S): *Centella asiatica* (L.) Urb. Also: *Hydrocotyle asiatica* Family: Umbelliferae (Apiaceae).

COMMON NAME(S): Gotu kola, hydrocotyle, Indian pennywort, talepetrako

BOTANY: *Centella asiatica* is a slender, creeping plant that grows commonly in swampy areas of India, Sri Lanka, Madagascar, South Africa and the tropics.

HISTORY: Gotu kola has been widely used to treat a variety of illnesses, particularly in traditional Eastern medicine. Sri Lankans noticed that elephants, renowned for their longevity, munched on the leaves of the plant. Thus the leaves became known as a promoter of long life, with a suggested "dosage" of a few leaves each day. Among the ailments purported to be cured or controlled by gotu kola are mental problems, high blood pressure, abscesses, rheumatism, fever, ulcers, leprosy, skin eruptions, nervous disorders and jaundice. Gotu kola has been touted as an aphrodisiac. Gotu kola should not be confused with the dried seed of *Cola nitide* (Vent.) (also known as kolanuts, kola or cola), the plant used in cola beverages. *Cola nitida* contains caffeine and is a stimulant, while gotu kola has no caffeine and has sedative properties.[1]

CHEMISTRY: Extracts of gotu kola contain the active principle madecassol, as well as asiatic acid and the glycoside asiaticoside. [2] Also present is isothankuniside. This compound has been used to derive another substance called BK compound (methyl 5-hydroxy-3,6-dioxo-23 (or 24)-nor-urs-12-ene-28-oate). [3] Below-ground parts of *C. asiatica* have been found to contain small amounts of at least 14 different polyacetylenes. The molecular structures of five of these have been determined: (1) 2,9-pentadecadiene-4,6-diyn-1-ol, acetate; (2) pentadeca-1,9-diene-4,6-diyne-3,8-diol, 8-monoacetate; (3) pentadeca-1,9-diene-4,6-diyne-3,8 diol, diacetate; (4) pentadeca-1,8-diene-4,6-diyne-3,10-diol, 10-monoacetate and (5) pentadeca (1,8)-diene-4,6-diyne-3,10-diol. Nine other polyacetylenes have been partially characterized.[4]

A recent phytochemical of *C. asiatica* revealed the presence of amino acids, flavonols, fatty acids, alkaloids, sterols, saccharides and inorganic salts. The bio-stimulant activity is attributed to asiaticoside, asiatic acid and madecassic acid. [5] A study of powdered gotu kola by microscopic and chemical identification methods has also recently been done.[6]

PHARMACOLOGY

Wound healing: *C. asiatica* extracts have been found to promote wound healing.[7] Cell culture experiments have shown that the total triterpenoid fraction of the extracts, at a concentration of 25 mcg/ml does not affect cell proliferation, total cell protein synthesis or the biosynthesis of proteoglycans in human skin fibroblasts. However, the fraction does significantly increase the collagen content of cell layer fibronectin, which may explain the action in wound healing. [8] The glycoside madecassoside has anti-inflammatory properties, while asiaticoside appears to stimulate wound healing. Experiments with rats showed that wounds heal by a process involving a dilation phase followed by a contraction phase. These phases were prolonged in rats undergoing repeated experimental wounding. Titrated extract of *C. asiatica* (TECA, 100 mg/kg), however, accelerated healing time.[7] A study employing rats and mice found that topically applied TECA rapidly penetrated to subcutaneous tissues and abdominal muscle in high concentrations, and had a greater effect on wound healing than oral administration. Asiatic acid was absorbed later than madecassic acid. The topical preparations of TECA were also able to penetrate to the plasma and deeper tissues. [9]

Other Topical Uses: TECA has been used as a scarring agent to stimulate wound healing in patients with chronic lesions such as cutaneous ulcers, surgical wounds, fistulas and gynecologic lesions. A clinical study evaluated TECA for treating bladder lesions in 102 patients with biharzial infections. Injections of TECA 2%, usually administered intramuscularly, for 1 to 3 months, produced cure or improvement in 75% of the cases, as determined from symptoms, urinary findings and cystoscopic findings. Healing occurred with little scar formation, thus avoiding much of the loss of bladder capacity that can result from biharzial infections. [10]

C. asiatica has also shown promise in treatment of psoriasis. When creams containing oil and water extracts of the leaves were administered each morning to seven psoriatic patients, five showed complete clearance of lesions within 3 to 7 weeks. One patient showed clearance of most lesions, and one showed improvement without clearance. One patient experienced a mild recurrence 4 months after treatment. Although this study was not controlled, a placebo effect was considered unlikely. Experience indicated that the creams were nontoxic and cosmetically acceptable, making them suitable for long-term use. [1]

Antifertility Effects: Crude extract of *C. asiatica* isothankuniside and BK compound were all found capable of significantly reducing the fertility of female Swiss albino mice when administered orally. The effective dosages were 20 to 80 mg of whole plant/kg body weight for the crude extract, 40 to 120 mg/kg for isothankuniside, and 5 mg/kg for BK compound. BK compound thus had the strongest effect.[3] Because this was only a preliminary screening study, the mechanism for this effect was not investigated.

Antihypertensive Effects: The efficacy of Centellase from *C. asiatica* in the treatment of venous hypertension has been evaluated, using a combined microcirculatory model.[11] The researchers conducted a single blind, placebo controlled randomized study of the effects of the total triterpenoid fraction (Centellase) in 89 patients with venous hypertension microangiopathy. The effects of Centellase were found significantly different from placebo in hypotensive activity on all the microcirculatory parameters investigated. No side effects were noted.

Varicose Veins: The effects of gotu kola extract on mucopolysaccharide metabolism were noted in subjects with varicose veins.[12] The total triterpenic fraction of the plant (60 mg/day for 3 months) elevated the basal levels of uronic acids and of lysosomal enzymes, indicating an increased mucopolysaccharide turnover in varicose vein patients. These results confirm the regulatory properties of *C. asiatica* extract on the metabolism in the connective tissue of the vascular wall.

Anticancer Effect: Perhaps the most interesting recent study on gotu kola is the finding that Centella is effective in destroying cultured cancer tumor cells. [13] The extract, a 5:1 concentrate extracted with methanol, was effective at a level of 100 mcg/ml. In addition, practically no toxic effects were detected in normal human lymphocytes.

Miscellaneous Effects: A French preliminary study showed TECA to produce histologic improvement in 5 of 12 patients with chronic hepatic disorders. [14]

A double-blind, placebo controlled study of 94 patients with venous insufficiency of the lower limbs indicated that TECA produced clinical improvement in this condition. The patients received 12 or 60 mg/day for 8 weeks. Improvement occurred in the subjective measures of the sensation of heaviness and pain in the legs, edema and overall patient assessment of efficacy, and in the objective measure of vein distensibility. The researchers concluded that TECA stimulated collagen synthesis in the vein wall, thus increasing vein tonicity and reducing the capacity of the vein to distend. In contrast, patients receiving placebo exhibited an increase in vein distensibility. Although there were no statistically significant differences between the two TECA dosage groups, data trends suggested that the effect of TECA was dose-related.[15]

The pharmacokinetics of the total triterpenic fraction of gotu kola have been studied, after single and multiple administrations to healthy volunteers. [16] Using a new HPLC procedure for detection of asiatic acid, the researchers found that after chronic treatment of two doses, the peak plasma concentration, AUC (area under the curve) and half-life were significantly higher than those observed after the corresponding single dose administration.

TOXICOLOGY: Preparations of *C. asiatica* have a reputation for having a relative lack of toxicity. However, contact dermatitis has been reported in some patients using preparations of fresh or dried parts of the plant. [2] This is not surprising in light of the topical irritant qualities of certain components of the plant. In the cited study of biharzial patients, some who received subcutaneous injections rather than intramuscular injections experienced pain at the injection site, and there was blackish discoloration of the subcutaneous tissues. These side effects may have been diminished with intramuscular injections. [10]

Relatively large doses of extract have been found to be sedative in small animals; this property is attributed to the presence of two saponin glycosides, brahmoside and brahminoside.

SUMMARY: Gotu kola is a plant widely used in traditional Eastern medicine and other forms of herbal therapy. Its most important pharmacologic effect appears to be the promotion of wound healing, particularly in chronic lesions. There is evidence to support the folk medicine use of gotu kola to promote wound healing and as an antifertility agent. Plant extracts appear to be of a low order of toxicity, although hypersensitivity reactions may occur in some people. Recent studies show that gotu kola has selective toxicity against tumor cells in vitro.

PATIENT INFORMATION — Gotu Kola

Uses: Traditionally used as treatment for a variety of ills and as aphrodisiac, gotu kola has demonstrated some efficacy treating wounds and varicose veins and destroying cancer cells in lab research. Evidence suggests is has antifertility, hypotensive and sedative effects.

Side Effects: Gotu kola causes contact dermatitis in some individuals.

Dosing: Doses of gotu kola in crude form range from 1.5 to 4 g/day. Various extracts standardized to asiaticoside content also are available and have been studied in clinical trials in venous insufficiency and wound healing at extract doses of 30 to 90 mg/day. Wound-healing studies have involved topical application of an ointment containing the extract.[17]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GOTU KOLA

GRAPE JUICE, PURPLE

DATE OF ISSUE: APR 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Vitis vinifera*, *V. labrusca*, *V. rotundifera*

COMMON NAME(S): European or "Old World" grapes (most common; 95% of grapes) (*V. vinifera*); American bunch grapes (*V. labrusca*); muscadine grapes (*V. rotundifera*)

BOTANY: Grapes grow in bunches (from 6 to 300) on woody, climbing vines. These fruits come in a variety of colors, including black, blue, golden, green, red, white, and purple. Certain flavonoids present in the purple grape varieties possess beneficial actions not seen in the others (see Wine monograph). *V. vinifera* is a deciduous climber with several stems, tendrils, clusters of pale, green flowers, and palm-shaped leaves. In addition to the kinds of grapes listed above, hybrid varieties of grapes (French hybrids) exist that were developed mainly in France for wine making. Grapes are native to southern Europe and western Asia but are cultivated in warm temperate regions throughout the world.[1,2] Grape juice is the fluid expressed from ripened grapes. They are passed through a separator, which removes the skins, stems, seeds, and pulp. The juice then is treated and pasteurized.[1]

HISTORY: Grape leaves have been seen in fossils dating back to prehistoric times. Grapes were domesticated in western Asia before 5000 BC and have been mentioned in Biblical writings and depicted in tomb paintings dating back to 2375 BC. Circa 1635, Jesuit fathers brought Spanish grapes to Mexico, establishing vineyards in what is now Socorro, New Mexico, the area of the earliest planting of grapes in the United States.[1] In 1652, Nicholas Culpeper recommended grapes as a mouthwash.[2] In the 1850s, California became involved in grape culture.[1] In 1927, physician A.M. Liebstein mentioned grapes as being beneficial for dyspeptic and febrile conditions, liver and kidney ailments, tuberculosis, hemorrhoids, varicose veins, osteomyelitis, gangrene, and cancer. *The Grape Cure* (1928, Johanna Brandt) claimed that grapes had cured the author's abdominal cancer.[3] Modern scientific studies demonstrate a variety of beneficial effects from grapes.

CHEMISTRY: Grapes are ~ 80% water and contain 70 calories/100 g. The sugar (carbohydrate) content is ~ 16%.[1] Commercial grape juice is lower in sucrose than other fruit juices.[4] Other sugars, amino acids, and organic acids in grape juice and wines have been detected.[5] The amino acid arginine has been separated from grape juice.[6] Grapes contain tartaric and carboxylic acids, including malic, citric, lactic, succinic, and shikimic acids.[2,7] Vitamins A, B_1, B_2, and C also are present in grapes, as are minerals including chromium and potassium.[1,2] Anthocyanins are found in grapes with red pigments,[2] as well as in other pigmented fruits such as the blackberry, strawberry, and blueberry.[8] A review discussing anthocyanins in grapes, juices, and wines is available.[9] Flavonoids including quercetin, catechins, myricetin, and kaempferol are the more important constituents in purple grape juice and red wine.[10] Catechin concentrations are substantial in red wine (27 to 96 mg/L) but low to negligible in white wine and commercially available grape juices tested in another report.[11] Other constituents found in grapes include tannins, inositol, choline, and pectin.[2] Glutathione and thiol-containing compounds have been found in the juice.[12] Isomers of resveratrol in grape juice and wine also are present,[13] as are antioxidants.[14]

PHARMACOLOGY: In general, grapes are nourishing and mildly laxative, offering support in the GI tract and liver. Red grape leaves are known to be astringent and anti-inflammatory. Red leaves and grapes are used in the treatment of varicose veins, hemorrhoids, and capillary fragility.[2] Grape juice is high in chromium, a mineral that is part of the glucose tolerance factor, which works with insulin to promote utilization of sugar.[1]

Grape juice possesses marked antiviral properties in vitro against such viruses as poliovirus and herpes simplex virus. Tannins may be responsible for these effects. Studies also have demonstrated grape juice as being antibacterial, drastically reducing tooth decay in animals. The caffeic acid constituent prevents cancer in animals. Raisins are linked to lower rates of cancer deaths in elderly patients.[3]

Attention has focused on purple grape juice and its beneficial effects in heart health. Certain flavonoids in purple grape juice and red wines may be responsible for keeping heart-damaging blood clots from forming. Aspirin is used for this purpose as well, but its effects against platelet aggregation are negated by adrenaline, which is released under stressful situations. Flavonoids are not affected by adrenaline, and thus are still available to prevent clot formation.[15] An older report demonstrates anti-platelet aggregation and thrombin production to be reduced by grape juice and red wine. However, the study suggests that the ethanol contained in the wine is the dominant anti-aggregatory component because of its greater ability to prevent platelet aggregation as compared with grape juice.[16] In a randomized, crossover study involving 10 patients, purple grape juice consumption for 1 week reduced the whole blood platelet aggregation response by 77% vs orange and grapefruit juices, confirming purple grape juice's effects in decreasing risk of coronary thrombosis and MI because of increased polyphenolic concentration present (~ 3 times more than the other juices).[17] Another report in 15 coronary artery disease (CAD) patients concluded that short-term ingestion of purple grape juice improved endothelium-dependent vasodilation and prevented LDL oxidation, reducing negative cardiovascular outcomes. This was shown to be caused by flavonoid components present.[10] Compared with controls, 14 patients with CAD, consuming 7 to 10 mL/kg/day of purple grape juice for 14 days, demonstrated increased lag time measurements, which determine cholesterol oxidation time. (The longer the lag time, the slower the onset of oxidation.) It was concluded that this delay in oxidation of LDL cholesterol is beneficial because it is usually a key contributor to the development of atherosclerosis. Pure grape juice's ability to slow onset of oxidation, reduce platelet activity, and increase nitric oxide production collectively may contribute to healthy cardiovascular function.[18]

TOXICOLOGY: None documented.

SUMMARY: Grapes date back further than 5000 BC. Flavonoids present in purple grape juice exert beneficial cardiac effects by reducing platelet aggregation, slowing onset of oxidation of LDL cholesterol, and improving endothelium-dependent vasodilation. Grape juice also has been shown to have antiviral and antibacterial effects, and may be linked to reduction of certain cancers.

PATIENT INFORMATION— Grape Juice, Purple

Uses: Flavonoids in purple grape juice possess beneficial cardiac effects. Grape juice also has antiviral and antibacterial effects and is mildly laxative.

Side Effects: No side effects have been reported with purple grape juice.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GRAPE JUICE, PURPLE

GRAPE SEED

DATE OF ISSUE: AUG 2002

REPLACES MONOGRAPH DATED: SEP 1995

SCIENTIFIC NAME(S): *Vitis vinifera* L. and *V. coignetiae* Pulliat. Family: Vitaceae

COMMON NAME(S): Grape seed, muskat, Procyanidolic oligomers (PCO), Proanthocyanidin, Oligomeric procyanidolic complexes (OPC) [1,2,3]

HISTORY: Both grape seed and pine bark contain PCO. PCO extracts have been marketed in France for decades as treatment for venous and capillary disorders (eg, retinopathies, venous insufficiency, vascular fragility). [1]

Red grape seeds are generally obtained as a by-product of wine production. When ground, these seeds become the source of grape seed oil. Red wine contains PCO, and when used in association with a nonatherogenic diet, may reduce the incidence of cardiovascular disease. [1,3,4]

CHEMISTRY: The highest concentration of proanthocyanidins is found in the skin or membrane of the grape seed. [3,4] Proanthocyanidin is part of a group of naturally occuring plant compounds called bioflavonoids. [3] The most active proanthocyanidins are those bound to other proanthocyanidins: mixtures of proanthocyanidin dimers, trimers, tetramers, and larger molecules such as PCO. [4,5,6]

Grape seed oil contains nutritionally useful essential fatty acids and tocopherols (vitamin E). [7] The methanol extract of the Oriental species (*V. coignetiae*) contains epsilon-viniferin, oligostilbenes, ampelopsins A, C, F, and the mixture of vitisin A and cis-vitisin A. [8] Dietary grape seed tannins and procyanidins (polyphenol oligomers) are reported.[9,10] 5´-Nucleotidase inhibitors designated as NPF-88BU-lA and NPF-88BU-lB (all polyphenolic compounds), respectively, have been isolated from the seeds and skin of the wine grape.[11]

PHARMACOLOGY: Most trials with grape seed extract are animal studies demonstrating mostly antioxidant, cytoprotective, and vascular effects. The majority of trials in humans study the uses of grape seed extract as an antioxidant and for various venous and capillary disorders.

Microvascular injury: Scavenging by procyanidins from *V. vinifera* seeds of reactive oxygen species involved in the onset and the maintenance of microvascular injury has been studied.[10] It was reported that procyanidins have a remarkable dose-dependent antilipoperoxidant activity. They also inhibit xanthine oxidase activity (the enzyme that triggers the oxy radical cascade). In addition, procyanidins non-competitively inhibit the proteolytic enzymes of collagenase and elastase and the glycosidases of hyaluronidase and beta-glucuronidase. These are involved in the turnover of the main structural components of the extravascular matrix collagen, elastin, and hyaluronic acid. [10]

Antioxidant effects: The antioxidant effects of grape seed proanthocyanidin extract (GSPE is an admixture of proanthocyanidins dimer, trimer, and tetramer: 54%,13%, and 6.8%) on the generation of nitric oxide in rat primary glial cell cultures have been investigated. [12] The data indicated that GSPE may exert its antioxidant and cytoprotective effect in rat glial cultures by preserving the basal glutathione status during increased nitric oxide generation. Therefore, the authors conclude that GSPE may be utilized under such pathological conditions. [12]

The antioxidant activity of a grape seed extract (300 mg of grape procyanidin extracts in 2 capsules) was investigated in a single-blinded, randomized, placebo-controlled crossover study of 20 young volunteers. Subjects were given 2 capsules or placebo for 5 days. Blood samples were taken at baseline and at the end of the study and then assayed for antioxidant activity as well as vitamin C and E levels. The study was repeated with a second treatment after a washout period of 2 weeks. On day 5, the authors concluded that the extract did not affect serum vitamin C and E levels, but serum total antioxidant activity was statistically significant ($P < 0.01$).[13]

Nutrition: The effects of dietary grape seed tannins on nutritional balance and on some enzymatic activities along the crypt-villus axis of rat small intestine have been studied.[9] This study did not reveal a significant tannin toxicity, except for a reduced dry matter and nitrogen digestibility. However, the tannins directly interfere with mucosal proteins, stimulating the cell renewal.[9] Another study involved a 1-year investigation in rats to determine if age-related insulin resistance could be overcome through the use of natural products (ie, included grape seed extract). [14] Although a combination of agents was used in the study, the authors concluded that the activity of the antioxidant supplements (eg, chromium polynicotinate, grape seed extract, zinc monomethionine) markedly lowered systolic blood pressure in normotensive rats, lowered HbA_{1c}, and reduced lipid peroxidation. [14]

The wine grape seeds can be used as health oils because of their high content of essential fatty acids and tocopherols. [7] A methanol extract of the Oriental medicinal plant *V. coignetiae* exhibited protective effects for liver cells in the in vitro assay method using primary cultured rat hepatocytes. Activity-guided fractionation of this extract produced epsilon-viniferin as an active principle. It also exhibited protection against carbon tetrachloride-induced hepatic injury in mice, shown by serum enzyme assay and pathological examination. Ampelopsin C and the mixture of vitisin A and cis-vitisin A were found to be strong hepatotoxins. [8] One study concluded that GSPE may offer a cytoprotective role in acetaminophen-induced hepatic DNA damage and apoptotic and necrotic cell death of liver cells. [15]

Capillary disorders: The effect of grape seed extract on capillary resistance disorders was studied in hypertensive and diabetic patients. Overall, results were obtained in an open trial of 28 patients and during a double-blind vs placebo-controlled trial of 25 patients. Patients received 150 mg/day of grape seed extract (ie, *Endotelon*). The drug was well tolerated in both groups and capillary resistance improved significantly ($P < 0.0005$ and $P < 0.005$).[16]

Miscellaneous: Other studies have shown that polyphenolic substances from the seeds and skin of the wine grapes ("Koshu") can strongly inhibit 5´-nucleotidase activities from snake venom and rat liver membrane; have significant therapeutic activity in Ehrlich ascites carcinoma; have inhibitory action against the growth of *Streptococcus mutans*, a carcinogenic bacteria; and inhibit glucan formation from sucrose.[11] The latter 2 actions may indicate that these principles can aid in the prevention of dental caries. Grape seed oil has been shown to be a safe and efficient hand-cleansing agent. [17]

TOXICOLOGY: No human toxicity has been reported for the grape seed, its oil, or its isolated constituents, except for hepatotoxicity in mice. [8] Scientific evidence for the use of grape seed extract during pregnancy also is unknown. Grape seed is contraindicated in patients with known hypersensitivity.

SUMMARY: The majority of trials in humans focus on the antioxidant activity of grape seed extract as well as its usefulness in the treatment of venous and capillary disorders. Grape seed oil appears to be safe and potentially useful as a dietary source of essential fatty acids and tocopherols. Some compounds from *V. coignetiae* show hepatoprotective activity while others exhibit hepatotoxic effects. Seed tannins directly interfere with mucosal proteins, thereby stimulating cell renewal. Procyanidins from the seeds may have the ability to maintain the microvascular system and the main structural components of the skin. Polyphenolic derivatives in the seeds and skin have anti-enzyme properties and therapeutic potential against Ehrlich ascites carcinoma. In addition, these substances may be useful in preventing dental caries.

PATIENT INFORMATION— Grape Seed

Uses: May have antioxidant and cytoprotective effects and provide possible relief from venous insufficiency.

Side Effects: No toxicity in humans has been reported. It is contraindicated in patients with known hypersensitivity to grape seed. Additional scientific studies are recommended to substantiate the historical claims as well as attain a profile of any potential serious side effects.

Dosing: Extracts of grape seeds containing mostly PCO have been studied in a variety of clinical trials in Europe for antioxidant properties, venous insufficiency, and ophthalmologic complaints at doses of 50 to 300 mg/day.[13,18,19]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GRAPE SEED

GRAPEFRUIT

DATE OF ISSUE: JUN 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Citrus Paradisi* Macfad., Rutaceae

COMMON NAME(S): Grapefruit

BOTANY: The grapefruit is a large, dimpled, round citrus fruit, measuring 3 to 6 inches in diameter. It descends from a cross between a pomelo (pummelo) or shaddock (*C. Grandis*), a large Malaysian citrus, and a sweet orange. Some believe the grapefruit could also have arisen as a mutation of another type of citrus tree. The fruit grows in clusters similar to grapes, and this may be the reason why the "grapefruit" was so named. The two main varieties of grapefruit include the Duncan (many seeds and good flavor) and the Marsh (seedless with less flavor). The pink varieties followed; the Foster (1907; seeded) and the Thompson (1913; seedless). The Ruby red-pulped grapefruit was developed in the late twenties in McAllen, Texas. Grapefruits can be considered a "New World" product, a species only a few hundred years old.[1,2,3] The juice of the fruit, including concentrate, accounts for approximately 42% of all US processed grapefruit products. [2]

HISTORY: In 1310 B.C., Greek historian Theophrastus wrote of how Citron was thought to be an antidote to poison and how it could also "sweeten the breath." Later, Pliny, a Roman naturalist, used the word "citrus" for the first time and labeled the fruit as a medicine. [4] The grapefruit, then called "small shaddock," was first mentioned by Griffith Hughes in 1750, as the "forbidden fruit" of Barbados. [1,2] The name "grapefruit" was said to have been first used in Jamaica in 1814. In 1823, the grapefruit was introduced in Florida by a French count, Odette Phillippe, but did not begin to gain popularity until the end of the nineteenth century. [1] Worldwide production of grapefruit today averages 4.3 million metric tons. [2]

In the 1930's, Hollywood's "Grapefruit Diet" came into vogue, including calorie intake to approximately 800 per day, and including grapefruit consumption at each meal. Weight was lost from this diet, but any diet based primarily on one food is too restrictive to be healthy because too many other important nutrients may be missing.[5]

Analysis of grapefruit seed extract has been performed.[6]

CHEMISTRY: The chemistry of citrus fruits has been reviewed. Components of citrus fruits include sugars, polysaccharides, organic acids, nitrogenous constituents, lipids, carotenoids (that contribute to color), vitamins, minerals, flavonoids and volatile components (that contribute to aroma). [7,8]

Grapefruit is high in water and fiber.[5] The whole fruit is also a good source of potassium, vitamin C, inositol, bioflavonoids and pectin. [2] However, the juice alone is not high in pectin.[4] In addition, grapefruit has no fat and is low in calories and sodium. The pink variety contains beta-carotene. [5] Folic acid is also present in grapefruit. The peel contains citral, an aldehyde that antagonizes the effects of vitamin A. [2]

Other constituents in grapefruit have been found to affect liver enzymes. 6 ^{1},7^{1}-dihydroxybergamottin, a cytochrome P450 inhibitor, has been identified.[9] Naringin, naringenin, limonin and obacunone also exhibit inhibitory effects in human liver microsomes (see Pharmacology). [10]

PHARMACOLOGY: In the US, the grapefruit is popular as a breakfast fruit, usually eaten in halves. Approximately 50% of the world grapefruit crop is made into juice.[2]

Nutrition studies have been performed that discovered grapefruit to be of value as a dietary supplement. [11] Grapefruit has also been used as a nutritional supplement for patients experiencing potassium loss.[12]

Grapefruit pectin has been found to reduce cholesterol and to promote regression of atherosclerosis. [4,13] Because the pectin resides in the cell walls of the fruit and not in the juice, the juice itself does not decrease blood cholesterol. [4] Other blood effects of grapefruit include induction of red cell aggregation by constituent naringin (per in vitro observation) and reduction of hematocrits in 36 human subjects who ingested one grapefruit per day. [14]

The Swedes have studied grapefruit for its anti-cancer effects. In a 1986 analysis, subjects who consumed citrus fruit daily had lower incidences of pancreatic cancer.[2]

A pharmacokinetic study suggests citrus flavanones to undergo glucuronidation before urinary excretion. [15]

A report discussing treatment of psoriasis with cyclosporine and grapefruit juice is available. [16]

Grapefruit juice has been found to increase the bioavailability of certain drugs by inhibition of the cytochrome P450 3A4 (CYP3A4) isozyme found in the liver and gut wall.[17,18,19,20,21] However, the effects of grapefruit juice are primarily on the isozyme found in the gut wall. As a result of this inhibition, more of the drug is absorbed and the plasma concentration increases. The elevated drug concentration may lead to an increase in the drug's activity and side effects. In some instances, the increase in drug concentration may be beneficial (see Toxicology).

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Grapefruit juice has been reported to interact with certain nonsedating antihistamines, benzodiazepines, the dihydropyridine class of calcium channel blockers, cyclosporine, estrogens and quinidine. The mechanism of the interaction probably involves inhibition of gut wall enzymes, specifically the CYP3A4 isozyme.

Antihistamines: In humans, grapefruit ingestion may increase the bioavailability of terfenadine (no longer available in US) [33,34,35,36] and probably astemizole. Altered cardiac repolarization (in poor metabolizers of terfenadine) [34] and increases in the QT interval[33] have been reported when terfenadine was taken with grapefruit juice compared with water. More than one metabolic pathway appears to be inhibited.[36] There is considerable patient variability in the pharmacokinetic effect of the interaction.[36] The clinical importance of this interaction has not been determined.

Benzodiazepines: In healthy human subjects, taking midazolam or triazolam with grapefruit juice has been reported to increase plasma concentrations and the area under the plasma concentration-time curve (AUC) of these benzodiazepines. [46,51] However, the clinical effects of taking midazolam or triazolam with grapefruit juice are likely to be minor.[46,47,51]

Calcium channel blockers: In humans, the bioavailability of the dihydropyridine calcium channel blockers, including amlodipine, felodipine, nifedipine, nimodipine and nisoldipine, may be increased by concurrent ingestion of grapefruit juice. [23,24,25,26,27,28,29,30,49,50] While the increases in peak plasma concentrations for amlodipine were slight (15%),[29] peak plasma concentrations of felodipine increased more than 300%, [23,24,27,32] nifedipine increased by nearly 35% and the hypotensive effects were enhanced,[51] nimodipine levels increased by 24%,[29] and nisoldipine plasma levels increased by 400%.[20] The bioavailability of diltiazem, a different class of calcium channel blocker (eg, a benzothiazepine) was not affected by grapefruit juice ingestion. [31]

Cyclosporine: Human studies have demonstrated that grapefruit juice alters the pharmacokinetics of cyclosporine. [22,37,38,39,40] Taking cyclosporine with grapefruit juice may result in an increase in plasma concentrations, [39,40] and AUC of cyclosporine. [22,40] In addition, concentrations of a cyclosporine metabolite may be increased. [40] An increase in neurologic side effects, including tremors, was reported when cyclosporine was taken with grapefruit juice. [40] Some patients are instructed by their physicians to take cyclosporine with grapefruit juice in order to administer a lower dose of cyclosporine and reduce cost to the patient. [22] Thus, grapefruit juice may provide an inexpensive, nontoxic alternative to drugs given to reduce the cyclosporine dose. [22] In this situation, patients should avoid fluctuations in their grapefruit juice ingestion.

Estrogens: In 13 healthy female volunteers, grapefruit juice increased plasma concentration of ethinyl estradiol by 37% and the AUC by 28% compared with ingestion of the estrogen with herbal tea. [43]

Quinidine: When studied in 12 healthy male volunteers, administration of quinidine with grapefruit juice, compared with water, delayed the absorption of quinidine and inhibited the metabolism of quinidine to its major metabolite (3-hydroxyquinidine). [44] The effects of quinidine on the QT_c interval were delayed and reduced by ingestion with grapefruit juice.

Miscellaneous: Other reports are available regarding the effect of grapefruit juice on caffeine metabolism, [41] inhibition of 11-beta-hydroxysteroid dehydrogenase [42] and shifting the metabolic ratios of clomipramine. [45] Grapefruit juice has been associated with hypotension in one patient. [48]

SUMMARY: The grapefruit is a popular breakfast fruit in the US. Approximately one-half of the world's grapefruit crop is made into juice. Grapefruit juice has been found to increase bioavailability of certain drugs by inhibition of the CYP3A4 gut wall enzyme system. Drugs affected by this system include some calcium channel blockers, terfenadine, cyclosporine and others. These drug-food interactions are important and warrant the counseling of patients by pharmacists and other healthcare workers.

PATIENT INFORMATION — Grapefruit

Uses: Grapefruit juice is used as a nutritional supplement for potassium loss. Grapefruit pectin can help reduce cholesterol and promote regression of atherosclerosis. Other effects include induction of red cell aggregation by constituent naringin, reduction of hemocrits and possible anti-cancer effects.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Grapefruit juice can create adverse effects by altering drugs metabolized by the CYP3A4 enzyme system (eg, some nonsedating antihistamines, benzodiazepines, selected calcium channel blockers, estrogens, quinidine, and cyclosporine). A case report exists about grapefruit juice-induced hypotension.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GRAPEFRUIT

GREEN TEA

DATE OF ISSUE: FEB 1999

REPLACES MONOGRAPH DATED: MAY 1993

SCIENTIFIC NAME(S): *Camellia sinensis* L. Kuntze. Family: Theaceae

COMMON NAME(S): Tea, green tea

BOTANY: *C. sinensis* is a large shrub with evergreen leaves native to eastern Asia, where it is cultivated extensively. The plant has leathery, dark green leaves, and fragrant, white flowers with 6 to 9 petals. Cultivated tea plants are trimmed to about 1.5 m to facilitate the harvest. [1,2]

HISTORY: The dried, cured leaves of *C. sinensis* have been used to prepare beverages for more than 4000 years.[3] The method of curing determines the nature of the tea to be used for infusion, and green tea is 1 type of cured tea. Green tea is prepared from the steamed and dried leaves; by comparison, black tea leaves are withered, rolled, fermented, and then dried.[4] Oolong tea is semifermented and considered to be intermediate in composition between green and black teas. [2,5] Green tea is less popular in America and Europe than the black tea varieties. [6] Tea has been used medicinally for centuries, and the Chinese regarded the drink as a cure for cancer, although the tannin component is believed to be carcinogenic. Tea has been known to act as a diuretic and has been used to relieve headaches.

Research stems from people believing tea may have positive healing benefits because of its continued use as a fluid supply for those suffering from illness and disease. Focused investigations on therapeutic effects began in Japan and China, and continued in Europe and the US. The polyphenol presence in tea may play a role in lowering heart disease and cancer risk.[3]

CHEMISTRY: The chemistry of tea is complex because of the numerous components that are formed during the curing and drying process. Tea leaves contain varying amounts of polyphenols (flavonols, depsides such as chlorogenic acid, coumarylquinic acid, and theogallin), and catechins (the flavonol group of polyphenols).[5] Separation of catechins in green tea using HPLC [7,8] and other mass spectrometric methods (eg, EIMS, FABMS, LC/ESIMS) has been performed.[9] Structure (-)-epigallocatechin gallate has been detected as well, and was found to be an acetyl-CoA carboxylase inhibitor. [10]

The method of preparing green tea precludes the oxidation of the green leaf polyphenols. The composition of green tea is very similar to that of the fresh leaf, except for a few enzymatically catalyzed changes that occur extremely rapidly following plucking. [5]

Other tea constituents include tannins (evaluation of content has been reported), [11] caffeine (1% to 4% = 10 to 50 mg/180 mL), theophylline, theobromine, other methylxanthines (in small amounts), protein (15% to 20%), fiber, sugars (5%), B-vitamins, ascorbic acid (present in fresh leaf but destroyed in making black tea), amino acid theanine, malic and oxalic acids, and fats. [2,4,5,6] Lignans and isoflavonoid concentrations have been analyzed in tea. [12] Essential oil constituents of green tea dihydroactinidiolide and p-vinylphenol have been isolated. [13] Other volatile oil components include hexenal, hexenol, aldehydes, phenylethyl alcohols, phenols, and geraniol.[4] The folacin content of tea has also been reported. [14]

PHARMACOLOGY: Areas of current pharmacologic interest concerning green tea include pharmacokinetic studies, lipid effects, dental caries inhibition, antimicrobial actions, antimutagenic and antioxidative actions, a wide variety of anticancer studies, and other miscellaneous effects.

Pharmacokinetics: The pharmacokinetics of green tea have been reported. Blood and urine levels have been investigated in humans. [15] Drinking green tea daily may maintain significant plasma catechin levels, which may exert antioxidant activity against lipoproteins in blood circulation. [16] HPLC determination of catechins and polyphenol components have been performed.[16,17,18,19]

Lipid effects: Green tea appears to have promising effects in lowering lipid levels in vitro and in animal studies. However, research in humans does not support these claims. In vitro testing found that green tea markedly delays lipid peroxidation, with the polyphenol components having the strongest actions. [20] Green tea was also found to possess significant serum and liver cholesterol-lowering effects in (diet-induced) hypercholesterolemic rats. HDL-total cholesterol ratio was increased while HDL and triglyceride levels were not affected.[21] Another report investigating effects of green and black tea vs other dietary antioxidants in hypercholesterolemic rabbits concluded that green tea consumption reduced aortic lesion formation by 31%. Black tea, vitamin E, and beta carotene had no effect. [22] Human consumption of green tea has been associated with a decrease in total cholesterol levels but not in triglycerides or HDL cholesterol levels; [10] in this survey, 9 or more cups of tea had to be consumed per day for a significant effect to be noted. [23] A report investigating green tea intake and its effect on cholesterol levels in 1000 Japanese patients did not support the tea's beneficial actions on serum lipid levels. [24]

Dental caries: Green tea exhibits antimicrobial actions against oral bacteria. [25] After 5 minutes of contact with a 0.1% green tea polyphenol solution, *Streptococcus mutans* was completely inhibited. Plaque and gingival index were decreased after a 0.2% solution was used to rinse and brush teeth. [26] In vitro and in vivo data suggest green tea's fluoride content (although in low concentrations), may increase the cariostatic action along with the other tea components. [27] A report in animal models also suggests fluoride content in conjunction with other tea constituents, such as tannins, to decrease the rate of caries formation. [28] After rinsing with green tea extract, the catechin components present in human saliva have been determined by HPLC, and were present in the saliva for up to 1 hour. [29] Green tea consumption may also be effective in reducing the cariogenic potential of starch-containing foods by inhibiting salivary amylase, which hydrolyzes food starch to fermentable carbohydrates.[30]

Antimicrobial: Green tea's antimicrobial effects have been well documented. Green tea inhibited the growth of diarrhea-causing bacteria *Staphlococcus aureus*, *S. epidermidis*, *Vibrio cholerae* O1, *V. cholerae* non O1, *V. parahaemolyticus*, *V. mimicus*, *Campylobacter jejuni*, and *Plesiomonas shigelloides*.[31] In vitro antibiosis of green tea was demonstrated against 5 pathogenic fungi. When dilutions of 1:100 of culture filtrate green tea isolate were sprayed on infected plants, insect populations were also successfully controlled. [32] Green tea extract also inhibits a wide range of pathogenic bacteria including MRSA (methicillin-resistant *S. aureus*). This activity may be caused by the catechin and theaflavin (and its gallates) components. [33] In mice inoculated with green tea extract, inhibition of *E. coli* bacterial growth was demonstrated.[34] In addition, when tested in human infected root canals, green tea extract had antibacterial actions against 24 bacterial strains. [35]

Antimutagenic: Antimutagenic activity against a variety of organisms has been evaluated from different tea components. [36,37] Flavonol constituents in both green and black teas contributed to antimutagenic potential against dietary carcinogens. [38] The catechin components have been shown to contribute to antimutagenicity as well.[39] The antimutagenic potential of green tea extracts may be caused by 2 different proposed mechanisms, 1 of which may involve a direct interaction between reactive genotoxic species of various promutagens and nucleophilic tea components present in the aqueous extracts. [40] The tea tannins have been shown to modify chromosomal changes in mutagen-treated cells and mice.[41]

Antioxidative: Tea antioxidants have been well recognized. [42] Antioxidative activity was studied in 25 tea types, the actions due, in part, to the catechins present. [45] Tea consumed with milk may affect in vivo antioxidation thought to be caused by the complexation of tea polyphenols by milk proteins. [46] An evaluation of longevity of 3300 Japanese women practitioners of chanoyu (a Japanese tea ceremony) suggests that their intake of green tea contributes to their longevity [41] by providing a degree of protection against fatal diseases. [47]

Anticancer: Studies and reviews in the general area of anticancer effects from green tea and its various components are vast. [42,48,49,50,51,52] Some reports find that

tea possesses anticarcinogenic effects, protecting animals and humans against cancer risk. [42,48,52] One epidemiologic review explains favorable effects from tea only if high intake occurs in high-risk populations. [53] Another study (prospective cohort) finds data unsupportive in the hypothesis that black tea consumption protects against 4 major human cancers.[54] In another report, no consistent patterns of evidence were found concerning black tea consumption influencing cancer rates. [55] One other epidemiological study suggests modest anticancer benefits with several investigations leading to the possibility of decreased risks of digestive tract cancer from tea consumption.[56]

The polyphenol components of green tea (including flavanones, flavonols, isoflavones, and catechins) may possess chemopreventative properties.[57,58,59,60,61,62,63,64] The polyphenol content of green tea has been shown to inhibit the in vitro and in vivo formation of N-nitrosation by-products, which have been established as cancer-inducing compounds. [65] Various catechins exhibit inhibitory actions on human tumor cell lines, including breast, colon, lung, and melanoma.[66] A report on the nonpolyphenolic fraction of green tea finds pheophytins to be potent antigenotoxic substances as well. [67]

Additive effects of tea and other components have been documented. Tea and curcumin (constituent from the spice turmeric, an inhibitor of cyclooxygenase and lipoxygenase) used in combination on certain cell types were noted to have a synergistic effect in chemoprevention. [68,69] Green tea in combination with anticancer drug doxorubicin enhanced inhibitory effects on tumor growth by 2.5-fold when tested in mice. [70]

There are many proposed mechanisms as to how green tea expresses its anticancer effects. Some of these include antioxidative reactions, enzyme activities, inhibition of pathways such as lipid peroxidation, irradiation, and TPA-induced epidermal ornithine decarboxylase, inhibition of protein kinase and cellular proliferation, anti-inflammatory activity, and enhancement of gap junction intercellular communication. [42,58,59,62,64]

Anticancer, GI reports: Several reports conclude the possibility of lowered risk of digestive tract cancers in consumers of green tea. [56] Animal studies support these claims. Green tea extract inhibited GI tumors in rats (induced by N-methyl-N'-nitro-n-nitrosoguanidine) by 88%. Green tea catechols combine with the N-nitro-compounds to reduce their carcinogenic activity.[71] Green tea and its catechins have also prevented GI carcinoma in mice[72] and displayed a preventative and blocking effect on esophageal cancer in rats as well. [73] The theaflavin fraction of tea was also tested in rat esophageal cancer models, significantly reducing tumor formation.[74]

Most human studies confirm green tea's positive effects in cancer prevention. Consumption of green tea may offer protective effects against digestive tract cancers. [75] A case control study in over 1000 patients with esophageal cancer suggests a protective effect against this type of carcinogenesis from tea consumption. [76] Findings of another report evaluating 931 colon cancer cases, 884 rectum cancer cases, and 451 pancreas cancer cases concluded that green tea consumption may lower the risk of these cancers as well.[77] Affected human stomach cells treated with green tea catechin extract led to growth inhibition and induction of apoptosis, suggesting possible stomach cancer protection.[78] Catechins have also contributed to inhibition of small intestine carcinogenesis. [79] In tube-fed patients given 1 cup of green tea (100 mg catechins) 3 times daily for 3 weeks, positive effects were seen against colon carcinoma. [80] One conflicting study found a direct correlation between drinking 5 or more cups of green tea a day and the preference for salty foods as a risk factor for pancreatic cancer among Japanese men. [81] A tutorial is available on chemoprevention of aerodigestive cancers.[82]

Anticancer, skin: Green tea offers chemopreventative effects against skin cancers of varying stages and is useful against inflammatory responses in cancers caused by known skin tumor promoters such as chemicals or radiation.[83] Green tea and its polyphenol fractions display a protective effect against mouse skin papilloma. [84] UV radiation-induced skin cancer in animal and human models.[85] and have inhibited photocarcinogenesis in mice in topical applications. [86]

Anticancer, various: Green tea's chemopreventative activities against hepatic and pulmonary carcinogenesis have been addressed. [87,88] The tea's anticancer effects against lung tumorigenesis,[89] smoke-induced mutations in humans,[90] pancreatic carcinogenesis,[91] and leukemia[92] have all been reported. Green tea can inhibit the carcinogenic effects of female hormones as well.[93] A recent Canadian report is available concerning the unconventional use of green tea to treat breast cancer. [94]

Miscellaneous effects: Two well-known components of green tea from a pharmacologic basis are caffeine and tannin. Caffeine is an effective central nervous system stimulant that can induce nervousness, insomnia, tachycardia, elevated blood sugar and cholesterol levels, high levels of stomach acid, and heartburn. [6] These components are also useful for headaches, enhancement of renal excretion of water, weight loss, and as a cardiotonic. Green tea is also used as an astringent, for wounds and skin disorders, and soothing insect bites, itching, and sunburn. Tea is also a sweat-inducer, a nerve tonic, and has been used for functional asthenia, eye problems (as a poultice for baggy or tired eyes), and as an analgesic. [1,2,4] Green tea has been employed in hepatitis treatment and for protection of the liver, as with induced injury by carbon tetrachloride in rats. [1,95] The plant has also reduced methylguanidine levels, thus slowing the progression of renal failure in rats as well. [96] Green tea's role in stroke prevention,[97] as a thromboxane inhibitor,[98] as a radioprotective in mice to prolong lifespan,[99] and as a hypotensive (from hot water extracts)[100] has been described.

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions: appendix.

TOXICOLOGY: There is evidence that in animals caffeine can be teratogenic, and the FDA has advised that women who are or may become pregnant should avoid caffeine-containing products.[6] However, studies in humans drinking moderate amounts of caffeine have shown inconsistent results, with more recent studies not demonstrating adverse effects on the fetus.[101,102] Caffeine-containing beverages may also alter female hormone levels, including estradiol. [103]

There is evidence that condensed catechin tannin of tea is linked to a high rate of esophageal cancer in regions of heavy tea consumption. This effect may be overcome by adding milk, which binds the tannin, possibly preventing its detrimental effects. [4] Catechins have also been linked to tea-induced asthma[104] and with rat hepatic microsomal cytochrome P450 enzyme interactions.[105] One study reports that catechins may have antiallergic effects, inhibiting type ? allergic reactions. [106] Certain green tea workers experienced shortness of breath, stiffness, pain in neck and arms, and other occupation-related problems. [107]

The daily consumption of an average of 250 mL of tea by infants has been shown to impair iron metabolism, resulting in a high incidence of microcytic anemia. [108] However, in another report, no inhibitory effects on iron absorption were found in elderly patients. [109]

SUMMARY: Green tea is a widely popular beverage, particularly in Asia. Because of its unique preparation process, green tea retains many of the chemical characteristics of the fresh leaf. Pharmacologically, a wealth of information is available concerning green tea's effects on lipid levels, dental caries prevention, antimicrobial, antimutagenic, and antioxidative actions. It appears that green tea components may exert a chemoprotective effect that may contribute to a reduced incidence of cancers and other life-threatening diseases. Because of the caffeine present in the tea, it should be avoided by pregnant women. The tea may be an asthma-inducing agent.

PATIENT INFORMATION — Green Tea

Uses: Traditionally consumed as a beverage, green tea retains many chemicals of the fresh leaf. It is thought to reduce cancer and other fatal diseases, lower lipid levels, help prevent dental caries, and possess antimicrobial, antimutagenic, antioxidative, and other effects.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions: appendix.

Side Effects: The FDA advises those who are or may become pregnant to avoid caffeine. Heavy consumption may be associated with esophageal cancer. Tea may impair iron metabolism.

Dosing: Green tea has been studied as a component of diet for its cancer preventative and caries preventative properties. A typical tea bag contains 2 g of leaf. Doses of 4 to 5 cups/day (corresponding to ca. 300 mg caffeine) are considered high, depending on the patient's caffeine tolerance. The content of polyphenols

increases with extended brewing time. Green tea extracts are available standardized to 25%, 60%, and 80% total polyphenols, compared with a content of 8% to 12% in the leaf. Use of this extract can avoid the inconvenience of drinking large volumes of liquids. [110,111]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GREEN TEA

GUAR GUM

DATE OF ISSUE: FEB 2002

REPLACES MONOGRAPH DATED: OCT 1993

SCIENTIFIC NAME(S): *Cyamopsis tetragonolobus*(L.) Taub. synonymous with *C. psoralioides*DC. Family: Fabaceae

COMMON NAME(S): Guar, guar flour, jaguar gum

BOTANY: The guar plant is a small nitrogen-fixing annual that bears pods, each containing a number of seeds. Native to tropical Asia, the plant grows throughout India and Pakistan and has been grown in the southern US since the beginning of the 20th century. [1]

Guar gum is a dietary fiber obtained from the endosperm of the Indian cluster bean. The endosperm can account for more than 40% of the seed weight and is separated and ground to form commercial guar gum.

HISTORY: Guar gum has been used for centuries as a thickening agent for foods and pharmaceuticals. It continues to find extensive use for these applications as well as the paper, textile, and oil drilling industries.

CHEMISTRY: Guar is a galactomannan polysaccharide that forms a viscous gel when placed in contact with water. It forms solutions that range from slightly acidic to neutral pH. Even at low concentrations (1% to 2%) guar gum forms gels in water. The viscosity of these gels is generally unaffected by the pH of the solution.

Food grade guar gum contains ˜ 80% guaran (a galactomannan composed of D-mannose and D-galactose units) with an average molecular weight of 220 kDa. However, guar gum is not a uniform product and its viscosity may vary in proportion to the degree of galactomannan cross-linking.

Because of this physical composition, guar gum-based matrix tablets are currently being evaluated as a method of administering sustained-release drugs including diltiazem,[2,3] and for colonic drug delivery of corticosteroids to patients with inflammatory bowel disease. [4]

PHARMACOLOGY

Hyperlipidemia: Guar gum has been shown to have positive effects on cholesterol at doses ranging from 12 to 15 g/day. Most short-term studies (< 1 year) in patients with mild to moderate hypercholesterolemia have demonstrated a decrease in serum total cholesterol levels ˜ 6.5% to 15% and in low density lipoprotein-cholesterol (LDL cholesterol) by between 10.5% and 25%, without any effect on triglycerides or high density lipoprotein-cholesterol (HDL cholesterol) levels.[5,6,7,8,9] A long-term study in 40 patients illustrated that the effects of guar gum on total cholesterol and LDL cholesterol are sustained (with continued use) over a period of 24 months.[10] A comprehensive review of the lipid-lowering effects of guar gum described a general hypothesis for the mechanism of this action: Guar reduces cholesterol absorption and increases bile excretion leading to increased hepatic turnover of cholesterol. It has been suggested that the effects of guar on LDL cholesterol metabolism are similar to those of the bile-sequestering agents. [11]

Guar gum also has been used as an adjunct to more conventional lipid-lowering therapy. Coadministration with lovastatin resulted in a larger decrease in total cholesterol levels (44%) compared with lovastatin alone (34%) after 18 weeks of treatment. [12] Guar gum has an unpleasant flavor. Placebo-controlled trials have used a number of methods in an attempt to mask this; using uncoated granules,[13] powders, crispbreads, and other flavored formulas.[14]

Diabetes mellitus: The ability of guar to alter viscosity[15] and thus affect GI transit results in delayed absorption of glucose and may contribute to its hypoglycemic activity. Guar reduces postprandial glucose and insulin levels in healthy subjects [15] and patients with type 2 diabetes mellitus.[16,17,18,19,20,21] No reduction in plasma C-peptide levels was observed, suggesting that guar gum attenuates the insulin concentration in peripheral venous blood by increasing the hepatic extraction of insulin.[21] These effects on glucose and insulin seem to be most pronounced when large amounts of guar gum are added to the diet, and when the fiber is administered with the glucose or food.[22] However, when dietary fats and proteins are not adequately controlled in the diabetic diet, the addition of guar has been shown to have little effect on postprandial glucose or C-peptide responses. [23]

GI motility: Preparations containing guar gum have been used extensively to promote normal GI motility and to maintain fecal bulk. [24] Guar preparations may delay gastric emptying time or GI transit, but these effects seem to be related to the type of meal and diet. Oral rehydration solution, supplemented with guar gum, may reduce the duration of diarrhea in young children. [25] Also, the addition of enzymatically modified guar gum to enteral formulas has been shown to increase GI transit time, increase fecal nitrogen excretion,[26] and reduce diarrhea.[27] This is achieved without any effects on normal absorption of glucose, amino acids, or fat, or any adverse effects on hematological, hepatic, or renal function. [28]

Weight loss: Because bulk-forming fibers may impart a "feeling of fullness," they have been used to help curb appetite. One small study has suggested that guar gum may have a more profound effect on satiety when added to a meal rich in fat than when added to a low-fat meal.[29] A meta-analysis presented the combined results of 20 randomized controlled trials in which guar gum (average daily dose, 9 to 30 g) was compared with placebo. [30] It was shown conclusively that guar gum is not efficacious for reducing body weight. Additionally, a number of studies using a partially hydrolized form of guar gum, which has no viscosity or bulking effect, have found no effect on appetite[31] or weight maintenance.[32] Although evidence for the effectiveness of fiber products as appetite suppressants is lacking, they remain popular ingredients in *otc* weight loss preparations.

Blood pressure: Guar gum has been reported to have varied effects on blood pressure. One small study of 10 elderly subjects showed a reduction in postprandial hypotension (defined as a decrease in systolic blood pressure > 20 mmHg occurring within 2 hours of the end of a meal). [33] Conversely, guar supplementation for 2 weeks was shown to reduce blood pressure by 9% in moderately overweight men.[34]

Intrahepatic cholestasis and pruritus in pregnancy: In 2 double-blind studies, guar gum diminished or prevented worsening of pruritus in 96 pregnant women with intrahepatic cholestasis. This outcome is related to bile acid concentration, which remained unchanged in the guar gum-treated patients but increased in the placebo recipients.[35,36] The authors suggest that guar gum is a safe alternative and possible treatment option in these patients.

INTERACTIONS: Guar gum may decrease vitamin and mineral absorption. Take guar gum 1 hour prior to or 2 hours after other medications.

TOXICOLOGY: In the colon, guar gum is fermented to short-chain fatty acids. Both guar and its resultant by-products do not appear to be absorbed by the gut. The most common adverse effects are GI, including GI pain, nausea, diarrhea, and flatulence. Approximately 50% of those taking guar experience flatulence; this usually occurs early in treatment and resolves with continued use. A dose of ˜ 3 g 3 times/day, not to exceed 15 g/day, can minimize GI effects. [37]

Guar gum may affect the absorption of coadministered drugs. Slowed absorption of digoxin, acetaminophen, and bumetanide, and decreased absorption of metformin, penicillin V, and some formulations of glyburide have been reported. [38] Bezafibrate, glipizide, and glyburide [39] are generally unaffected by coadministration. [5]

Guar gum in a weight-loss product was implicated as causing esophageal obstruction in a patient who exceeded the recommended dosage. [40] In a review, 18 cases of esophageal obstruction, 7 cases of small bowel obstruction, and possibly 1 death were associated with the use of *Cal-Ban 3000*, a guar gum-containing diet pill. [41] The water-retaining capacity of the gum permits it to swell 10- to 20-fold and may lead to luminal obstruction, particularly when an anatomic predisposition exists. Take guar with large amounts of liquid.

Occupational asthma has been observed among those working with guar gum.[42] Because of its potential to affect glycemic control, guar gum should be used cautiously in diabetic patients. Guar gum is not teratogenic and does not affect reproduction in rats.[43]

SUMMARY: Guar gum forms a mucilaginous mass when hydrated. When taken continuously, this material has been shown to reduce total serum cholesterol and LDL cholesterol levels by ˜ 10% and 15%, respectively. In addition, guar has been found to reduce postprandial insulin and glucose levels. Guar is used as a common food additive and is not associated with adverse effects in the low quantities generally found in foods. Severe GI obstructions have been reported with the use of some guar-containing dietary supplements.

PATIENT INFORMATION— Guar Gum

Uses: Guar gum is a food additive shown to reduce serum cholesterol. It appears to have positive effects on blood glucose. Do not use guar gum to promote weight loss.

Interactions: Guar gum may decrease vitamin and mineral absorption. Take guar gum 1 hour prior to or 2 hours after other medications.

Side Effects: Guar gum may cause GI obstruction. Use guar gum cautiously in diabetic patients. Flatulence and other symptoms of GI distress are common during initial use.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GUAR GUM

GUARANA

DATE OF ISSUE: MAY 2000

REPLACES MONOGRAPH DATED: MAY 1991

SCIENTIFIC NAME(S): Paullinia cupana Kunth var. *sorbilis* (Mart.) Ducke or *P. sorbilis* (L.) Mart. Family: Sapindaceae

COMMON NAME(S): Guarana, guarana paste or gum, Brazilian cocoa, Zoom

BOTANY: Guarana is the dried paste made from the crushed seeds of *P. cupana* or *P. sorbilis*, a fast-growing woody perennial shrub native to Brazil and other regions of the Amazon.[1] It bears orange-yellow fruits that contain up to 3 seeds each. The seeds are collected and dry-roasted over fire. The kernels are ground to a paste with cassava and molded into cylindrical sticks, which are then sun-dried. Today, the most common forms of guarana include syrups, extracts, and distillates used as flavorings and a source of caffeine by the soft drink industry. Guarana also is used as an ingredient in herbal weight loss preparations usually in combination with ma huang.

HISTORY: Guarana has played an important role in the Amazonian Indians' society. It is often taken during periods of fasting to improve tolerance of dietary restrictions. In certain regions, the extract is believed to be an aphrodisiac and to protect from malaria and dysentery. [2,3] In the 19th century, guarana became popular as a stimulating drink in France,[1] and in 1880 was introduced as an official drug in the US Pharmacopeia, where it remained listed until 1910. [4] Natural diet aids, which rely on daily doses of guarana, have been advertised in the lay press. Guarana is occasionally combined with glucomannan in natural weight loss tablets. The advertisements indicate that the ingredients in guarana have the same chemical makeup as caffeine and cocaine but can be used for weight reduction without any of the side effects of these drugs. This is not entirely correct.

The stems, leaves, and roots of guarana are used as a fish-killing drug in Central and South America.

PHARMACOLOGY: Guarana is used by Brazilian Indians in a stimulating beverage used like tea or coffee; it is sometimes mixed with alcohol to prepare a more intoxicating beverage. In 1840, caffeine was identified as guarana's principal constituent, with a level ranging from 3% to greater than 5% by dry weight. [2]

By comparison, coffee beans contain ˜ 1% to 2% caffeine and dried tea leaves vary from 1% to 4% caffeine content.[5] The related alkaloids theophylline and theobromine have also been identified in the plant. Guarana is also high in tannins (primarily catechutannic acid and catechol), present in a concentration of 5% to 6% dry weight; these impart an astringent taste to the product. Guarana contains no cocaine.

The appetite suppressant effect is related to the caffeine content. The "zap of energy" that guarana tablets are reported to give is also due to caffeine. This stimulating effect is so widely recognized that guarana is sometimes called "Zoom."

Trace amounts of a saponin known as timbonine, related to compounds reported in timbo fish poisons used by Amazonian Indians, have been reported. [2]

Guarana extracts have been shown to inhibit aggregation of rabbit and human platelets following either parenteral or oral administration, possibly due to inhibition of platelet thromboxane synthesis.[6]

Some researchers claim that part of the revitalizing effects of guarana may be because of its antioxidant action. [7]

Numerous investigational studies have shown the ability of the sympathetic stimulant ephedrine, when coupled with caffeine, to have a synergistic effect on increasing metabolic rates with subsequent increased energy expenditure (thermogenesis), and to have lipolytic effects. [8] These effects have resulted in a statistically significant weight loss in animal and human trials when combined with diet.

In one animal study, behavioral effects in rats and mice subsequent to acute and chronic guarana administration were observed. [7] In this study, groups of animals treated with guarana in doses of 2000 mg/kg showed no difference when compared with control groups for the parameters of motor activity, tremor, or salivation. Another study showed an increase in physical capacity when mice were subjected to a stressful situation, such as forced swimming, after 3 to 6 months of guarana treatment.[9]

There are few human clinical trials concerning the safety and efficacy of guarana. In a small study, 3 groups of normal volunteers ranging from 20 to 35 years of age were given either placebo, 25 mg caffeine, or 1000 mg of guarana containing 2.1% caffeine daily. After 4 days, no reproducible improvement in cognition was noted in any group using neuropsychological testing, assessment of sleep quality, and a State-Trait Anxiety Inventory. [10] In another study, the effects of long-term administration of guarana on the cognition of healthy, elderly volunteers were studied. Guarana did not cause statistically significant memory improvement. [11]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: There are no published reports describing severe toxicity from guarana, but people sensitive to caffeine should use guarana with caution. This includes patients taking herbal weight loss preparations. Guarana use has led to excessive nervousness and insomnia. Use of guarana is contraindicated in pregnancy and lactation.[12] Given its high tannin content, excessive use may lead to an increased risk of cancer of the oropharynx.

SUMMARY: Guarana contains high concentrations of caffeine and related alkaloids and its pharmacologic effects are similar to those of coffee or tea. Commercially available weight-reduction products containing caffeine offer standardized quantities of caffeine at often lower prices than those containing guarana. Use guarana with caution in people with cardiovascular disease. The use of guarana as a natural energizer and weight loss aid cannot be recommended and should be discouraged unless used as a flavoring agent in beverages and in patients without contraindications to caffeine ingestion.

PATIENT INFORMATION — Guarana

Uses: Guarana has been used as a natural energizer, cognitive stimulant, flavoring for beverages, and as a component in natural weight loss products; however, it cannot be recommended as a natural energizer or weight loss aid.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Excessive nervousness, insomnia, and other health risks in patients sensitive to caffeine.

Dosing: Guarana paste is used as a stimulant at a dose of 1 g, usually dissolved in water or juice. The caffeine content is between 3.6% and 5.8%. [13]

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "G" MONOGRAPHS
  GUARANA

GUAYULE

DATE OF ISSUE: OCT 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Parthenium argentatum* A. Gray Family: Asteraceae

COMMON NAME(S): Guayule (pronounced "why-oo-lay")

BOTANY: Guayule is a common shrub native to the Chihuahuan desert of northern Mexico and the adjacent Big Bend region of Texas. The plant can be readily grown in the arid regions of the southwestern US.

HISTORY: Guayule had a history as a domestic source of rubber. In the early 1900s, guayule accounted for almost 50% of all the natural rubber consumed in the US and 10% of consumption worldwide.[1] A variety of factors, including the Great Depression and the Mexican Revolution, combined to destroy the industry. The US mounted an intensive research program under the Emergency Rubber Project to identify a domestic source of natural rubber as supplies from Southeast Asia dwindled because of World War II. The work led to the re-evaluation of guayule. The project was ended after the war, following the development of synthetic rubber and the return of cheap *Hevea* rubber. In 1977, interest in guayule was renewed when the National Research Council noted that the increasing demand for imported natural rubber could result in domestic shortages. The escalating price and variable supply of foreign petroleum, along with the great advantage that guayule can be harvested mechanically, made guayule rubber production attractive from both economic and national security standpoints. [2]

CHEMISTRY: The physical and chemical properties of guayule rubber, which is composed of polymeric cisisoprenoid units, are essentially identical to those of *Hevea* rubber. Guayule rubber is found in parenchymatous cells of the stem and root tissue as a latex. [3] Studies of over 75 native guayule plants have identified at least three prominent plant forms, termed Groups I, II and III, which differ in their leaf shape, trichome morphology and rubber content. [4] Rubber levels range from about 17% in Group I to 6% in Group III. Guayule grows in close association with a related desert plant, *P. incanum*(mariola). Morphologic and biochemical data indicate the presence of mariola genes in Group II and III guayule, resulting in morphologic changes and decreased rubber content. Group II plants are the most common, and the development of higher rubber-bearing plants should be guided by genetic assessments of guayule stock. Cross-breeding methods have been used to develop improved-yield varieties, and the application of bioinducers can stimulate the production of latex, with a resultant 2- to 6-fold increase in the amount of rubber.[5]

The processing of guayule plants leaves behind several by-products that may add to the economic value of guayule rubber production. The process yields large amounts of woody fiber (bagasse), which may serve as a fuel or in the manufacture of paper. To obtain a high-quality rubber, it is necessary to deresinate the crude product. The resin fraction may equal the rubber content. This resin has too high a boiling point to be used as gasoline, but it might be converted to an automotive diesel fuel.[6] Acetone extracts of woody guayule tissue have as their major components sesquiterpene esters composing 10% to 15% of the total, triterpenoids accounting for 27% and fatty acid triglycerides accounting for 7% to 19%. The sesquiterpenes are in part artifacts of heat processing. The major triterpene compounds are C-30 argentatins. Organic acid content varies, but the major aromatic acid is cinnamic acid and the major fatty acid is linoleic acid.

Aqueous extraction yields polysaccharides accounting for 63% of the extract. These are not a good source of fermentable sugars. [7] Guayule had been seen as a potential economic boon to poor native American Indians. Similar to proposals for jojoba, guayule represents an easily grown, economically sound, renewable resource that may be cultivated in economically depressed areas of the southwest.

In recent studies, researchers have found that guayule plants accumulate large amounts of rubber inside the stem tissue parenchyma cells. The rubber particles develop packed within discrete organelles. These are made up mainly of a lipophilic, cis-polyisoprene core, small amounts of lipids and various proteins (most abundant is the M[r]53,000 rubber particle proteins [RPP]). Based on cDNA cloning and spectroscopic analyses, RPP has been placed in the CYP74 family of P450s and further established it as the first P450 localized in rubber particles as well as the first eukaryotic P450 to be identified outside endoplasmic reticulums, mitochondrion or plastids. One researcher has described the sesquiterpenes, guayulins C and D in guayule.

TOXICOLOGY: Guayule contains a potent contact allergen, long known to pose a hazard to guayule farmers and processing-plant employees. [10] More recent investigations of acetone extracts resulted in the isolation of guayulin-A, a potent elicitor of contact dermatitis. This sesquiterpene cinnamic acid ester induces strong erythema in animals within 24 hours of application in concentrations as low as 0.003% (0.5 nM), which persists for almost 2 weeks. The compound is present in stems and leaves at levels of 0.05% to 0.3%. Guayule processing plants are now designed to minimize worker contact with resins. The allergenicity of guayulin-A may cause unexpected difficulties in the cross-breeding of *Parthenium* species to develop high-yield strains. Guayule readily undergoes hybridization with mariola and *P. tomentosum* var. stramonium, close desert relatives. These species contain sesquiterpene lactones that are cytotoxic and produce skin reactions in persons sensitized to other species of Asteraceae. Preliminary investigations of crosses of *P. tomentosum*with guayule indicate the presence of guayulin-A and stramonin-B (a cytotoxic pseudoguaianolide) in the first generation of experimental hybrids. [11]

SUMMARY: Guayule is slowly becoming an economically important rubber substitute, although its commercial development has not been as rapid as once hoped. Its more widespread cultivation may result in an increased incidence of allergic dermatitis among guayule farmers.

Guayule rubber plant is made up of a cis-polyisoprene core. The sesquiterpenes guayulin C and D have been described.

PATIENT INFORMATION — Guayule

Uses: Guayale is used in the production of rubber. Its use as a fuel is being investigated.

Side Effects: Contact with Guayule can cause strong erythema.

The potency of its allergen (guayulin A) has been equated to that of poison ivy.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GUAYULE

GUGGUL

DATE OF ISSUE: SEP 2003

REPLACES MONOGRAPH DATED: FEB 1995

SCIENTIFIC NAME(S): *Commiphora mukul* (Hook. ex Stocks) Family: Burseracaea.

COMMON NAME(S): Guggul, guggal, gum guggal, gum guggulu, gugulipid

BOTANY: The guggul plant is widely distributed throughout India and adjacent regions. It is in the same genus as *C. myrrha*, the myrrh mentioned in the Bible. Guggul and gum guggulu are the names given to a yellowish resin produced by the stem of the plant.

HISTORY: The plant has been used in traditional Ayurvedic medicine (Asiatic Indian plant medicine) for centuries in the treatment of a variety of disorders, [1] most notably arthritis, and as a weight-reducing agent in obesity. [2] More recently, extracts of the plant have been investigated for their ability to reduce serum lipid levels. A commercial product (*Guggulow*) has been introduced in the US claiming the cholesterol-lowering properties of the plant. This has raised interest in the activity of the plant.

CHEMISTRY: The majority of the published research studies on the plant and its extracts have originated in India. [3] Guggul contains resin, volatile oils, and gum. Several pharmacologically active components have been identified in the plant, including guggulsterones (E- and Z-stereoisomers) [4] and gugulipid, both found in the ethyl acetate extract of the plant.[5,6,7] Studies have shown that the guggulsterones are antagonist ligands for the bile acid receptor (BAR) farnesoid X receptor (FXR), which is activated by bile salts, thus reducing cholesterol.[8,9,10] A new triterpene, myrrhanol A, has been discovered to have potent anti-inflammatory effects.[11]

PHARMACOLOGY

Hypolipidemia: When treated with 500 mg gugulipid for 12 weeks, a lowering of serum cholesterol (24% average) and serum triglycerides (23% average) was observed in 80% of patients.[12] A crossover follow-up to this preliminary investigation compared gugulipid with the antihyperlipidemic drug clofibrate (eg, *Atromid-S*) in 233 patients. With gugulipid, the average fall in serum cholesterol and triglycerides was 11% and 17%, respectively. These effects were evident within 3 to 4 weeks of starting therapy. Hypercholesterolemic patients responded better to the gugulipid therapy than did hypertriglyceridemic patients. High-density lipoprotein (HDL) cholesterol increased in 60% of responders to gugulipid therapy. Clofibrate had no effect on this parameter. [12]

A 24-week, double-blind, placebo-controlled study of gugulipid involving 61 patients resulted in a decrease in total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides compared with no changes in the placebo group. [13]

One study of healthy subjects conducted in the United States demonstrated a reduction in total serum cholesterol. [3]

Obesity: Guggulsterone has been shown to stimulate thyroid activity.[14] This effect has been used to promote gugulipid as a weight loss product that increases the body's rate of metabolism. A small trial with 58 adult obese patients demonstrated that diet and guggulu taken over 30 days showed increased weight loss in patients who weighed more than 90 kg.[15]

Cardiac and fibrinolytic effects: Guggulsterone has also been shown to exert a protective effect on cardiac enzymes and the cytochrome P450 system against drug-induced myocardial necrosis.[16] *Commiphora mukul* in combination with *Inula racemosa* (another Ayurvedic botanical) was studied in 200 patients with ischemic heart disease. It was found to improve patients' ECG readings and decrease episodes of dyspnea and chest pain. [17] Gum guggul fraction increased fibrinolytic activity and decreased platelet adhesiveness.[18]

Anti-inflammatory: Extracts of the plant have an anti-inflammatory action[11] and inhibit carrageenan-induced rat paw edema in animal models.[19] Guggul was shown to be as effective as ibuprofen in an animal model of acute and chronic inflammation.[20] A recent outcome study in 30 patients showed significant improvement ($P < 0.0001$) in osteoarthritis symptoms after taking 500 mg *Commiphora mukul* 3 times per day with food for 1 month.[21]

Acne: One small study has shown guggulsterone to be as effective as tetracycline in the treatment of nodulocystic acne. [22]

TOXICOLOGY: While the human safety profile (including children, pregnant or nursing women, and patients with severe hepatic or renal disease) of the extract has not been well described, no significant adverse events were reported in clinical studies; the adverse effects were primarily GI and several cases of headache, hiccup, and rash.[1,3,13]

Guggul may stimulate thyroid hormone production; dosage adjustment of thyroid medication may be required.[14]

Gugulipid has been shown to reduce bioavailability of propranolol and diltiazem. Cross-class effects are unknown. Concomitant use should be avoided. [23]

Increased fibrinolytic activity of guggul can potentially add to the risk of bleeding in patients taking anticoagulants/antiplatelet medications. [18]

Availability and dosages: Various formulations (eg, tablets, capsules, powders) of guggul are available. Guggul and gugulipid are typically standardized to provide a fixed amount, normally 2.5%, of guggulsterones. However, commercial over-the-counter products have been tested by liquid chromatography to contain significantly less, to very little or none of claimed guggulsterones.[6,7] Standardization of herbal products is warranted.

Hypercholesterolemia: 75 to 150 mg standardized guggulsterones daily.[3,15,24]

Obesity: Guggulu 250 mg 3 times/day.[15]

Acne: Gugulipid (standardized to 25 mg guggulsterone) twice daily for 3 months. [22]

SUMMARY: Guggul and its extracts have been used for centuries in traditional Indian medicine. An increasing amount of evidence suggests that components of the plant can exert a lipid-lowering effect possibly equivalent to that of clofibrate. *Commiphora mukul* has also been proven to improve symptoms of osteoarthritis of the knee.

Since drug interactions have been recorded, advise patients taking medication(s) to check with a health care professional before starting any form of guggul.

PATIENT INFORMATION — Guggul

Uses: Traditionally used to treat arthritis, obesity, and other disorders, guggul has been shown to lower cholesterol and triglycerides and to stimulate thyroid activity in a few small studies.

Side Effects: Adverse GI effects have been reported.

Drug Interactions: During coadministration, gugulipid significantly reduces propranolol and diltiazem bioavailability. Guggul can also potentially add to bleeding risk in patients taking anticoagulants/antiplatelet medications.

Disease State Concerns: Dosage adjustment of thyroid medication may be necessary.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GUGGUL

GYMNEMA

DATE OF ISSUE: AUG 1993

REPLACES MONOGRAPH DATED: NOV 1989

SCIENTIFIC NAME(S): *Gymnema sylvestre* R.Br. It has been referred to in some texts as *Asclepias geminata* Roxb., *Gymnema melicida*Edg., and *Periploca sylvestris* Willd.[1] Family: Asclepiadaceae

COMMON NAME(S): Meshashringi, gurmar, merasingi

BOTANY: *Gymnema sylvestre* is commonly found in Africa and India. Its distribution has become worldwide however, and it is recognized in the traditional medicinal literature of many countries including Australia, Japan and Vietnam. The leaves are most commonly used, but the stem also appears to have some pharmacologic action.

HISTORY: Gymnema has played an important role in Ayurvedic medicine for centuries. Its use has been confined primarily to the management of diabetes and similar hypo/hyperglycemic conditions. As early as 1930 the pharmacologic effect of the plant was being investigated. [2] The plant has been used alone and as a component of the Ayurvedic medicinal compound "Tribang shila," a mixture of tin, lead, zinc, *G. sylvestre* leaves, neem (*Melia azadirachta*) leaves, *Enicostemma littorale*, and jambul (*Eugenia jambolana*) seeds. The plant also is used in traditional African medicine.

More recently, the plant has been identified by the natural products industry in North America and Europe and a number of commercial over-the-counter herbal products are now available that contain varying amounts of gymnema. These products generally are associated with an ability to control blood glucose levels or to contribute to overall metabolic control.

CHEMISTRY: Few studies have closely investigatedthe details of the composition of *G. sylvestre*. It appears that the compound gymnemic acid (gymnemin) maybe responsible for most of the plant's pharmacologic activity. Gymnemic acid also has been identifiedin a number of related members of the Asclepiadaceae and represents a mixture of at least nine closely related acidic glycosides, the major component being gymnemic acid A1. [3]

PHARMACOLOGY: A number of studies have evaluated the effects of *G. sylvestre* on blood sugar in animals.[4] In one typical study, rats were administered an alcoholic extract of *G. sylvestre* (100 mg/kg daily for one month) through a stomach tube. The rats were made diabetic by the administration of anterior pituitary extract. By the second week, the mean blood sugar level was significantly lower among the animals receiving the gymnema extract (74 mg/dL) than among those who did not (106 mg/dL). This difference was maintained for the duration of the study. The blood glucose level among these treated animals was no different from a control group that did not receive pituitary or gymnema extract. These data indicated that extracts of the plant could exert a clinically measurable hypoglycemic effect in diabetic animals.[5]

In another study, *G. sylvestre* extract (100 mg/kg daily) was compared to tolbutamide (eg, *Orinase*) (5 mg/kg daily) given to rats for a month. Both treatments caused a statistically significant reduction in blood glucose levels compared to controls in normal rats after one month. Both drugs also effectively reduced blood sugar levels in diabetic rats after one month (controls: 88 mg/dL; *G. sylvestre*: 74 mg/dL; tolbutamide: 73 mg/dL).[6] These results suggested that gymnema extracts exerted a hypoglycemic effect following oral administration and that the pharmacologic effect approximated that of tolbutamide. It should be noted that the doses used would be equivalent to a 7 g dose of extract for a typical man. A more dramatic effect was noted when the extract was administered parenterally to rats. [7]

Although the exact mechanism of the plant's hypoglycemic activity has not been established, it appears to act in a manner similar to that of the sulfonylurea drugs, stimulating the release of endogenous insulin stores or perhaps by sensitizing cells to the effects of insulin.

A solution of gymnemic acid inhibits the ability to taste bitter or sweet flavors (such as quinine or sugar), but maintains the ability to taste sour, astringent or pungent substances. It is not clear whether gymnemic acid also is responsible for the hypoglycemic effect of the drug, although most evidence points in this direction.

TOXICOLOGY: Little is known about the safety of this plant. The animal studies that reported the hypoglycemicefficacy of the plant did not provide details of animal safety. The plant has not been associated with published reports of human toxicity. Because of its documented hypoglycemic effect, it is possible that as few as a dozen tablets of some otc preparations could cause a demonstrable hypoglycemic reaction in humans.

SUMMARY: *Gymnema sylvestre* is a plant that has found use in the traditional medicine of a number of societies for the management of blood sugar disorders. Pharmacologic evaluations of the plant have found it to possess hypoglycemic activity approximating that of tolbutamide. Little is known about the long-term safety of the plant, but it generally has not been associated with human toxicity. It represents one of a number of plants that should be investigated in more detail for its potential as a hypoglycemic agent.

PATIENT INFORMATION— Gymnema

Uses: The plant has been used in traditional medicine, most notably to control blood glucose.

Side Effects: Gymnema is not known to be toxic, but caution should be exercised as to its hypoglycemic effect. Gymnemic acid inhibits the ability to taste bitterness or sweetness.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "G" MONOGRAPHS
    GYMNEMA

"H" MONOGRAPHS

HAWTHORN

DATE OF ISSUE: JUN 1999

REPLACES MONOGRAPH DATED: JAN 1994

SCIENTIFIC NAME(S): *Crataegus oxyacantha*L., *C. laevigata* (Poir.) DC, and *C. monogyna* Jacquin. Family: Rosaceae

COMMON NAME(S): Hawthorn, English hawthorn, haw, maybush, whitethorn[1]

BOTANY: Hawthorn is a spiny bush or small tree that grows up to 7.5 m in height. Its deciduous leaves are divided into three to five lobes. The white, strong-smelling flowers grow in large bunches and bloom from April to June. The spherical bright red fruit contains one nut (*C. monogyna*) or two to three nuts (*C. oxyacantha*).[1] Morphological and microscopical observation of certain Chinese hawthorn species has been performed. [2]

HISTORY: The use of hawthorn dates back to Dioscorides, but the plant gained widespread popularity in European and American herbal medicine only toward the end of the 19th century. The flowers, leaves, and fruits have been used in the treatment of either high or low blood pressure, tachycardia, or arrhythmias. [3] The plant is purported to have antispasmodic and sedative effects. Hawthorn has been used in the treatment of atherosclerosis and angina pectoris. Preparations containing hawthorn remain popular in Europe[4,5] and have gained some acceptance in the US.[6]

CHEMISTRY: The leaves, flowers, bark, and fruits contain the flavonoid pigments hyperoside and vitexin-rhamnoside, leucoanthocyanidins, and the lactone crataeguslactone (a mixture of ursolic, oleanic, and crataegolic acids). [4,7] Flavonoid constituents from hawthorn have been frequently reported. [8,9,10,11] Glycoflavonoid structural characteristics have been evaluated. [12] Procyanidine and 2,3-cis-procyanidin have been isolated from hawthorn. [13,14] Chlorogenic acid from *C. pyracantha Pers.* has been found.[15] Analysis of active hawthorn components has been reviewed.[16]

PHARMACOLOGY: Hawthorn's beneficial roles in cardiovascular disease have been extensively reviewed. [17,18,19,20] Pharmacokinetic, pharmacodynamic, and metabolic studies on hawthorn have been performed.[21,22,23]

Because of its strong cardiac activity, hawthorn has been suggested to be of use in CHF [24,25] and cardiac performance.[26] The plant is known to contain cardiotonic amines.[27] The flavonoids cause an increase in coronary flow and heart rate and a positive inotropic effect. In isolated animal hearts, the inhibition of the enzyme 3´,5´-cyclic adenosine menophosphate phosphodiesterase may be a mechanism by which hawthorn exerts its cardiac actions. [28] When tested in rat cardiac myocytes, hawthorn produced strong contraction of heart tissue, along with increases in energy turnover in certain processes. [29] Another study evaluated hawthorn in combination with digoxin to treat heart disease.[30] At least one report exists on the plant's potential antiarrhythmic effects. [31]

Hawthorn flavonoid components also possess vasodilatory action.[28,32] Extracts of hawthorn dilate blood vessels, in particular coronary blood vessels, resulting in reduced peripheral resistance and increased coronary circulation. In vitro increases in coronary circulation ranging from 20% to 140% have been observed following the administration of a dose equal to ˜ 1 mg of the dry extract.[17]

Hawthorn also exhibited vasorelaxant effects in isolated rat mesenteric arteries.[33] A double-blind study of the related species *C. pinnatifida* and its effect on 46 angina cases has been performed.[34]

Hawthorn is also known to be beneficial in myocardial ischemia.[35,36] The flavonoid, monoacetyl-vitexinrhamnoside, possesses marked anti-ischemic properties in several in vitro models, suggesting improvement in myocardial perfusion.[37] Hawthorn's effects on oxygen-deprived rat heart cells have been reported. [38] The plant's influence on myocardial ischemia in dogs has also been evaluated. [39,40] Other studies concerning circulation aspects have been addressed, including peripheral arterial circulation disorder[41] and varicose symptom complex.[42]

Hawthorn has been studied in the prevention and treatment of atherosclerosis. A hawthorn preparation in combination was administered to animals, resulting in lower cholesterol, triglycerides, blood viscosity, and fibrinogen levels vs controls. [43] Another report finds tincture of hawthorn to increase bile acid excretion and decrease cholesterol synthesis in rats. The mechanism involves an up-regulation of hepatic LDL-receptors, resulting in a greater influx of cholesterol into the liver. Hawthorn was also found to enhance cholesterol degradation.[44] A drink containing hawthorn has lipid-lowering effects when studied in rats and humans. [45]

Hawthorn has been studied for its effects on hypertension.[46,47] The plant has active components which cause vasorelaxation in rat mesenteric arteries. [33]

Other effects of hawthorn include oxygen species scavenging activity, [48] anticomplementary activity,[49] and the ability to effectively treat elective mutism, a rare syndrome in which children with normal verbal capabilities refuse to speak for prolonged time periods. [50]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: The acute parenteral LD_{50} of *Crataegus*preparations has been reported to be in the range of 18 to 34 mg/kg, with that of individual constituents ranging from 50 to 2600 mg/kg.[17] Acute oral toxicity has been reported to be in the range of 18.5 to 33.8 mg/kg. [51] In humans, low doses of hawthorn are usually devoid of adverse effects.[17] No serious adverse drug reactions have been reported from hawthorn, and it appears to be safe and effective for CHF. [24] However, higher doses have the potential to induce hypotension and sedation. The health professional and user must be aware of the potential of hawthorn to affect heart rate and blood pressure. Hawthorn may pharmacodynamically interfere with digoxin or digoxin monitoring. [52] This proposed interaction has not been documented clinically. Since digoxin has a narrow therapeutic index, it would be prudent for patients taking digoxin to avoid hawthorn.

Hawthorn extract may increase the intracellular concentrations of cyclic AMP by influencing the activity of the enzyme phosphodiesterase, and it also may influence other mechanisms that activate adenylcyclase.[17] At least one report is available on hypersensitivity reaction to hawthorn, [53] and toxiderma as a result of the fruits of the plant.[54] Hawthorn toxicity in general has been evaluated.[51]

SUMMARY: Hawthorn is often found in popular herbal remedies, in particular those marketed in Europe. It is not as popular in the US, where the literature contains relatively few *otc* products or herbal product information, although some health food stores carry the product. Hawthorn seems to have beneficial effects in cardiovascular disease such as ischemia, angina, and atherosclerosis. The plant also possesses lipid-lowering and anti-hypertensive actions. No major toxicities have been reported. More studies are needed to fully evaluate its potential in these conditions.

PATIENT INFORMATION — Hawthorn

Uses: Hawthorn has been used to regulate blood pressure and heart rhythm, to treat atherosclerosis and angina pectoris, and as an antispasmodic and sedative.

Interactions: Hawthorn may pharmacodynamically interfere with digoxin or digoxin monitoring.

Side Effects: Hawthorn is reportedly toxic in high doses, which may induce hypotension and sedation.

Dosing: The usual recommended dose of hawthorn leaves and flowers is 4.5 to 6 g/day. Several standardized extracts (*Crataegutt*, *Faros 300*, *Cardiplant*) are available that have been used in clinical trials at doses from 160 to 900 mg/day. The content of oligomeric proanthocyanidins or flavonoids is used for standardization of these extracts.[47,55,56,57,58]

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Document Bibliographic Information:
- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
      HAWTHORN

HIBISCUS

DATE OF ISSUE: APR 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Hibiscus sabdariffa* L. Family: Malvaceae

COMMON NAME(S): Hibiscus, karkade, red tea, red sorrel, Jamaica sorrel, rosella, soborodo (Zobo drink), Karkadi, roselle, sour tea

BOTANY: Hibiscus is native to tropical Africa but today grows throughout many tropical areas. This strong annual herb grows to = 1.5 m and produces elegant red flowers. The flowers (calyx and bract portions) are collected when slightly immature. The major producing countries are Jamaica and Mexico. [1]

HISTORY: The hibiscus has had a long history of use in Africa and neighboring tropical countries. Its fragrant flowers have been used in sachets and perfumes. In areas of northern Nigeria, this plant has been used to treat constipation. [2] Fiber from *H. sabdariffa* has been used to fashion rope as a jute substitute.[3] The fleshy red calyx is used in the preparation of jams, jellies, and cold and warm teas and drinks.[3,4] The leaves have been used like spinach.[3] The plant is used widely in Egypt for the treatment of cardiac and nerve diseases[5] and has been described as a diuretic. In Iran, drinking sour tea for the treatment of hypertension is a popular practice. [6] It has been used in the treatment of cancers.[1] The mucilaginous leaves are used as a topical emollient in Africa. [7] In Western countries, hibiscus flowers often are found as components of herbal tea mixtures. People of Thailand consume roselle juice to quench thirst. [8] Karkade seed products (ie, karkade defatted flour, protein concentrate, protein isolate) have been studied for their nutritional and functional value. [4]

CHEMISTRY: A variety of compounds have been isolated from the hibiscus plant. As expected from their vivid color, hibiscus flowers contain various anthocyanins (about 1.5%) and other pigments.[9,10] *H. sabdariffa* also has been found to contain saponins, a natural detergent.[2] The flowers contain beta-sitosterol, traces of an alkaloid,[11] and sitosterol-beta-D-glucoside.[12]

Oxalic, malic, citric, stearic, and tartaric acids have been identified. These, along with 15% to 28% of hibiscic or hibiscus acid (lactone of hydroxycitric acid) most likely contribute to the tartness of the herb and its teas. Crude karkade seed oil also has been discovered to contain saturated fatty acid (palmitic) and unsaturated fatty acids (oleic and linoleic).[4] Protocatechuic acid (PCA), a phenolic acid, also has been isolated from *H. sabdariffa* L.[13]

High amounts of protein have been found in karkade protein isolate (88.15%), karkade protein concentrate (62.24%), karkade defatted flour (50.63%), and karkade whole seed flour (26.48%).[4] The latter also has been found to contain high amounts of crude oil, ash, and carbohydrate. [4] Karkade seed products also have been found to contain high amounts of the amino acids, arginine, aspartic acid, and glutamic acid. [4]

PHARMACOLOGY: The plant has been used as a mild laxative, an effect that may be in part due to the acids and/or saponins described above. Pharmacologic evaluations of hibiscus extracts have produced conflicting results. A 5% solution caused a slight increase in intestinal motility in vitro, while higher concentrations reduced it. Complete inhibition of intestinal motility was observed in vitro with more concentrated water extracts. [11] In a different study, extract prepared from the fresh and fleshy calyx of hibiscus demonstrated a mild cathartic activity in rats at doses of 400 and 800 mg/kg without increases in peristaltic activity. [2]

Assessment of the water and oil absorption capacity, bulk density, and emulsifying activity has estimated that karkade seeds might be harvested for sources of protein and oil to increase cultivation and economic value.[4]

Comparison of consumption of 16 and 24 g/day of roselle juice did not demonstrate a beneficial effect on the prevention of renal stones. Urinary changes seen in the 16 g/day group (ie, increased ion concentration of calcium and oxalate) actually may increase the risk of stone formation. However, the 24 g/day group showed a tendency to decrease ion concentration of calcium and oxalate; thus, a study with higher doses may be valuable to ascertain potential effects in preventing renal stone formation.[8]

The extract reduced uterine motility in vitro and had essentially no effect on respiratory rate. [11] There is no evidence that doses of hibiscus from teas have a sedative effect. When injected IV in dogs, a 10% aqueous extract of the flowers caused a rapid but short-lived dose-dependent decrease in mean blood pressure. A randomized clinical trial evaluated the effect of sour tea available commercially in Iran on essential hypertension on 54 otherwise healthy volunteers. A decrease in systolic and diastolic pressure, when compared with controls, was seen in the sour tea group. After cessation of drinking the sour tea, a rise in both systolic and diastolic pressures occurred. The exact mechanism of how tea prepared from *H. sabdariffa* decreases blood pressure is still unknown.[6] Although no adverse effects were seen in this study, the use of sour tea for treating hypertension requires further study.

Aqueous extracts of hibiscus appear to exert a slight antibacterial effect. Extracts have been found to inhibit the movement of human and canine taenias and a 4% solution killed the worms in ˜ 30 minutes in vitro.[11] A 15% aqueous extract prevented the growth of *Mycobacterium tuberculosis* in vitro, and 10 mL doses of a 20% extract prevented growth of the bacillus in infected rabbits.[14] However, these data require confirmation and the antibacterial effect of the plant should not be considered clinically relevant.

Roselle tea extract has shown high inhibition against porcine pancreatic a-amylase (PPA). Proposed uses for this inhibition are for decreased glucose absorption and to inhibit replication of HIV.[15]

PCA has shown potential as a chemopreventive agent against tumor promotion and possesses anti-inflammatory properties. A study in mice demonstrated that topical application of PCA inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced tumor promotion and edema.[13] PCA also has been found to inhibit the survival of human promyelocytic leukemia HL-60 cells by inducing apoptosis in vitro.[16]

Additionally, hibiscus anthocyanins have shown antioxidant activity in protecting against *tert*-butyl hydroperoxide-induced hepatotoxicity in rats. Application and action in humans has yet to be investigated.[17]

INTERACTIONS: Consumption of the Sudanese beverage, Karkadi (*H. sabdariffa*), concomitantly with the antimalarial agent, chloroquine, produced a statistically significant reduction in the area under the curve of chloroquine, thus potentially reducing its antimalarial efficacy. [18]

TOXICOLOGY: Hibiscus flowers generally are considered to be relatively nontoxic. However, a 30% aqueous extract of the flowers had an LD-50 of 0.4 to 0.6 mL in mice following intraperitoneal injection.[11] Animals injected with this toxic dose were dull and apathetic and died within 24 hours.

SUMMARY: Hibiscus is a popular plant whose flowers are found in numerous herbal tea preparations. The flowers contribute color and a pleasant taste to beverages. In normal concentrations, the teas would not be expected to exert any pharmacologic action. Potential uses of different ingredients contained in *H. sabdariffa* include chemoprevention, antioxidation, and inhibition of HIV.

PATIENT INFORMATION — Hibiscus

Uses: The leaves and calyxes have been used as food and the flowers steeped for tea. Hibiscus has been used in folk medicine as a diuretic, mild laxative, and treatment for cardiac and nerve diseases and cancer. Mucilaginous leaves have been used as a topical emollient. Roselle juice is used to quench thirst.

Interactions: Hibiscus beverage has the potential to decrease effectiveness of the antimalarial medication, chloroquine.

Side Effects: The flowers are considered relatively nontoxic.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HIBISCUS

HOLLY

DATE OF ISSUE: OCT 1996

REPLACES MONOGRAPH DATED: NOV 1987

SCIENTIFIC NAME(S): *Ilex*, *I. aquifolium*, *I. opaca* and *I. vomitoria*. Family: Aquifoliaceae

COMMON NAME(S): A number of members of the genus *Ilex* are referred to as "holly." Holly, English holly, Oregon holly and American holly are the species most often associated with the ornamental Christmas holly. Yaupon, Appalachian tea, cassena, deer berry, Indian holly, Indian black drink are also commonly discussed with the hollies.

BOTANY: The *Ilex* species are evergreen trees or shrubs with stiff leathery leaves. The flowers are often white and produce fruits that range in color from black to bright red to yellow. The plants are found throughout most of the eastern and southern United States.

The genus *Ilex* consists of over 400 species worldwide. It requires a wet and equable climate and shows a worldwide distribution, except in arctic or arid regions. The major areas of distribution are Central and South America, with Brazil alone having 60 species, and Asia which has at least 112 different species. The North American species are largely ornamental and derived from Central and South America. [1]

HISTORY: The plants in the holly family have been used as ornamentals and in herbal medicine for centuries. Early history records the European pagans offering holly branches as gifts during the Saturnalia. Early Christians decorated their homes with holly during Christmas, a practice still continued today. [1] The early settlers in the southeastern United States made yaupon tea from *I. vomitoria*, reserving a stronger decoction for use as an emetic. *I. opaca* fruit tea had been used as a cardiac stimulant by the American Indians; the Chinese had used it to treat coronary disease.

One of the most economically important species, *I. paraguayensis* or Mate tea (see separate monograph) has long been cultivated and used in Brazil and Paraguay as a tea-like beverage containing caffeine. The mixed leaves of *I. cassine*, *I. vomitoria* and *I. dahoon* were also used for another hot drink called yaupon or black drink. Drinkers used it ceremonially to "cleanse" themselves, probably due to its sweat- and vomiting-inducing effects. Another beverage made from the leaves of *I. cassine* and *I. vomitoria* was used as a stimulant tea in the Southern US during the Civil War. [1]

CHEMISTRY: A fair amount has been written about the chemistry of the holly. Most contain tannins. Analyses done on the leaves of *I. aquifolium* described the presence of tannic acid, a bitter glycoside (ilicin), ilexanthin (rutin), and ilicic acid. [2] Some members of the genus, such as *I. paraguayensis* St. Hill (yerba mate) contain xanthine alkaloids such as caffeine in levels as high as 2%. Other species contain saponins and triterpenes. [3]

One review on the chemistry of *Ilex* documented hundreds of compounds isolated from *Ilex* from the late 1800s up to 1987. Selected examples of the various classes of chemical constituents include phenols and phenolic acids (p-hydroxybenzoic acid, arbutin), anthocyanins (pelargondin 3-bioside, cyanidin 3-glucoside), flavonols and flavons (rutin, kaempferol), terpenoids (alpha-amyrin, ursolic acid), sterols (sitosterol, ergosterol), purine alkaloids (caffeine, theobromine), amino acids (aspartic acid, glutamic acid), miscellaneous nitrogen compounds (trigonelline, choline), fatty acids (oleic, linolenic), alkanes and alcohols (nonacosane, mellisyl alcohol), carbohydrates (sugar alcohols, sucrose), vitamins and carotenoids (ascorbic acid, thiamine).

PHARMACOLOGY: Many *Ilex* species seem to be devoid of significant pharmacologic activity; however, some are capable of inducing vomiting through a local irritant action. Saponins are found in some species of *Ilex* but their absorption through intact mucosa is minimal. Saponins generally cause severe diarrhea and GI upset.

One extensive review provides a cosmopolitan view of the folkloric uses of *Ilex*. These include the use of *I. pubescens* in the traditional medicine of China for treating coronary heart disease, *I. cornuta* for dizziness and hypertension, *I. aquifolium* leaves for intermittent fevers and rheumatism as well as for its antipyretic, astringent, diuretic and expectorant properties, and the use of *I. opaca* leaves as a diuretic, tonic, purgative and cardiac stimulant. Earlier reports from the early 1930s indicate that the dried powder emulsion made from the leaves and berries of *I. aquifolium* and *I. opaca* possessed the pharmacological activity of digitalis. Several studies have confirmed the depurative, stimulant and diuretic actions of *I. paraguayensis* and related these effects to its high purine content. More recent studies have shown that *I. asprella* constituents (asprellic acids A and C) have shown cytotoxicity against RPMI-7951 and KB cells, whereas asprellic acid B was inactive.

TOXICOLOGY: Although they are not usually considered to be poisonous, ingestion of the holly berry may cause gastrointestinal disturbances such as vomiting and diarrhea, and may result in stupor if eaten in quantity. [5] Their ingestion should be considered dangerous to small children with the probable fatal dose having been estimated to be 20 to 30 berries. [6]

A case of 2-year-old identical twins who ingested a "handful" of holly berries (*I. opaca*) has been reported. [7] Both children vomited for more than 6 hours and one became drowsy; 20 hours after ingestion, both had an episode of green watery diarrhea. Both were asymptomatic 30 hours after ingestion of the berries. This report indicated that the gastrointestinal effects associated with this plant could be so severe that its presence could cause dehydration and electrolyte imbalance. The drowsiness experienced by one of the children may have been induced by ipecac.

General schemes are available for treating holly poisoning. They involve induction of vomiting if large quantities of berries are ingested, followed by activated charcoal and a saline cathartic. Excess stimulation caused by theobromine may be countered with barbiturates or benzodiazepines. The central nervous system should be monitored.

The leaves of most species are generally considered to be nontoxic, although the spines of some leaves may tear or puncture skin and mucous membranes.

SUMMARY: Holly leaves and berries are used as common ornamentals, particularly at Christmas time. The ingestion of small amounts of holly berries may not induce toxicity; however, because of the potential for severe vomiting and diarrhea, all cases of holly berry ingestion should be referred to a physician. The leaves of some species of holly have been used to make herbal teas, but there is no evidence to indicate that they are effective in the treatment of any disorder.

While several chemical studies and some folkloric studies reveal potential for the development of medications from holly, none have reached the clinical stage to the extent that any *Ilex* can be recommended for the treatment of any disorder. One species (*I. asprella)* has antitumor properties, but it also needs further examination. *I. paraguayensis* is used in Paraguay and Brazil and is covered under a separate monograph, Mate tea.

PATIENT INFORMATION — Holly

Uses: Primarily used as a holiday decoration. Historically used in teas as an emetic and a CNS stimulant.

Side Effects: Although no fatalities have been reported, 20 to 30 berries is the estimated lethal dose in small children. Ingestion can cause vomiting, diarrhea, stupor, dehydration and electrolyte imbalance.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HOLLY

HONEY

DATE OF ISSUE: MAY 2001

REPLACES MONOGRAPH DATED: OCT 1995

SCIENTIFIC NAME(S): Honey, clarified as strained honey, mel

COMMON NAME(S): Honey, purified honey, miel blanc (French), honig (German)

BOTANY: Honey is a bee-concentrated and processed product of nectar from the flowers of numerous plants. This saccharine secretion is deposited in honeycombs by bees (*Apis mellifera* L., Fam. *Apidae*). The most desired and flavorful honeys come from the nectar of such flowers as the white clover blossom, raspberry blossom, and basswood flower.[1] Purified honey is prepared by melting honey at a moderate temperature, skimming off any impurities, and diluting with water to a density of 1.35 to 1.36 g/mL at 20°C.

HISTORY: The honey used for flavoring medicinals was first known historically as a flavored sweetening agent and was once the official honey of the National Formulary. Its use dates back to ancient times, with Egyptian medical texts (c. between 2600 and 2200 BC) mentioning honey in at least 900 remedies. [2] Almost all early cultures universally hailed honey for its sweetening and nutritional qualities, as well as its topical healing properties for sores, wounds, and skin ulcers. During wartime it was used on wounds as an antiseptic by the ancient Egyptians, Asyrians, Greeks, Romans, Chinese, and even by the Germans as late as World War I.

The 1811 edition of *The Edinburgh New Dispensatory*states, "From the earliest ages, honey has been employed as a medicine . . . it forms an excellent gargle and facilitates the expectoration of viscid phlegm; and is sometimes employed as an emollient application to abscesses, and as a detergent to ulcers." [2] It has consistently appeared in modern use for the same purposes by the laity and medical profession. Today, bees are commonly kept in Europe, the Americas, Africa, and Asia; at least 300,000 tons of honey are produced annually. Honey is used directly as a sweetener or fermented into a sweet-tasting mead, cyser, or metheglin. [3]

CHEMISTRY: Bees and other insects extract a thin, aqueous fluid (nectar) from the nectaries of various flowers. The composition of the nectar varies, but certain flowers offer distinct flavors to the different honeys. Some honeys can be poisonous if the nectar is obtained from poisonous plants (eg, mountain laurel, jimson weed, azalea, rhododendron[4]). When taken in by the bee, the nectar is modified by the secretions from glands in the head and thorax so that levulose, dextrose, and sucrose are formed. The color of honey varies. Honey is a thick, syrup-like liquid ranging in color from light yellow to goldenbrown. It is translucent when fresh, but darkens to opacity when old and can become granular through the crystallization of dextrose. Generally, honey has a characteristic odor and a sweet, faintly acrid taste. Honey is naturally mildly acidic. While honey varies in composition, its principle constituents are a mixture of dextrose and levulose in almost equal amounts ranging from 65% to 80% of one or the other. Sucrose ranges from 0.5% to up to 8%; dextrin from 1% to up to 10%.[1]

There have been numerous reports on an antimicrobial honey distillate fraction and related antifungal compounds. [5,6,7,8] These studies have shown that the activity is not simply due to the high sugar content. Thus far, the active antimicrobial principles have not been fully identified.

PHARMACOLOGY: Today, as in earlier times, honey is used as an ingredient in various cough preparations. It is also used to induce sleep, cure diarrhea, and treat asthma.[2] A review of literature from 1984 to March 2001 found at least 25 scientific articles verifying honey's wound and topical ulcer healing powers. A representative sample of these include articles on honey for wounds, ulcers, and skin graft preservation; [9] an analysis of 40 cases where honey was used on wounds and showed a positive (88% healing) effect;[10] honey and its healing properties for leg ulcers;[11] the successful use of honey for superficial wounds and ulcers;[12] honey as a wound-healing agent with antibacterial activity;[13] and the use of honey in wound management.[14] A number of related activities and unique medical applications include the following: The successful use of honey for treating *Helicobacter pylori*, the gastric ulcer causative agent;[15,16,17] effectiveness in treating burns;[18,19,20] usefulness in managing abdominal wound disruption in 15 patients after cesarean section; [21] use in treating senile cataracts[22] and postherpetic opacities of the cornea;[23] and moderate antitumor and pronounced antimetastic effects in rat and mice tumors.[24] A recent study showed that the application of commercial honey to surgical wounds in mice impeded subsequent tumor implantation.[25]

Interestingly, potent antibacterial peptides (apidaecins and abaecin) have been isolated and characterized in the honeybee (*Apis mellifera*) itself,[26,27] and a new potent antibacterial protein named royalisin has been found in the royal jelly of the honeybee. [28]

The antibacterial activity in diluted honey with the right pH (range 3.2 to 5) is attributed to hydrogen peroxide (H_2O_2), an enzymatic byproduct of the formation of gluconic acid from glucose. However, most of the antibacterial activities of honey are lost after heating or prolonged exposure to sunlight. [29,30] Honeydew honey from the conifer forests of the mountainous regions of central Europe and honey from manuka (*Leptospermum scoparium*) in New Zealand have been found to have high antibacterial activity. Manuka honey has a high level of activity against a variety of bacteria including *Staphylococcus aureus* and *epidermis*, *Streptococcus pyogenes*, and Enterobacteriaceae.[31,32,33,34] Active manuka honey (and its Australian equivalent) is the only honey commercially available that is tested for its antibacterial activity. It contains an additional antibacterial component found only in honey produced from Leptospermum plants called the "Unique Manuka Factor (UMF)." [35] Manuka honey was found to be a safe alternative topical antibiotic when compared with povidone iodine for the prophylaxis of dialysis catheter-related sepsis. [36]

TOXICOLOGY: Generally, honey is considered safe as a sweet food product, a gargle and cough-soothing agent, and a topical product for minor sores and wounds. However, medical reports indicate that honey can be harmful when fed to infants because some batches contain spores of *Clostridium botulinum*, which can multiply in the intestines and result in botulism poisoning. [37,38] Infant botulism is seen most commonly in 2- to 3-month old infants after ingestion of botulinal spores that colonize in the GI tract as well as toxin production in vivo. Infant botulism is not produced by ingestion of preformed toxin, as is the case in foodborne botulism. Clinical symptoms include constipation followed by neuromuscular paralysis (starting with the cranial nerves, then proceeding to the peripheral and respiratory musculature). Cases are frequently related to ingestion of honey, house dust, and soil contaminated with *Clostridium botulinum*. Intense management under hospital emergency conditions and trivalent antitoxin are recommended, although use of the latter in infant botulism has not been adequately investigated. [39]

SUMMARY: Honey is widely used as a nutritive agent for its flavor and caloric value. Its topical use for various wounds and skin ulcers is ancient and has been validated for its efficacy. Ongoing standardization and double-blind clinical trials should continue to prove its usefulness as an antibacterial and healing agent. Active manuka honey (from New Zealand and its Australian equivalent) is the only honey commercially available that is tested for its antibacterial activity. Be cautious in honey's use in infant formulations; botulism may result from *Clostridium botulinum* spores present in contaminated samples. Pollen in honey also may cause allergic reactions in some individuals. Recent studies on antibacterial peptides (apidaecins and abaecin) from the honeybee itself, may help explain its pharmacological activity.

PATIENT INFORMATION— Honey

Uses: Honey has been used as remedy for hundreds of ills, including as a gargle and as topical treatment for sores and wounds. Modern research lends support for this use in statistical findings and in isolation of antimicrobial and antifungal elements. Most of the antibacterial activities of honey are lost after heating or prolonged exposure to sunlight. There has been successful use of honey in treating *Helicobacter pylori*, burns, wound disruption in cesarean-section patients, senile cataracts, and corneal opacities.

Side Effects: Contaminated honey containing botulism spores can poison infants. Some people may have allergic reactions to pollen in honey. Honey made from the nector of poisonous plants can be poisonous.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HONEY

HOPS

DATE OF ISSUE: AUG 2003

REPLACES MONOGRAPH DATED: MAY 1991

SCIENTIFIC NAME(S): *Humulus lupulus* L. Family: Cannabaceae (Marijuana family)

COMMON NAME(S): Hops

BOTANY: Hops is a perennial climbing vine extensively cultivated worldwide. Male and female flowers are located on separate plants; the cone-shaped fruits are known as strobiles, which are collected in the fall and carefully dried.

HISTORY: Hops have been used for centuries to flavor and preserve beer. The bitter, aromatic taste of beer is mostly due to the hops content. Hops extracts are also used for other flavoring purposes in the food industry. Medical uses of hops and lupulin include aiding digestion, mild sedation, diuresis, and treating menstrual problems. Hops pickers have reported sedation during harvest, and hops flowers have been added to pillows for relief of nervous conditions.

CHEMISTRY: The most characteristic constituents of hops are the bitter principles, known as alpha- and beta-acids. In the plant the alpha-acids occur as humulone, cohumulone, and adhumulone.[1,2] During the brewing process, these compounds are isomerized to the iso-alpha-acid series of compounds, that possess the bitter taste.[3] The beta-acid series of compounds include lupulone and congeners; [1,2] this series is destroyed during brewing. The relative proportions of the bitter acids affect the quality of the hops, and many methods have been developed for quantifying hop acids in different varieties, including nuclear magnetic resonance (NMR)[1,4] and high-pressure liquid chromatography (HPLC).[5,6] The complex profile of hop acids is dependent on genetics, cultivation, and storage conditions. Long-term storage of hops leads to major deterioration in quality.

The essential oils of hops are less characteristic but are still important to hop quality. Over 100 volatile compounds have been identified, with gas chromatography and gas chromatography-mass spectroscopy (GC-MS) being key techniques for analysis.[7,8] Caryophyllene, beta-myrcene, and humulene are the most abundant constituents of hops volatile oils.

A third group of hops constituents is the prenylflavonoids. Xanthohumol is the dominant prenylflavonoid of hops, [9] with 8-prenylnaringenin also of importance.[10] A GC-MS method has been developed for the latter,[10] while liquid chromatography-tandem mass spectrometry (LC-MS) has been used to directly quantify prenylflavonoids and their isomerization products in beer and hops extracts. [11] The variation in prenylflavonoids between hops varieties has also been studied. [12] The fate of xanthohumol as hops is processed into beer has been studied; 20% to 30% is converted to isoxanthohumol. [13] The metabolism of xanthohumol in rat and human liver microsomes has also been characterized.[14,15]

PHARMACOLOGY

Sedative: The observation that hops pickers often experienced sedation prompted investigation of hops for sedative principles. The compound 2-methyl-3-buten-2-ol was isolated and found to reduce the spontaneous movement of rats when given intraperitoneally. [16] The small amounts found in hops[7] makes it unlikely that this compound completely explains hops sedation. Hops is often included in combination with valerian in sleep aids; studies of such products have found that valerian is more important to the pharmacologic activity than hops.[17,18,19]

Phytoestrogenic : 8-prenylnaringenin was found to be a potent estrogen receptor agonist in estrogen-responsive cells, while other hops phenolics were less active (isoxanthohumol, 6-prenylnaringenin) or had no activity (xanthohumol).[20] The amounts present in beer were considered to be too small to cause estrogenic effects. Use of hops in breast enhancement products; however, was cause for concern.[21,22] Estrogenic effects in vivo were observed in mice given isolated 8-prenylnaringenin in drinking water at 100 mcg/mL, using uterine vascular permeability as an endpoint. [23] Similar results were obtained in evaluation of hops extract for the treatment of menstrual symptoms.[24]

Cancer chemoprevention: Hops bitter acids have substantial effects on metabolic enzymes. Colupulone adsorbed on brewers' yeast was found to induce cytochrome P-450 3A in mice, an enzyme capable of N-demethylation of ethylmorphine.[25,26] However, short-term assays for aflatoxin or benzpyrene activation through colupulone induction of CYP450 did not find a change in mutagen activation. [27] While beer and other alcoholic beverages have been found to inhibit mutagenesis induced by carcinogens in an Ames test, the compounds responsible were not identified. [28] In a later study, several hops prenylflavonoids inhibited carcinogenic amine activation by CYP1A2.[29]

Humulone was identified as the active hops constituent that inhibited phorbol ester-induced inflammation in mice. [30] The same group later demonstrated that humulone was active in blocking tumor promotion in the classical two-stage model of carcinogenesis. [31] Several different hops prenylflavonoids demonstrated antiproliferative and cytotoxic effects in breast, colon, and ovarian human cancer cell lines. [32] 8-prenylnaringenin was shown to upregulate the cadherin and catenin genes in human breast cancer cells.[33] A comprehensive evaluation of xanthohumol as a cancer chemopreventative agent found that it warented clinical investigation because it had distinct activities at the initiation, promotion, and progression stages of carcinogenesis. [34]

Antibiotic and other: The hop bitter acids have antibacterial and antifungal activity important for the preservative function of hops in beer. When tested at the normal pH of beer (4.0), isohumulone inhibited bacterial growth at concentrations at which it is normally found in beer. [35] The prenylflavonoids of hops were shown to be more effective antioxidants than nonprenylated flavonoids.[36] Humulone potently suppressed COX-2 gene expression at the level of transcription.[37] Xanthohumols inhibited diacylglycerol acyltransferase, an effect of possible importance in lipid metabolism.[38] Polyphenolics of hops were shown to inhibit alpha-acid oxidase activity, thereby providing an internal control over hops' acid metabolism.[39] Hops proanthocyanidins were shown to inhibit neuronal nitric oxide synthetase and efficiently scavenge reactive nitrogen species.[40]

TOXICOLOGY: As an historical food constituent, hops has "generally recognized as safe" (GRAS) status by the FDA, however; use of medicinal quantities of hops may pose more risk than common levels of exposure in food use. Dogs appear to be somewhat sensitive to hops compounds. A malignant hyperthermic reaction was observed in 5 dogs who consumed boiled hops residues used in home brewing.[41] A subchronic toxicity study of the hops alpha-acids was conducted in dogs; while high doses induced vomiting, the animals generally tolerated lower doses without ill effects. A wide safety margin for humans was extrapolated from this experiment.[42]

SUMMARY: In addition to its use in brewing beer, hops has been used as a mild sedative, for menstrual complaints, and has been proposed as a cancer chemopreventative. It is generally welltolerated by humans.

PATIENT INFORMATION— Hops

Uses: Hops have been used for flavoring; hops and lupulin have been used as a digestive aid, for mild sedation, diuresis, and treating menstrual problems, but no clinical studies are available to confirm these uses.

Side Effects: There are no reported side effects when used in moderation.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HOPS

HOREHOUND

DATE OF ISSUE: SEP 1996

REPLACES MONOGRAPH DATED: JUN 1988

SCIENTIFIC NAME(S): *Marrubium vulgare* (Tourn.) L. Family: Labiatae

COMMON NAME(S): Horehound, hoarhound, white horehound

BOTANY: Horehound is native to Europe and Asia and has been naturalized to other areas, including the United States. [1] It is a perennial aromatic herb of the mint family. The plant grows to a height of about three feet and has oval leaves covered with white, woolly hairs. Horehound bears small, white flowers in dense whorls which bloom from June to August.

HISTORY: The leaves and flower tops of the horehound have long been used in home remedies as a bitter tonic for the common cold. They are now used primarily as flavorings in liqueurs, candies and cough drops. In addition, extracts of the plant had been used for the treatment of intestinal parasites and as a diaphoretic and diuretic. A different genus, the black horehound (*Ballota nigra*), is a fetid-odored perennial native to the Mediterranean area that is sometimes used as an adulterant of white horehound.

CHEMISTRY: The bitter principle of horehound is the volatile oil marrubiin, a diterpene lactone. Some researchers believe, however, that marrubiin is an artifact, generated from premarrubiin during isolation. In addition to marrubiin, horehound contains a sterol in an esterified form that is related to compounds found in other plants of the Labiatae family, and a sesquiterpene that has two nonconjugated double bonds and can be isolated from the nonsaponifiable fraction of extracts. [2]

At least six flavonoids have been isolated from the herb: Apigerin, luteolin, apigerin 7-glycoside, luteolin 7-glycoside, quercetin 3-glycoside and quercetin 3-rhamnoglycoside. Two crystalline precipitates from horehound have been found to contain four additional unidentified flavonoids. [3] Horehound contains normal alkanes and four types of branched alkanes: 2- methylalkanes, 3-methylalkanes, 2-(omega-1)-dimethylalkanes and 3-(omega-9)-dimethylalkanes. These molecules are in the C27-C33 series, with odd-numbered chains predominant. Two- and 3-methylalkanes are present in approximately equal proportions in short-chain compounds.[4]

In a related species, *Marrubium alysson*, five known glycosides: verbascoside, leucoseptoside A, martynoside, forsythoside B, leucosceptoside B and a new phenylpropanoid glycoside, alyssonoside, were isolated. [5]

Further constituents of horehound are essential oil made up of 0.06% mono and sesquiterpenes, 2.6% to 2.9% tannic acid, resinous substances (eg, ursolic acid), sterols (eg, beta-sitosterol), mucilaginous materials, bitter glycosides and pure marrubina (1,2,5-trimethylnaftalene). [6]

PHARMACOLOGY: Horehound has been used traditionally as an expectorant and continues to find a place in cough lozenges and cold preparations. The volatile oil has been reported to have expectorant and vasodilatory effects. Similarly, marrubiin stimulates secretion by the bronchial mucosa. [7]

A study in rats tested the hypothesis that marrubiin stimulates bile secretion. There was no evidence of this, but marrubiin acid, prduced by saponification of marrubiin, and the sodium salt of marrubiin acid did stimulate bile secretion. This effect was temporary. [8] Aqueous extracts of horehound are said to be serotonin-antagonists in vitro.[9]

In a recent study using rabbits, *Marribium vulgare* was found to have hypoglycemic effects.[10] This may be important for possible use as an antidiabetic agent.

TOXICOLOGY: Marrubiin has an LD_{50} of 370 mg/kg when administered orally to rats.[8] While marrubiin has been reported to have antiarrhythmic properties, it may also induce cardiac irregularities in larger doses.

SUMMARY: Horehound is an aromatic herb that has been widely used in folk remedies. It is most often classified as an expectorant. The active principle of the plant is marrubiin, metabolites of which may also influence bile secretion. Recently, a hypoglycemic effect has been reported. Although widely known, horehound has not been the subject of a large body of literature in the West.

PATIENT INFORMATION — Horehound

Uses: Horehound has been used as a flavoring, expectorant, vasodilator, diaphoretic, diuretic and treatment for intestinal parasites. It reportedly has hypoglycemic effects and influences bile secretion.

Side Effects: Large doses may induce cardiac irregularities.

Dosing: Horehound is given for digestive complaints as a crude herb at a daily dose of 4.5 and asa pressed juice of the herb at 30 to 60 mL. [12]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HOREHOUND

HORNY GOAT WEED

DATE OF ISSUE: SEP 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Epimedium grandiflorum*L. Family: Berberidaceae

COMMON NAME(S): Horny goat weed, Chien-Hsieh, Yin-Yang-Hua (arrow-leaf barrenwort)

BOTANY: Horny goat weed is a rhizomatous perennial herb. It is native to Japan, Korea, and parts of China and grows on hillsides and in cliff crevices and shady areas. The stems contain between 1 to 3 basal leaves. HGW has light yellow, violet, red, and white flowers, which appear in spring, along with oval fruits. [1]

HISTORY: *Epimedium* species have been used as tonics in Chinese herbal medicine to enhance sexual performance by increasing testosterone production, sexual energy, and overall well-being.[2,3]

CHEMISTRY: The medicinal properties of the plant are primarily contained within the leaves and roots. The roots of the plant contain flavonol glycosides and ikarisosides B, C, D, E, and F.[2,4,5] The aerial parts of the plant contain more than 30 nonflavonoidal glycosides. [4,6,7] Minor constituents include ionone derivative glycoside B_{10}, dihydrophenanthrene glycoside icariside A_5, and bibenzyl glycoside A_6. The glycosides of the dihydrophenanthrene and bibenzyl derivatives are found only in the genus *Epimedium*.[4]

PHARMACOLOGY: The results of a chemical study of the flavonoid icariin, isolated from the aerial parts of *E. grandiflorum*, alluded to evidence of a hypotensive pharmacological effect. However, in vivo studies on this hypotensive action are lacking. [8]

One article reports on a therapy using *E. grandiflorum*with vitamin C in treating viral myocarditis. Although the results may be statistically significant, further studies are needed to determine clinical significance. [9]

Historically, horny goat weed was said to possess aphrodisiac effects and improve impotence, spermatorrhea, and premature ejaculation. Some manufacturers claim the product has been used as a "natural sexual stimulator" for years in China and Japan. However, clinical trial data are lacking to support these claims. [3]

TOXICOLOGY: Further studies may be warranted to determine the toxicological profile of the plant. It is contraindicated in patients with known hypersensitivity reactions to *Epimedium*, as well as during pregnancy because of the lack of clinical studies.

SUMMARY: Historically, *E. grandiflorum* has been used as a tonic in Chinese herbal medicine to enhance sexual performance by increasing testosterone production. Although the product still is marketed today, clinical trial data are lacking to support these claims.

PATIENT INFORMATION— Horny Goat Weed

Uses: Historically used as a natural sexual stimulator by increasing testosterone production. However, clinical trial data are lacking to support these claims.

Side Effects: Contraindicated in patients with known hypersensitivity reactions to *Epimedium*. Because of the lack of clinical trial data, use during pregnancy is contraindicated.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
  "H" MONOGRAPHS
  HORNY GOAT WEED

HORSE CHESTNUT

DATE OF ISSUE: OCT 1998

REPLACES MONOGRAPH DATED: FEB 1995

SCIENTIFIC NAME(S): *Aesculus* Family: Hippocastanaceae. The most common members of the genus in the US and Europe are *A. hippocastanum* L. (horse chestnut), *A. californica* Nutt. (California buckeye) and *A. glabra* Willd. (Ohio buckeye).

COMMON NAME(S): Chestnut, horse chestnut, California buckeye, Ohio buckeye, buckeye.

BOTANY: Members of the genus *Aesculus* grow as trees and shrubs, often attaining heights of 75 feet. The fruit is designated a capsule with a thick, leathery husk that contains from 1 to 6 dark seeds (the nuts). As the husk dries, the nuts are released. The pink and white flowers of the plant grow in clusters. The tree is native to the Balkan woods and western Asia, but is now cultivated worldwide.[1]

HISTORY: Because of their widespread prevalence, chestnuts have been used in traditional medicine and for a variety of other commercial applications for centuries. Extracts of the bark have been used as a yellow dye, and the wood has been used for furniture and packing cases. In the western US, the crushed unripe seeds of the California buckeye were scattered into streams to stupefy fish, and leaves were steeped as a tea to remedy congestion. The horse chestnut has been used as a traditional remedy for arthritis and rheumatism.[2] Extracts are available commercially for oral, topical, and parenteral administration for the management of varicose veins and hemorrhoids.[2]

Even though the seeds are toxic, several traditional methods were employed to rid them of their toxicity. Seeds were buried in swampy, cold ground during the winter to free them of toxic bitter components, then eaten in the spring after boiling.[3] Indians roasted the poisonous nuts, peeled, and mashed them, then leached the meal in lime water for several days, creating a meal used to make breads.[4]

CHEMISTRY: The seeds of *Aesculus* contain a variety of complex constituents. The seed oil contains 65% to 70% oleic acid.[5] The seeds contain protein, ash, and 74% carbohydrate.[4] In addition, 5 triterpene oligoglycosides from horse chestnut seeds have been isolated.[6] The main anti-inflammatory constituent aescin (escin) is present in the plant.[1] This mixture of triterpene glycosides has been radioimmunoassayed,[7] and investigated by HPLC where it was obtained from both cotyledon and stem parts.[8] Triterpenoid saponins are also present in the plant.[1] Sapogenols hippocaesculin and barringtogenol-C 21-angelate have been obtained from fruit parts.[9] Flavonol glycosides quercitrin and its aglycone are also found. Coumarin glycosides found in horse chestnut include fraxin, scopolin, and their aglycones.[10] From the seeds, a lectin and its amino acid composition have been determined.[11] Other constituents include allantoin, sterols, leucocyanidin, leucodelphinidin, tannins, adenine, adenosine, carotin, choline, citric, and uric acids.[4,10] Members of the genus produce the toxic glycoside esculin (aesculin in some texts). This poorly characterized toxin is found in the twigs, sprouts, leaves, and nuts.[5]

PHARMACOLOGY: Commerical extracts of horse chestnut have been evaluated in the treatment of a number of disease states, primarily by European investigators. An extract of the plant (containing 50 mg of triterpene glycosides) decreases venous capillary permeability and appears to have a "tonic" effect on the circulatory system.[12] Constituent aescin inhibits the increase of (induced) vascular permeability in mice and rats.[13] A commercial horse chestnut extract, which contains 70% aescin, has been found to possess a number of pharmacologic properties in vitro and in vivo, including the ability to contract the canine saphenous isolated vein and to potentiate the contractile response to norepinephrine.[14] The bark yields aesculin, which improves vascular resistance and aids in toning vein walls. This is desirable for such ailments as hemorrhoids, varicose or problematic veins, leg ulcers, or frostbite.[1] Triterpene and steroid saponins from horse chestnut are effective in treating or preventing venous insufficiency in another report. Enzyme studies demonstrate that elastase (enzymes involved in turnover or perivascular substances) inhibition may be a mechanism involved.[15] Aesculin reduces capillary wall permeability by decreasing fluid retention, by increasing the permeability of capillaries, and allowing reabsorption of excess fluid back into the circulatory system.[1] Aescin displayed moderated diuretic activity in rats, markedly increasing renal loss of sodium, chloride, and potassium.[16] Anti-inflammatory effects of horse chestnut preparations also have been reported.[1,17] One reference reported a dosage of 20 mg/day (max) IV administration of preparation aescin to be effective in preventing or treating post-op edema.[18] Aescin extract reduces cutaneous capillary hyperpermeability induced by histamine or serotonin, and it decreases the formation of chemically induced rat paw edema.[14] In patients with chronic venous insufficiency, these extracts have been found to be effective in reducing patient complaints, along with objective measures of edema.[19] In a placebo controlled study, horse-chestnut seed extract improved edema signs and symptoms in patients suffering from venous edema of chronic deep vein incompetence.[20]

The bark of the horse chestnut has been found to possess anti-inflammatory activity, primarily due to the presence of the steroids stigmasterol, alpha-spinasterol, and beta-sitosterol.[21]

Other varied pharmacological effects of horse chestnut preparations include: Treatment of whooping cough from a decoction of the leaves,[1] hypoglycemic activity in rats,[22] fever reduction,[1,4] ability to absorb the skin-damaging UV-B radiation in suntan products,[10] trophic effect on rat muscle by constituent proanthocyanioin-A2,[23] and antimicrobial actions from recently isolated antifungal proteins.[24]

The pharmacology, pharmacokinetics, and toxicology of horse chestnut saponin (escin) has been reviewed.[25,26]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: *Aesculus* (horse chestnut) is classified by the FDA as an unsafe herb;[4] all members of this genus should be considered potentially toxic.[27] A number of components have been attributed toxic properties, including glycosides and saponins. Potential toxins identified in the genus include nicotine, quercitin, quercitrin, rutin, saponin, and shikimic acid.[4]

The most significant toxic principle is esculin. Poisoning is characterized by muscle twitching, weakness, lack of coordination, dilated pupils, vomiting, diarrhea, depression, paralysis, and stupor.[28] The nut is the most toxic part of the plant.[29] Children have been poisoned by drinking tea made from the leaves and twigs, and by eating the seeds; deaths have been reported following such ingestion. Amounts as little as 1% of a child's weight may be poisonous. Gastric lavage and symptomatic treatment have also been suggested.[28]

The LD_{50} of a single dose of the water-soluble portion of alcoholic extracts of horse chestnut seeds was calculated to be 10.6 mg/g body weight in chicks and 10.7 mg/g in hamsters. Extracts of the seeds of the Ohio buckeye were nontoxic to chicks and hamsters fed 80 mg/g in this study.[30]

Honey made mainly from the California buckeye has been reported to be toxic. A potential association between nasal cancer and long-term exposure to wood dusts, including dust from chestnut trees, has been reported.[31] Aflatoxins have been identified in some commercial skin cleansing products containing horse chestnut. Since aflatoxins are potent carcinogens that can be absorbed through the skin, it is imperative that strict quality control be applied to topical products containing potentially contaminated horse chestnut material.[32]

Horse chestnut pollen is allergenic and often associated with the development of allergic sensitization, particularly in urban children.[33]

A case report describes drug-induced hepatic injury to a 37-year-old male, induced by venoplant (horse chestnut extract preparation) given for treatment of bone fracture inflammation.[34]

An analysis of serious plant poisonings in Switzerland from 1966 to 1994 reveals horse chestnut to be responsible for 3 allergies and 2 anaphylactic shock episodes.[35]

SUMMARY: Chestnuts of the genus *Aesculus*should be considered toxic and cannot be recommended for internal use. However, they have a long history in traditional medicine, and recent research suggests that components of the horse chestnut may improve venous compliance and reduce edema in patients with chronic venous insufficiency.

PATIENT INFORMATION— Horse Chestnut

Uses: Sweet chestnuts, used as food, are of a separate genus than the horse chestnuts or buckeyes of traditional medicine, which are potentially useful against edema, inflammation, and venous insufficiency.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: All parts of plants in the *Aesculus* family are potentially toxic, especially the seeds. Horse chestnut has been classified by the FDA as an unsafe herb. Buckeye sawdust and horse chestnut components in skin cleansers are potentially carcinogenic. Even buckeye honey may be toxic.

Dosing: Horse chestnut extracts typically are standardized on content of triterpene glycosides, calculated as the major component, escin. Doses corresponding to 20 to 120 mg of escin have been used for venous insufficiency.[36,37]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HORSE CHESTNUT

HORSERADISH

DATE OF ISSUE: JUN 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Armoracia rusticana* Gaertn., Mey. and Scherb. Sometimes referred to as *A. lapathiofolia* Gilib. Family: Cruciferae

COMMON NAME(S): Horseradish, pepperrot, mountain radish, red cole, great raifort

BOTANY: Horseradish is a large-leafed, hardy perennial native to eastern Europe (eg, Russia, Poland, Finland) and western Asia. [1,2] More than 20 plants have been called "horseradish" throughout the ages. The plant is deep-rooted, may grow to a height of 1 m, and develops clusters of 4-petaled white flowers during the spring.[2] It is cultivated commercially for its thick, fleshy, white roots that have a strong, irritating, and intensely pungent taste. Some hybrids are sterile; therefore, the plant is generally propagated through root cuttings.

HISTORY: Horseradish has been cultivated and used as a medicine and condiment for approximately 2000 years. [1] Early settlers brought the horseradish plant to America, and the plant was commonplace in gardens by the early 1800s. Hardy varieties were obtained through plant selection and grown easily in the Midwest.

The root has a long history of use in traditional medicine. Topically, it was applied to the skin to reduce pain from sciatica and facial neuralgia. [1,3] Internally, it was used to expel afterbirth, relieve colic, increase urination, and to kill intestinal worms in children. [1,3]

The horseradish root is used as a condiment and may be grated and mixed with other flavorings to make sauce or relish. [3] Young tender leaves have been used as a potherb and as a salad green. Horseradish is one of the "five bitter herbs" (horseradish, coriander, horehound, lettuce, nettle) consumed during the Jewish holiday of Passover.

CHEMISTRY: The medicinal component is the root. The pungency of horseradish is due to the release of allylisothiocyanate and butylthiocyanate that occur in combination with the glucosinolates sinigrin[5] and 2-phenylethylglycosinolate. The pungency is released only upon crushing. The isothiocyanates are released from glucosinolates by the action of thioglucosidases, which are commonly referred to as myrosinase. [6] More than 6 volatile glucosinolates have been identified using gas chromatography-mass spectroscopy (GC-MS) analysis.[7] Other constituents of the root include asparagine, resin, ascorbic acid, and peroxidase enzymes. [2]

To preserve the quality of horseradish, the root is commonly dehydrated, freeze-dried, and powdered. [8]

Peroxidase enzyme is extracted from the root and is used as an oxidizer in commercial chemical tests such as blood glucose determinations. [9] The enzyme also has been used as a molecular probe in rheumatoid arthritis studies. [10]

PHARMACOLOGY: Horseradish is widely known for its pungent, burning flavor. Despite the potential for severe irritation, horseradish is generally recognized as safe for human consumption as natural seasoning and flavoring.

Topical application may cause an erythematous rash or allergic reaction because of the glucosinolate content. [4]

An extract of horseradish has been shown to inhibit the enzyme cholinesterase. [11]

Intravenous administration of horseradish peroxidase caused a marked hypotensive effect in cats. The hypotensive effect was completely blocked by aspirin and indomethicin, but not antihistamines. It is hypothesized that horseradish peroxidas acts by stimulating the synthesis of arachidonic acid metabolites. [12]

Dried and grated horseradish root fed in dosages of 100, 300, and 500 mg/kg mixed with food inhibited the growth of *Mycobacterium leprae* in mice in 1 study. The authors concluded that dried and grated horseradish root increased myeloperoxidase activity of blood neutrophils, enhanced antimicrobial functions of phagocytes, decreased leukocytosis, and normalized total blood cell count in mice with experimental leprosy. The most efficacious dose was 300 mg/kg mixed with food. Therapy duration of 5, 8, and 11 months produced no toxic effects on the functional activity of the liver (alanine and aspartate transaminases) in the control and intact animals.[13]

TOXICOLOGY: The isothiocyanates may irritate mucous membranes upon contact or inhalation. However, ingestion of large amounts can cause bloody vomiting and diarrhea.[14]

SUMMARY: For nearly 2000 years, horseradish has been cultivated and used as a medicine and condiment. The plant has a long history of traditional use. The pungency of the root develops upon enzymatic hydrolysis of thiocyanate-containing compounds. These irritants may cause severe inflammation to mucous membranes.

PATIENT INFORMATION — Horseradish

Uses: Horseradish has been used as a condiment, GI stimulant, diuretic, vermifuge, and externally for sciatica and facial neuralgia. However, there are no clinical trials to support any use for horseradish.

Side Effects: Irritant effects on GI mucosa. Consuming large amounts of the root may cause bloody vomiting and diarrhea. External use may cause erythematous rash. Horseradish is part of the cabbage and mustard family, so it may depress thyroid function. Use is best avoided during pregnancy and lactation because the allylisothiocyanates are toxic mucosal irritants. The isothiocyanates may irritate mucous membranes upon contact or inhalation. However, ingestion of large amounts can cause bloody vomiting and diarrhea.[14]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HORSERADISH

HORSETAIL

DATE OF ISSUE: MAR 2003

REPLACES MONOGRAPH DATED: OCT 1991

SCIENTIFIC NAME(S): *Equisetum arvense* L. Family: Equisetaceae

COMMON NAME(S): Horsetail, bottle brush, scouring rush, shave grass, Dutch rush, pewterwort[1,2,3]

BOTANY: This plant is native to Europe, North America, North Africa, and northern Asia.[4] Horsetail is a pteridophyte more closely related to ferns than to flowering plants and produces spore-sacs that are visible during March through September.[1] This small, deep-rooted, rush-like perennial grows to about 0.3 m. It has hollow, pointed stems, scale-like leaves, and no flowers. Horsetail grows best in moist and shady areas.[3]

HISTORY: Traditionally, the plant has been used as a diuretic, an antitubercular drug, and in the treatment of genitourinary and respiratory disorders, arthritis, and bleeding ulcers.[2] Owing to the abrasive nature of its high silica content, horsetail has been used to clean dishes, sand wood, and polish metal.[3] Externally, it has been used in cosmetics[5] and as an astringent to stop bleeding[6] and stimulate wound healing.[7]

CHEMISTRY: The stems of horsetail contain 5% to 8% of silica and silicic acids. The plant contains about 5% of a saponin called equisetonin, in addition to the flavone glycosides isoquercitrin, equisetrin, and galuteolin.[8] The sterol fraction of *E. arvense* contains beta-sitosterol, campestrol, isofucosterol, and trace amounts of cholesterol.[9] The alkaloid nicotine is present in minute amounts (less than 1 ppm)[8] but may account for a portion of the pharmacologic activity of the plant. The plant contains more than 15 types of bioflavonoids, as well as manganese, potassium, sulfur, and magnesium.[2,10] The cytokinin isopentenyladenosine has been identified in fertile fronds.[11]

PHARMACOLOGY: The plant exerts slight diuretic activity, which may be due to the combined effects of equisetonin and the flavone glycosides. The historical data reporting the use of horsetail in the treatment of urological disorders, tuberculosis, or to enhance wound healing have been neither confirmed nor disproved.

TOXICOLOGY: Horsetail has been listed as an herb of undefined safety by the FDA.[12] Ingestion of large amounts of the fern may be toxic. There have been reports of children being poisoned by using the stems as blowguns or whistles.

Crude horsetail contains the enzyme thiaminase, which destroys the B-vitamin thiamine. Thiaminase poisoning may lead to permanent liver damage.[1] The Canadian Health Protection Branch prohibits this enzyme in dietary supplements, and supplement manufacturers must provide supportive documentation of its removal.[2]

In animals, the ingestion of horsetail produces muscle weakness, ataxia, weight loss, abnormal pulse rate, cold extremities, and fever.[13] These symptoms are similar to those seen in nicotine intoxication. Hay composed of 20% or more *E. arvense* produced these symptoms in 2 to 5 weeks.[7]

E. palustre contains toxic alkaloids,[2,10] and cattle appear to recognize the odor of this species of horsetail and refuse to eat hay contaminated with about 12% *E. palustre*.[14] Horsetail also may induce seborrheic dermatitis in animals.[15,16]

SUMMARY: Horsetail continues to find some use in OTC herbal preparations. It contains small amounts of nicotine and other physiologically active compounds and is a marginally effective diuretic.

PATIENT INFORMATION— Horsetail

Uses: Horsetail has been used as a diuretic, in the treatment of kidney and bladder ailments, as an astringent to stop bleeding and stimulate healing, as an antitubercular drug, and as a cosmetic component, although there is a lack of clinical trials.

Side Effects: Horsetail is of undefined safety and may be toxic, especially to children. Avoid use during pregnancy.[17]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HORSETAIL

HUPERZINE A

DATE OF ISSUE: MAY 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Isolated from *Huperzia serrata* (Thunb.) Trev. Family: Lycopodiaceae (club moss)

COMMON NAME(S): Qian Ceng Ta = Chien Tseng Ta. Other products that contain huperzine A are Memorzine, Brainmax, Neuroflow

BOTANY: Huperzine A is isolated from the club moss *Huperzia serrata*, also known as *Lycopodium serratum* Thunb. Club mosses are primitive, vascular plants that were dominant in the Carboniferous period when they grew to the size of trees and contributed to the coal deposits then being formed. They differ from true mosses by having specialized fluid-conducting tissues, but like mosses, they reproduce by means of spores, which are either clustered into small cones or borne in the axils of the small scale-like leaves. Some species of *Lycopodium* are called ground pine or creeping cedar, especially those that resemble miniature hemlocks with flattened fan-shaped branches often used for Christmas decorations.

HISTORY: The club moss *H. serrata* has been used in Chinese folk medicine under the name Qian Ceng Ta, for the treatment of bruises, strains, swelling, and schizophrenia.[1] It also has been used for fever.

CHEMISTRY: The novel alpha-pyridone alkaloids of huperzines A and B were isolated in 1986 from *H. serrata*.[2] The identity of huperzine A with selagine, an alkaloid isolated earlier from a *Lycopodium* species, was established in 1989. The structure of selagine originally proposed was incorrect. [3] X-ray crystallography provided a final confirmation of the structure, [4] and nuclear magnetic resonance (NMR) assignments have been made.[5] The huperzine structure is distinctly different from many of the alkaloids isolated from club mosses,[6] though systematic investigations of Chinese club mosses have found huperzine A in numerous species.[7] The yield of huperzine A from *H. serrata* is reported to be about 0.1% on a dry weight basis.[8] A number of syntheses of huperzine A have been published,[1,9,10,11] and the structure-activity relationships of analogs with regard to cholinesterase activity have been investigated in detail. [12]

PHARMACOLOGY: Huperzine A is a specific, reversible inhibitor of acetylcholinesterase and is active at low nanomolar concentrations. A crystallographic analysis of a huperzine A complex with the enzyme from an electric eel has been published.[13] More detailed analyses of huperzine B and the enantiomer of natural huperzine A also have been made.[14] These structural biological investigations have assisted in an understanding of the pharmacophore and in rational design of analogs.[15,16,17,18] Huperzine A's profile vs 2 cholinesterase isoforms from different brain regions has been compared with the other cholinesterase inhibitors tacrine, donepezil, rivastigmine, and physostigmine. Huperzine A preferentially inhibited the tetrameric (G4) form of cholinesterase in all brain regions, while the other drugs were most active against the monomeric (G1) form.[19] Racemic huperzine A was less active vs rat cholinesterase in vivo than the natural compound, [20] which is consistent with the findings of the crystallographic studies. [14]

In neuronal cell cultures, huperzine A reduces cell death caused by glutamate, [21] nitric oxide,[22] or hydrogen peroxide.[23] The latter effect involves the apoptosis-related genes p53 and bcl-2.[24] Similarly, oxygen and glucose deprivation of pheochromocytoma cells leads to apoptosis through regulation of the same genes; these effects were blocked by huperzine A and donepezil.[25,26] Further studies of apoptosis and the role played by caspase-3 in cultured rat cortical neurons found that huperzine improved neuronal survival by inhibiting the mitochondrial apoptotic pathway. [27]

Patch-clamp studies of rat hippocampal neurons have demonstrated that huperzine A is capable of inhibiting *N*-methyl-D-aspartate (NMDA)-induced currents while having no effect on kainate- or alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate-induced currents. [28] Other studies by the same laboratory found a very weak inhibition of potassium currents by huperzine A.[29,30]

Huperzine A was capable of displacing the NMDA receptor ligand MK-801 from rat brain membranes with an IC-50 of 37 micromolar. Tacrine was also weakly active at the same concentration; however, binding inhibition and cholinesterase potencies did not correlate. [31] Furthermore, both enantiomers of huperzine A had similar potency in this assay.[32] Spermine shifted the dose response curve to the right, suggesting that huperzine A is a weak, noncompetitive NMDA receptor antagonist acting at polyamine binding sites.[33]

Studies with beta-amyloid peptide fragments have shown huperzine A to oppose its suppression of long-term potentiation in rat hippocampal slices, [34] protect against induction of oxidative injury in pheochromocytoma cells,[35,36] and block apoptosis in rat cortical neurons.[37] This protection was not stereospecific, indicating that cholinesterase was probably not involved in these neuroprotective effects. [38] In a whole animal model, huperzine A reversed the negative effects of beta-amyloid protein on maze learning.[39]

Other whole animal models of learning and memory have shown huperzine A to have activity. Huperzine A protected gerbils from neuronal damage and cognitive deficits produced by transient ischemia.[40] Similar results were found in rats with hypoxic/ischemic brain injuries[41] and by chronic cerebral hypoperfusion.[42] Scopolamine-induced impaired maze performance was improved by huperzine A, while tacrine and E2020 were less effective. [43,44] In macaques treated with reserpine, yohimbine, or scopolamine, huperzine A improved working memory.[45,46] It also was effective in improving memory in otherwise untreated, aged macaques.[46]

Huperzine A is selective for brain acetyl cholinesterase over plasma butyryl cholinesterase. [47] It possesses analgesic properties in common with other cholinergic drugs.[48] The antinociceptive actions of huperzine were reduced by antisense inhibition of the M1 muscarinic receptor in mice and by scopolamine but not naloxone. [48] Finally, huperzine A was isolated as the insecticidal and antifeedant principle from a New Zealand club moss. [49]

Treatment of Alzheimer disease (AD): A variety of cholinergic agents, including cholinesterase inhibitors, have been studied for symptomatic treatment of AD. [50] Human clinical studies of huperzine A for AD have been conducted only in China. [51,52] The pharmacokinetics of huperzine A in humans was evaluated by high pressure liquid chromatography; the drug was rapidly absorbed, widely distributed to tissue, and eliminated at a moderate rate. [53] An early efficacy study in 56 multi-infarct and senile dementia patients and 104 patients with senile or presenile memory disorders found efficacy, as evaluated by the Wechsler memory scale, at doses of 0.05 and 0.03 mg twice daily, respectively. Side effects were minimal, but treatment was limited to 2 to 4 weeks. [54] A double-blind, placebo-controlled trial in 50 Alzheimer patients over 8 weeks found improvement in memory, cognitive, and behavioral scores with 0.2 mg of huperzine A twice daily. [55] A similar study of 60 AD patients over 60 days compared tablet and capsule formulations, finding both dosage forms comparably effective in reducing oxygen-free radicals and improving psychological ratings.[56] A larger randomized study (N = 202) of mild to moderate AD patients found that huperzine A improved cognitive function, activity of daily life, and noncognitive disorders over a 12-week period compared with placebo. [57]

Soman nerve gas antidote: Huperzine A's potent inhibition of cholinesterase also has made it a candidate for prevention of poisoning by the nerve agent soman and other organophosphates. In contrast to pyridostigmine, huperzine A crosses the blood-brain barrier and, therefore, may be effective in preventing seizures and other neuropathology caused by soman.[58] In mice, huperzine A provided longer lasting protection against soman poisoning than pyridostigmine (6 hours vs 90 minutes). [59] In rats, it protected against soman-induced seizures and lethality. [60]

TOXICOLOGY: Huperzine A is approved for use as a drug for the treatment of AD in China; however, it is regulated as an herbal supplement in the United States.[61] Several firms (Solgar, Pharmavite, GNC, Kingchem, and NOW Foods) filed the required premarket notifications with the FDA between 1997 and 2000 for

huperzine A products manufactured in China from natural sources.[62] The marketing of a pure pharmaceutical compound as a supplement raises questions about the scope and intent of the Dietary Supplement Health and Education Act of 1994 legislation that makes this possible. The acute oral LD-50 of huperzine A in rats has been reported as 4.6 mg/kg in an FDA filing. Other FDA filings report oral LD-50 values of 5.2 mg/kg in mice and 26 mg/kg in rats. Typical human doses in clinical trials have been 0.05 mg twice daily.

SUMMARY: Huperzine A is an alkaloid isolated from a Chinese club moss. It is a potent and specific inhibitor of acetylcholinesterase. Clinical trials in China have shown some evidence of efficacy in AD; however, huperzine A is only available in the United States as a dietary supplement. It is also under investigation for prevention of nerve gas poisoning. There is little published evidence concerning its safety.

PATIENT INFORMATION— Huperzine A

Uses: Historically, huperzine A has been used for the treatment of bruises, strains, swelling, schizophrenia, and fevers. It is being studied for potential use in treating Alzheimer disease and preventing nerve gas poisoning.

Side Effects: There is little published evidence concerning its safety.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HUPERZINE A

HYSSOP

DATE OF ISSUE: SEP 1996

REPLACES MONOGRAPH DATED: JAN 1987

SCIENTIFIC NAME(S): *Hyssopus officinalis* L. Family: Labiatae

COMMON NAME(S): Hyssop. It should be noted that there are a number of other common plants found in North America that go by a variation of the name "hyssop." These include giant hyssop (*Agastache* sp.), hedge hyssop (*Gratiola officinalis*L.), and water hyssop (*Bacopa* sp.); none of these plants are members of the genus *Hyssopus*, nor are they all members of the Family: Labiatae.

BOTANY: Hyssop is a perennial plant which is native to the Mediterranean region and has been imported to and naturalized in the United States and Canada. It grows along roadsides and is sometimes found as a garden herb. Its thin pointed leaves extend onto a central herbaceous stem that is sessile in form. The tubular flowers grow from the upper leaf axils and bloom small blue flowers from July to October. The fruit contains four "nutlets," each having one seed. Hyssop is quite similar in appearance to other members of the mint family. It grows to about 2 feet. Its volatile oil imparts a highly aromatic camphor-like smell. [1]

HISTORY: Hyssop has been noted for centuries in herbal medicine. In addition, there are a number of references in the Bible to plants called "hyssop," although there is considerable controversy regarding the actual identity of these plants. There is little evidence that the plant mentioned in Bible was actually " *H. officinalis*."

The ancient use of this plant was an insecticide, insect repellent and pediculicide. [2] The plant has been used in herbal medicine for the treatment of sore throats, colds, hoarseness and as an expectorant.[3] Some herbalists also believe that hyssop has beneficial effects for asthma, urinary tract inflammation and appetite stimulation.[1] Its effectiveness in relieving gas and colic are also listed under its medicinal uses. [2]

Although an extract of the leaves has been suggested for the treatment of wounds, there does not appear to be strong evidence for its effectiveness as an antibacterial.

Extracts of plant have been used in perfumes and to flavor liqueurs, sauces, puddings and candies. [4]

CHEMISTRY: As a member of the mint family, hyssop contains a number of fragrant, volatile components. Pinocamphone, isopinocamphone, alpha- and beta-pinene, camphene and alpha-terpinene make up about 70% of the volatile oil. [5] The plant contains 0.3% to 2% of this volatile oil. Other constituents include glycosides (hyssopin as well as the flavonoid glycosides, hesperidin and diosmine), 5% to 8% tannin, oleanolic acid, ursolic acid, ß-sitosterol, marrubiin and resins. Other substituents reported are pinocampheol, cineole, linalool, terpineol, terpinyl acetate, bornyl acetate, *cis*-pinic acid, *cis*-pinonic acid, myrtenic acid, myrtenol methyl ether, *d*-2-hydroxyisopinocamphone, methyl myrtenate, cadinene and other unidentified compounds totalling more than 50 in number. [4]

Crude hyssop also contains 0.5% rosmarinic acid and total hydroxycinnamic derivatives at 2.2%. [4] Another recent gas chromatographic study confirms the presence of the above constituents of *H. officinalis* and states percentage values for them, the most prevalent being pinocamphone (69.1%). [6]

PHARMACOLOGY: Still used today by herbalists for its beneficial effects, hyssop's volatile oil represents the most important fraction of this plant. It may have some small beneficial effect in the treatment of sore throats and as an expectorant.

Hyssop oil is used to fragrance perfumes and soaps. It was found to be nonirritating to the skin in both animal and human studies. [4]

Extracts of dried leaves of *H. officinalis* exhibit strong antiviral activity against HIV, probably due to the caffeic acid, tannins and unidentified high molecular weight compounds present.[7] Anti-HIV activity was also recently found in a study where an isolated polysaccharide inhibited HIV-1 replication. [8] Both studies suggest this anti-HIV activity may be useful in healing AIDS patients.

TOXICOLOGY: Hyssop is classified among plants "generally recognized as safe (GRAS) " by the FDA; however, three recent studies demonstrate convulsant actions associated with the plant's use in rats. Commercial preparations of hyssop essential oils produced convulsions in rats at 0.13 g/kg and death at 1.25 g/kg. [9]

The neurotoxicity of hyssop appears to be related to two terpene ketones: Pinocamphone and isopinocamphone. [9] In a similar study, IP injections of hyssop essential oil, ranging from 200 mcl/kg to 4 mcl/kg, produced a generalized crisis in rats that led from convulsions to death. The authors concluded that hyssop essential oils are not as safe as most people believe.[10] The convulsions were later determined, by electrocortical evidence, to be of CNS origin. [11]

SUMMARY: Hyssop represents a useful herbal compound. It is used commercially as a flavoring agent and as an ingredient in cough and cold preparations. It appears to exert its demulcent and expectorant effects through the action of its volatile oil. However, it must be used with caution because of its convulsive effects.

More studies are needed to verify the reported antiviral therapeutic efficacy which may be of use in HIV infected patients.

PATIENT INFORMATION— Hyssop

Uses: Hyssop is used as flavoring, fragrance, insecticide, insect repellent and cough and cold treatment.

Side Effects: The essential oils have produced fatal convulsions in rats.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "H" MONOGRAPHS
    HYSSOP

"I" MONOGRAPHS

IBOGA

DATE OF ISSUE: OCT 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Tabernanthe iboga*. Family: Apocyanaceae.

COMMON NAME(S): Iboga

BOTANY: The iboga plant is native to Gabon, Zaire and the Congo and is the only member of the dogbane family known to be used as an hallucinogen. [1] The plant is cultivated throughout west Africa.[2] The yellow-colored root is used in traditional medicine and is the source of the hallucinogenic principle.

HISTORY: The growing use of iboga has been said to be an important force against the spread of Christianity and Islam in its native growing regions. [1] The root of the plant is used in initiation rites of some African cultures. The plant is believed to be an aphrodisiac and stimulant. Large doses are used to induce a euphoric state in which people are said to be able to communicate with the spirits of their ancestors. In addition, the plant is consumed by those who believe it can reveal objects reputedly buried by individuals subjected to the intoxicant during their former lives. Failure to retrieve these hidden treasures has resulted in "sudden and mysterious deaths" among villagers.[2] The use of iboga is legally prohibited in the United States. [3]

CHEMISTRY: Indole alkaloids comprise approximately 6% of the root[3] and ibogaine is the principle indole alkaloid among the dozen or more identified to date. [4] Other related alkaloids include ibogamone, tabernanthine, and iboluteine. [3] The root contains a tannin.

PHARMACOLOGY: The dried root bark is chopped into a fine powder often mixed with other hallucinogenic plants. Alternately, the root is chewed to obtain the desired effect.

Ibogaine is a cholinesterase inhibitor. [3] As such, the effects of iboga are secondary to increases in synaptic concentrations of acetylcholine.

The pharmacologic effects are dose-dependent and range from mild excitation and euphoria to visual and auditory hallucinations. Related pharmacologic effects of cholinergic hyperactivity include slowing of the heart rate, hypotension, convulsions, paralysis, and respiratory arrest. [1,3] Hallucinations are typically accompanied by anxiety and apprehension and may only occur with doses large enough to cause death. [3]

Tabernanthine demonstrates cardiac conduction effects characteristic of a calcium channel antagonist; it also has other pharmacologic actions that are due to the inhibition of cellular calcium metabolism and are related to the turnover of intracellular calcium that is released by noradrenaline. [5,6]

SUMMARY: Iboga is an hallucinogen that is popular in western and central Africa. While it is considered a powerful drug, the hallucinatory effects are usually only experienced at the highest doses, which are also the doses most likely to induce death. Ibogaine is a cholinesterase inhibitor and related alkaloids also exhibit calcium channel blocking activity.

PATIENT INFORMATION — Iboga

Uses: Iboga is used ritually as a hallucinogen.

Side Effects: Iboga is illegal in the United States. It can cause paralysis and eventually death.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "I" MONOGRAPHS
    IBOGA

INDIAN FRANKINCENSE TREE

DATE OF ISSUE: JUN 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Boswellia serrata* Roxb. Family: Burseraceae

COMMON NAME(S): Indian frankincense tree, "salai guggal" (term for the gum resin of the tree)

BOTANY: The *Burseraceae* family of trees and shrubs has 18 genera and 540 species that grow mostly in tropical regions of America, North Africa and Arabia. Most species contain resin ducts in the bark, which yield the products myrrh and frankincense. [1] The *Boswellia serrata* tree grows on dry hilly areas throughout most of India. When the bark is cut, the "aromatic balsam" or "gum resin" oozes out and is used for medicinal purposes. [2]

HISTORY: The Indian frankincense tree is related to the tree that brought forth the frankincense given as a gift to baby Jesus by the wise men. Ayurvedic medicine has been practiced in India for thousands of years, using different parts of the tree for asthma, rheumatism, dysentery, skin ailments, ulcers, blood purification, bronchial conditions and wound treatment.[2] Frankincense is also used to perfume clothes, hair and rooms. It is enjoyed at traditional festivities such as weddings or religious celebrations.[1]

CHEMISTRY: The gum resin of *Boswellia serrata* contains the biologically active boswellic acid (3-alpha-hydroxy-urs-12-en-23-oic acid) and its derivatives. [3]

Boswellin (patented product of Sabinsa Corporation)[2] is the standardized ethanol extract of *Boswellia serrata* gum resin. It contains 60% to 65% boswellic acids and can be found in health food stores.[2]

Isolation and identification of a 4-O-methyl-glucuronoarabinogalactan from *Boswellia serrata* have been performed.[4]

Other compounds found in the gum resin include volatile oils, terpinols, arabinose, xylose, galactose, uronic acids, beta-sitosterin and phlobaphenes. [5]

PHARMACOLOGY: Anti-inflammatory activity has been studied in animals.[3] The plant extract displays marked anti-inflammatory action as well as anti-arthritic activity with no significant side effects in rats.[6] A mixture of boswellic acid and its derivatives is used in India to treat arthritis. [3]

Boswellic acids in vitro are specific inhibitors of 5-lipoxygenase, the key enzyme of leukotriene biosynthesis. Leukotrienes are biochemicals in the body that maintain inflammation. Boswellic acids may offer an alternative to corticosteroid and NSAID therapy in treating such inflammatory conditions as arthritis, tendinitis or bursitis. [2,3] One report evaluates boswellic acid inhibition on leukotriene synthesis (via 5-lipoxygenase), finding it to have no effect on 12-lipoxygenase, cyclooxygenase or the peroxidation of arachnidonic acid by iron and ascorbate, suggesting the boswellic acid component to be a specific, non-redox inhibitor of leukotriene synthesis. [7] Similar results were found in rat peritoneal neutrophils. [8,9]

Boswellia serrata in an herbomineral combination was studied in 42 osteoarthritic patients in a randomized, double blind, placebo controlled crossover study. Pain and disability scores were significantly decreased but radiological assessment showed no change. [10]

In an immunological study, boswellic acids have also been shown to possess anti-complementary activity via C3-convertase inhibition. [11] C3-convertase is involved in the production of anaphylatoxin.[16]

Salai guggal, the gum resin exudate of *Boswellia serrata*, has been evaluated for effects on: Glycosaminoglycan metabolism in rats,[12] humoral immune response, inhibiting infiltration of polymorphonuclear leukocytes in rats [13] and some analgesic and psychopharmacological effects.[14]

In patients given *Boswellia serrata* gum resin preparation (350 mg 3 times daily) for 6 weeks compared with sulfasalazine (1 g 3 times daily), parameters of ulcerative colitis (eg, stool properties, histolopathology, rectal biopsies, blood work) were improved. Remission was 82% with the resin and 75% with sulfasalazine. Ulcerative colitis, also an inflammatory disease, seems to benefit from Boswellia's ability to inhibit 5-lipoxygenase as well. [15]

TOXICOLOGY: The limited data available on toxicity of the Indian frankincense tree include: No side effects, [2,5] no cytotoxic effect,[13] no effects on cardiovascular, respiratory or CNS function, no ulcerogenic effects[6] or "side effects observed...did not necessitate withdrawal of treatment."[10]

SUMMARY: The Indian frankincense tree is well known for its gum resin, which is used for frankincense and myrrh. This species (of which there are many), *Boswellia serrata*, has been used in ayurvedic medicine for thousands of years, treating such ailments as asthma, dysentery, skin problem, ulcers and wounds. The constituent boswellic acid is known to be a specific inhibitor of 5-lipoxygenase, an enzyme responsible for synthesis of leukotrienes that maintain inflammation. Clinical trials are available studying its anti-inflammatory effects in the treatment of arthritis and colitis. The toxicity profile is low, with most studies reporting no side effects.

PATIENT INFORMATION — Indian Frankincense Tree

Uses: The extract of Indian frankincense tree has anti-inflammatory activity. Boswellic acids may play a role in preventing formation of anaphylatoxins during severe acute allergic reactions.

Side Effects: Although data are limited, no side effects have been reported that necessitated stopping treatment.

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- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "I" MONOGRAPHS
    INDIAN FRANKINCENSE TREE

INDIGO

DATE OF ISSUE: NOV 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Indigofera* species including *I. tinctoria* (French indigo) and *I. suffruticosa* Mill. (Guatemalan indigo) formerly known as *I. anil* L. Family: Fabaceae (Leguminosae).

COMMON NAME(S): Common or Indian Indigo; not to be confused with false, wild or bastard indigo (*Baptisia tinctoria* L), a native North American plant from which a blue dye is obtained from the leaves.[1,2]

BOTANY: These plants are perennial shrubs that reach a height of 1 m to 2 m. The French and Guatemalan varieties differ in the shape and size of the leaflets and pods.

HISTORY: Indigo refers to several species of *Indigofera* that are known for the natural blue colors obtained from the leaflets and branches of this herb.[1] Before the development of synthetic aniline and indigo dyes, indigo plants were grown commercially in the East Indies and South and Central America. Indigo was a popular dye during the middle ages.[1] It has been used medicinally as an emetic; the Chinese used the plant to purify the liver, reduce inflammation and fever and to alleviate pain.[1] Extracts of *I. tinctoria* have been reported to have nematicide activity and the leaf and plant juice have been used to treat cancers, particularly of the ovaries and stomach.[3] In addition, the plant has been used for the treatment of numerous ailments ranging from hemorrhoids to scorpion bites.

CHEMISTRY: The blue dye is produced during the fermentation of the leaves, which is commonly accomplished with caustic soda or sodium hydrosulfite.[1] A paste exudes from the fermenting plant material and this is processed into cakes that are finely ground. The blue color develops as the powder is exposed to air.

Indigo dye is a derivative of indican, a glucoside[3] component of numerous *Indigofera* species and this is enzymatically converted to blue indigotin.[1] This colorfast dye is combined with stabilizers and other compounds to produce a wide range of colorants. Today, almost all indigo used commercially is produced synthetically.

PHARMACOLOGY: Little is known about the pharmacologic effects of *Indigofera* species. Preliminary evidence suggests that *I. tinctoria* may have a protective effect against carbon tetrachloride-induced hepatotoxicity,[4] which is opposite to the hepatotoxic effect observed with other members of this genus. The related *I. aspalathoides* has been reported to possess anti-inflammatory activity.[5]

TOXICOLOGY: Indigo appears to be a mild ocular irritant.[3] Dermatitis is common among indigo dyers but there is no direct evidence that this is linked to exposure to the plant or dye.[3] *I. spicata* is recognized as a teratogen due to the presence of indospicine. Indospicine also is hepatotoxic.[6,7] In animals, it causes cleft palate and embryo lethality.[8] *I. endacaphylla* (creeping indigo) has been responsible for livestock poisonings and deaths.[1]

SUMMARY: The *Indigofera* species have been used for centuries as a natural source of an exquisite blue dye. While the medicinal uses and claims for the plants are numerous, there is little evidence to verify these effects. Several species of *Indigofera* are toxic.

PATIENT INFORMATION — Indigo

Uses: Chiefly a source of dye, indigo has also been used as a nematicide and treatment for a range of ills including scorpion bites and ovarian and stomach cancer.

Side Effects: Some species are toxic and cause birth defects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "I" MONOGRAPHS
    INDIGO

IPECAC

DATE OF ISSUE: AUG 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Cephaelis ipecacuanha*A. Rich. Also known as *Psychotria ipecacuanha.* Other *Cephaelis* species include *C. acuminata* (Cartagena ipecac).[1] Family: Rubiaceae

COMMON NAME(S): Ipecac, ipecacuanha, golden root, Rio or Brazilian ipecac, Matto Grosso ipecac, Costa Rica ipecac

BOTANY: The ipecac is a small perennial tropical plant that grows to about 2 feet in height. Horizontal roots extend from its slender underground stem. At maturity, the roots have a dark brown or red covering, a bitter taste and a musty odor. The plant is native to the humid forests of Bolivia and Brazil where large plantations have been established to commercialize the collection of ipecac root. Much of the root crop continues to be harvested from the wild, particularly in South America. [2] India is also an important producer of ipecac.

HISTORY: Brazilian Indians valued ipecac as a remedy for dysentery and this information was brought to Europe by Portuguese missionaries. [3] The dried root and rhizome are the source of the medicinally useful products. Ipecac has been widely used in its syrup form as a potent and effective emetic. Ipecac powder had been used to induce sweating at the onset of influenza and small amounts of the extract have been incorporated into cough syrups as expectorants. Emetine, derived from the root, has been used for more than a century to treat dysentery. [1]

CHEMISTRY: The root and rhizomes of ipecac contain a number of closely related isoquinoline alkaloids in a total concentration of up to 2.5% by weight of the root.[1] These are primarily emetine, cephaeline and psychotrine. Because leaves contain less than 0.5% emetine, they are usually not processed commercially. More than a half-dozen additional alkaloids are distributed thoughout parts of the plant. Emetine may be manufactured commercially by the chemical modification of either cephaeline or psychotrine.

PHARMACOLOGY: The syrup induces vomiting in 15 to 60 minutes, and is most effective when accompanied by fluid intake. Ipecac induces vomiting both by an irritant action on the intestinal mucosa and produces reflex vomiting and diarrhea; it also exerts a central emetic action. [5] Emetine has primarily a central action on the chemoreceptor trigger zone.

Both cephaeline and emetine are active amebicides, although emetine is more active. Emetine injected intramuscularly is distributed systemically and kills the motile trophozoites of *Entamoeba histolytica*in doses smaller than are effective against cysts.[5] The drug inhibits cell protein synthesis. [5] The drug does not reach high levels in the gut and therefore is not effective against amebic dysentery. It is useful for amebic abscesses and hepatitis.

TOXICOLOGY: Ipecac extracts can be highly toxic when given either acutely or chronically. Powdered ipecac is a respiratory irritant and pharmacists may develop rhinitis or asthma following repeated exposure to the powder during compounding procedures. [1]

Cephaeline is more toxic than emetine, causing more nausea and vomiting.[4] Emetine, which constitutes more than half of the total ipecac content, is a cardiotoxin. [4] If given over a period of time or in total doses exceeding 1 g, the cumulative effect of emetine may lead to myositis at the injection site, gastrointestinal and nervous system symptoms, hematuria and circulatory collapse. Emetine is therefore given in low doses for a short period of time, with a break of several weeks between treatment regimens. Emetine can irritate skin if applied topically. The synthetic compound 2,3-dihydroemetine is often used to treat amebiasis; it may lead to less cardiotoxicity but may be less effective than emetine.[1,5]

Fluid extract of ipecac had largely been abandoned because of the large number of fatal overdoses that were occurring when the product was mistaken for syrup of ipecac. The fluid extract is 14 times more concentrated than the syrup and as little as 10 ml has been fatal. [4] By comparison, syrup of ipecac, which is kept in most households as a first-aid emetic, has demonstrated a remarkable safety profile. As much as 105 ml of the syrup has been retained in a child with only minor changes in the ECG. However, at least one fatality has been reported with the syrup, this in a 26-year-old woman who had drank 3 to 4 bottles of the syrup each night over a 3-month period in order to lose weight.[6] Another case described a woman who ingested 200 ml ipecac syrup per week for 3 months to lose weight who developed myopathy, which resolved to normal 4 months after stopping ipecac use.[7] This myopathy may be accompanied by cardiomyopathy.[8]

SUMMARY: Ipecac is a widely used natural product that is an effective emetic whose components have been used to treat dysentery. Ipecac and its constituents should be used cautiously because their misuse can lead to serious acute and chronic toxicities.

PATIENT INFORMATION— Ipecac

Uses: Ipecac has been used as an emetic and treatment for dysentery. It has amebicidal components.

Side Effects: Ipecac extracts can be highly toxic and should not be confused with syrup of ipecac.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "I" MONOGRAPHS
    IPECAC

"J" MONOGRAPHS

JEWELWEED

DATE OF ISSUE: MAR 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Impatiens* L. Several members of this genus (ie, *I. balsamina, I. capensis*[1] and *I. biflora*[2]) have been referred to as jewelweed. Some texts indicate that jewelweed can refer to any member of the genus. Family: Balsaminaceae.

COMMON NAME(S): Jewelweed, jewel weed, jewel balsam weed, touch-me-not, garden balsam[3]

BOTANY: The *Impatiens* are tender, succulent herbs that are commonly grown as bedding and house plants. Jewelweed is sometimes called the "touch-me-not." This name alludes to the presence of a seed capsule made of a soft fleshy tissue that tends to expell its contents if touched or shaken.

HISTORY: Jewelweed has long been recognized as an herbal remedy for the treatment of topical irritation, most notably for the treatment of poison ivy rash. The juice (sap) of the jewelweed has been used by Native Americans, particularly those living in Appalachia, as a prophylactic against poison ivy rash and as a treatment after the eruptions have occurred.[1] Jewelweed extracts are not generally found in commercial topical products.

CHEMISTRY: While little is known about the chemical composition of many of the *Impatiens* species, it has been reported that the compound 2-methoxynaphthoquinone, derived from *I. balsamina*, demonstrates antifungal activity.[1]

PHARMACOLOGY: Several attempts have been made to verify that jewelweed extracts, when applied topically, have a beneficial effect on poison ivy eruptions. However, the scant data available to date indicate that jewelweed extract is not particularly effective for this indication.

Results of a recent *Prevention* [magazine] Home-Remedy Survey found that only 53% of the respondents who applied jewelweed to poison ivy rash obtained "good" relief from itching. (These findings were derived from approximately 350 respondents who had tried jewelweed, 7% of the total survey group.) [4]

Another small, uncontrolled study compared the effects of an aqueous jewelweed extract and water in reducing poison ivy irritation. In both subjects, the reaction remained significant after 3 days; in one of the subjects, areas treated with *I. biflora* extract demonstrated more severe and widespread reactions than control areas or those areas treated with water. Since water is believed to degrade *Toxicodendron* oleoresin and possibly have a small clinical effect of its own, any benefit could be due to the water rather than to the jewelweed.[2]

TOXICOLOGY: There are no published reports of significant toxicity associated with the topical use of jewelweed extracts. The safety of internal ingestion of jewelweed is not well-defined.

SUMMARY: Jewelweed is a popular herbal remedy for topical irritation, such as that produced by poison ivy. However, results of small, poorly controlled assessments of the herb's activity suggest that it has little or no significant beneficial effect against itching or other topical manifestations of the irritation.

PATIENT INFORMATION — Jewelweed

Uses: Jewelweed has traditionally been used as topical prevention and treatment for poison ivy rash.

Side Effects: None known for topical use.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "J" MONOGRAPHS
    JEWELWEED

JIAOGULAN

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Gynostemma pentaphyllum* (Thunb.) Makino. Family: Cucurbitaceae (Squashes)

COMMON NAME(S): Jiaogulan, Penta tea, Amachazuru (Japan), Southern ginseng, Dungkulcha (Korea)

BOTANY: *Gynostemma pentaphyllum* is a climbing, perennial vine native to China, Japan, and parts of southeast Asia. The plant is dioecious, that is, it carries male and female flowers on separate plants. While the plant grows abundantly and is harvested from the wild, it has been brought under cultivation and tissue culture has been achieved.[1,2,3,4] Adulteration by *Cayratia japonica* has been noted.[3]

HISTORY: Jiaogulan has been incorporated into traditional Chinese medicine only in the last 20 years. The plant has a history of folk use in the Guizhou province in China. Its properties are said to have been investigated when a Chinese census revealed a large number of elderly people in the province reported using the plant. Investigation as a potential sweetening agent stimulated chemical investigations in Japan. Commercialization and scientific study of the leaves have been promoted by provincial Chinese authorities, and the discovery that several ginseng saponins occur in the leaves has prompted aggressive promotion of the product as a substitute for ginseng. The appearance of jiaogulan in American commerce has been heralded by publication of a popular book. [5]

CHEMISTRY: A large series of dammarane triterpene saponins, gypenosides 1-82, have been isolated from the leaves, principally by Takemoto's group.[7,8,9,10,11,12,13,14] Several of these saponins are identical to those found in ginseng. Specifically, gypenoside 3 is identical to ginsenoside Rb1, gypenoside 4 is identical to ginsenoside Rb3, gypenoside 8 is identical to ginsenoside Rd, and gypenoside 12 is identical to ginsenoside F2. Many of the other gypenosides are closely related structurally to the ginsenosides and include the 6´-malonyl derivatives characteristic of ginseng. [15] The content of saponins is comparable to that of ginseng roots. However, wide variation in the amount and nature of gypenosides has made production of a product standardized with specific gypenosides somewhat problematic. Most current products are standardized on total saponin content. The reasons for this variation have been investigated but have not been fully elucidated.

Other constituents reported from *Gynostemma pentaphyllum* include sterols with the ergostane, cholestane, and stigmastane skeletons, [16,17,18,19,20] with several examples containing an acetylenic functionality, which is considered unusual in plants. [21] The flavonoid glycosides rutin, ombuoside, [22] and yixingensin[23,24] have also been identified.

The related species *G. compressum* Chen and Liang have yielded dammarane saponins related to the gypenosides. [25]

PHARMACOLOGY: Though the plant contains ginseng and ginseng-like saponins, it has not been reported to contain the other types of biologically active compounds, acetylenes, and polysaccharides found in ginseng. Thus, while ginseng pharmacology presents a reasonable starting point for investigation, jiaogulan cannot be considered as pharmacologically identical to ginseng.

Hyperlipidemia: Oral administration of a gynostemma decoction in combination with *Nelumbo nucifera* and *Crataegus cuneata* was found to lower triglycerides and cholesterol in rats and quail. However, a dose response was not demonstrated. [26] Administration of an aqueous extract of the whole plant to rats in chow over 12 weeks resulted in a reduction in serum levels of total cholesterol and beta-lipoproteins. [27] A second study in mice and rats given 200 mg/kg PO of the crude saponin demonstrated lower total cholesterol (TC) and VLDL but increased HDL/LDL. [28] A clinical study of hyperlipoproteinemic subjects also found a decrease in TC with increased HDL/TC at a dose of 10 mg given 3 times daily for 30 days. [29] A study of 105 patients confirmed these effects. [30]

Lipid peroxidation: An antioxidant effect of gypenosides was reported in phagocyte, endothelial cell, and liver microsome systems. [31] Further study by the same group [32] explored these effects in vascular endothelial cells injured by hydrogen peroxide. Rat microsome studies also have found similar effects for crude gypenosides. [33]

Adaptogenic: Despite the wide reputation of ginseng as an adaptogen, few studies have been published on the topic. Chen [34] found an increased tolerance to fatigue in forced swimming and hanging models in mice, and enhanced tolerance to anoxia, along with potentiation of pentobarbital hypnosis.

Cardio- and cerebrovascular effects: The hot water extract of *Gynostemma pentaphyllum* was found to activate platelet aggregation. However, the active principle was not elucidated. [35] Gypenosides inhibited platelet aggregation in another study. [36] In rabbits, crude gypenosides decreased heart rate, increased stroke volume, dilated blood vessels, and reduced blood pressure while slightly increasing cardiac output. [37] Purified gypenosides 5 and 10 were found to lower systolic and diastolic blood pressure, decrease coronary, brain, and peripheral blood vessel resistance, raise coronary flow, and lower heart rate in dogs. [38] Crude gypenosides protected against cerebral ischemic damage in a rabbit model. [39]

Cancer and immunologic effects: An extract of *Gynostemma* inhibited the growth of a rectal adenocarcinoma cell line, [40] while total gypenosides inhibited growth of A549, Calu 1, and 592/9 carcinoma cells more potently (1 to 10 mg/L) than Hela and Colo 205 cells. [41] Both callus and field grown *Gynostemma* increased the lifespan of mice bearing Ehrlich's ascites carcinoma, an effect attributed to immune enhancement. [42] Crude gypenosides also had activity versus S-180 cells both in vitro and in vivo. [43] Gypenosides protected against cyclophosphamide-induced bone marrow and spermatozoal mutagenesis when given orally at 40 to 160 mg/kg to mice. [44] Similar treatments enhanced immune function in another report. [45] Cancer patients given jiaogulan granules after chemotherapy showed improved immune function by several endpoints. [46]

Other: Experimental senility in mice induced by D-galactose was attenuated by intraperitoneal (IP) injection of *Gynostemma* aqueous extract. [47]

TOXICOLOGY: The LD50 in mice for the aqueous extract has been reported as 2.8 g/kg IP. However, LD50 for the oral route could not be determined. [34] Another study found an oral LD50 of 49 g/kg for the crude extract with no organ toxicity at 4 g/kg daily for 90 days. [48] A third study of two different extracts found an LD50 of 1 to 2 g/kg IP in mice. [49] A rat LD50 of 1.9 g/kg IP has also been reported. [34] Side effects reported in clinical studies included severe nausea and increased bowel movements. [50]

SUMMARY: *Gynostemma pentaphyllum* and its extracts are relatively nontoxic, with extensive chemical characterization and numerous pharmacologic studies supporting use in hyperlipidemia and as an immune stimulant. Several of its bioactive saponins are identical and most are closely related to the ginsenosides found in ginseng.

PATIENT INFORMATION — Jiaogulan

Uses: Studies on *Gynostemma* have found that the plant is effective in regulating blood pressure, strengthening the immune system, lowering cholesterol, and in increasing stamina and endurance properties. *Gynostemma* has also been found to have hyperlipidemic, lipid peroxidation, adaptogenic, anticancer, cardio- and cerebrovascular effects.

Side Effects: The side effects of *Gynostemma* include severe nausea and increased bowel movements.

Dosing: The adaptogenic use of jiaogulan is standardized on an extract containing 85% gypenosides, with a daily dose of 60 to 180 mg gypenosides recommended; however, published studies to justify this dose are lacking.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "J" MONOGRAPHS
    JIAOGULAN

JOJOBA

DATE OF ISSUE: SEP 1995

REPLACES MONOGRAPH DATED: JUL 1988

SCIENTIFIC NAME(S): *Simmondsia chinensis*(Link) Schneider and *S. californica* Nutall. Family: Buxaceae

COMMON NAME(S): Jojoba

BOTANY: *Simmondsia chinensis* is a desert shrub indigenous to Arizona, California and Northern Mexico. It grows in a number of deserts worldwide including Israel's Negev Desert. A woody evergreen shrub with thick, leathery, bluish-green leaves and dark brown nutlike fruit. Male and female flowers are borne on separate plants, the number of each being about equal. The plant can withstand extreme daily fluctuations of temperature. It thrives in well-drained, coarse desert soils and coarse mixtures of gravels and clays.[1] The mature plant produces about 5 to 10 pounds of seeds, which range between the coffee bean and peanut in size. It is an important forage plant for desert bighorn sheep and mule deer. While birds and rodents eat the seeds, it is toxic to humans and most animals. [2]

HISTORY: Indians and Mexicans have for a long time used jojoba oil as a hair conditioner and restorer, and in medicine, cooking and rituals. In the United States, jojoba is considered a viable cash crop for the southwestern Indians, and the Bureau of Indian Affairs has funded most of the studies in this area. [2,3]

With the banning of the sale of sperm whale oil in 1973, the cosmetic industry turned to jojoba oil for use in shampoos, moisturizers, sunscreens and conditioners. It has further potential as an industrial lubricant, since it does not break down under high temperature or pressure. [4] A major disadvantage to its use is its relatively high cost.

CHEMISTRY: Jojoba seeds produce 50% by weight a colorless, odorless oil. The oil is almost completely (97%) composed of straight chain monoesters of C-20 and C-22 acids and alcohols with two double bonds. The acids have been identified as mixture of cis-11-eicosenoic (C-20) and cis-13-docosenoic (C-22, erucic) acids. The alcohols have been identified as mixtures of cis-11-eicosenol, cis-13-docosenol and cis-15-tetracosenol (C-24). [5] These alcohols are potentially valuable in the production of detergents, wetting agents and dibasic acids. [3] Also included are small quantities of sterols (less than 0.5% of a total mixture of Campesterol, Stigmasterol and Sitosterol). Jojoba oil is essentially triglyceride-free. [1,5]

PHARMACOLOGY: Jojoba is most commonly recognized as an ingredient in cosmetics and other topical preparations. JMC Technologies, a jojoba marketing and research cooperative, reports that studies with jojoba oil conducted at Ben Gurion University Medical Center (Israel) indicate that the wax may be of value in the management of acne and psoriasis.[6] Other topical irritations such as sunburn and chapped skin appear to respond to topical jojoba therapy. While this data is largely unpublished and requires confirmation, there is a substantial body of anecdotal evidence that suggests the wax is beneficial in alleviating minor skin irritations.

There has also been considerable interest and success in marketing jojoba preparations promoted to stimulate hair growth and rejuvenation. Jojoba oil penetrates skin and skin oils easily—unclogging hair follicles and preventing sebum buildup which could lead to hair loss. [7]

In a rabbit study, ingestion of jojoba oil as a 2% supplement to an atherogenic diet produced a 40% reduction of blood cholesterol, although the mechanism by which this occurred was not determined.[8]

Recent study has shown antioxidant activity of jojoba. This activity is related to the content of a-tocopherol found in the leaves. [9]

Jojoba oil is presently used in cosmetic and personal care products. Recommended oil ingredient levels include: skin care preparations, 5% to 10%; shampoos and conditioners, 1% to 2%; bar soaps, 0.5% to 3%.[7]

TOXICOLOGY: The LD-50 of crude jojoba wax is greater than 160 g/kg in mice.[10] In ocular tests, it was only slightly irritating (comparable to olive oil) and its application resulted in less irritation than liquid paraffin. Hypoallergenic sensitivity to the wax has been reported, [10] and cases of contact dermatitis have been reported in persons using jojoba oil as shampoo or hair conditioner. [4]

Topical administration of the refined wax to guinea pigs for 20 weeks resulted in no systemic effects; a reversible swelling accompanied by reduced skin flexibility and an increased sensitivity to shaving was observed. There were, however, no histological changes in skin tissues. These effects were most likely due to an occlusive-like action created by the wax. This mechanism is inconsistent with data provided by JMC Technologies which indicate that jojoba's effects result from percutaneous absorption and subsequent incorporation into dermal tissue.

Subcutaneous injection of 1 mL/kg for 7 weeks in test animals resulted in no systemic effects, although some systemic accumulation was observed. [11]

Jojoba oil is 14% erucic acid, a causative factor in myocardial fibrosis. [8] Although no direct relationship has been established between this compound and jojoba toxicity, jojoba should not be ingested in any form. *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* grow well on jojoba seed meal, metabolizing toxic simmondsin and other toxicants remaining in the meal after removal of the oil. The treated meal is nontoxic to mice, poultry, sheep and cattle. [12,13]

SUMMARY: A combination of social, economic and political factors have generated increased interest in the use of jojoba oil in cosmetics and industrial lubricants. If its hypocholesterolemic potential is to be realized, long-term studies must be undertaken.

PATIENT INFORMATION— Jojoba

Uses: Jojoba oil has traditionally been used in cosmetics, medicine and cooking. It appears to alleviate skin irritations and help guard against hair loss.

Side Effects: Jojoba should not be ingested. Seeds are toxic. One component contributes to myocardial fibrosis. Sensitive individuals may develop contact dermatitis.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "J" MONOGRAPHS
    JOJOBA

JUNIPER

DATE OF ISSUE: FEB 1997

REPLACES MONOGRAPH DATED: OCT 1987

SCIENTIFIC NAME(S): *Juniperus communis* Family: Cupressacea

COMMON NAME(S): Juniper

BOTANY: The genus *Juniperus* includes 60 to 70 species of aromatic evergreens native to Northern Europe, Asia and North America. The plants bear blue or reddish fruit variously described as berries or berry-like cones. Junipers are widely used as ornamental trees. The cone is a small green berry during its first year of growth and turns blue-black during the second year. The small flowers bloom from May to June.

HISTORY: Juniper berries (the mature female cone) have long been used as a flavoring in foods and alcoholic beverages such as gin. Production by apothecaries and other historical uses for gin have been reported.[1] Gin's original preparation used juniper for kidney ailments. The berries also serve as seasonings, for pickling meats and as flavoring for liqueurs and bitters. Other uses include perfumery and cosmetics. Oil of juniper, also known as oil of sabinal, is used for preserving catgut ligatures.[2] Juniper tar is also used for its gin-like flavor and in perfumery. In herbal medicine, juniper has been used as a carminative and as a steam inhalant in the management of bronchitis. It has also been used to control arthritis.

CHEMISTRY: Juniper berries contain about 2% volatile oil, juniperin, resin (about 10%), proteins, and formic, acetic, and malic acids. In addition, fatty acid, sterol and terpene content has been analyzed by gas chromatography, identified from extracts of ripe and unripe juniper berries.[3] The dried ripe fruit contains oil of juniper, pinene, cadinenes, camphene and a number of diterpene acids.

The volatile oil is composed of more than 50% monoterpenes (pinene, myrcene, sabinene) with many minor constituents. Variability in juniper oil is seen, particularly between first year fruits vs third year fruits.[4] Steam distillation of the berries yields mono- and sesquiterpenes from the oil.[5] In other studies, isolation, chemical characterization and composition of the essential oil of juniper are described, revealing 23 compounds.[6,7]

Isolates of dimeric proanthocyanidins (tannin-producing), from bark extracts of *Juniperus communis* have also been reported,[8] as well as determination of polyprenols in the juniper pine needles.[9]

PHARMACOLOGY: Juniper berry oil has been used as a diuretic. This activity is most likely due to the action of terpinen-4-ol, which is known to increase renal glomerular filtration rate.[10] This activity appears to be a local irritant effect. Juniper berries are often found in herbal diuretic products. The effects of juniper berry oil with regard to urinary tract disease has also been reported.[11]

Juniper has been used in phytotherapy and cosmetics in the eastern Mediterranean area.[12] Reported therapeutic uses of juniper include juniper baths for treatment of neurasthenic neurosis[13] and management of scalp psoriasis in its tar form in combination with other tars.[14]

In traditional Swedish medicine, *Juniperus communis* has been used to treat wounds and inflammatory diseases. A recent study evaluates its inhibitory activity on prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis in vitro.[15]

Dried berries of juniper and juniper decoction have been evaluated into recent animal studies. Results support hypoglycemic activity in streptozotocin-diabetic mice.[16,17] Further proof is necessary to determine if this effect can be beneficial for human diabetics.

Berry extracts increase uterine tone and should, therefore, not be ingested by pregnant women. Anti-implantation/anti-fertility activity has been determined in female rats by three similar studies, with one study reporting 60% to 70% efficacy.[18,19,20]

In a recent study, the antioxidative effects of juniper are discussed.[21]

Of interest in veterinary medicine, treatment of psoroptic mange in sheep with extract of *Juniperus communis* has been reported.[22]

TOXICOLOGY: Adverse effects in humans are generally of an allergic nature. These include occupational allergy affecting the skin and respiratory tract[23] through a sensitivity to airborne juniper pollen.[24] Two reports note that Chinese, Japanese and Filipinos tend to be more sensitive to juniper pollens than Caucasians.[25,26] Juniper and other related pollens affect 13% to 36% of patients with pollen allergies.[27]

Epidermal contact with juniper tar (eg, preparation for psoriasis treatment) can cause potentially carcinogenic DNA damage in human tissue.[28]

Single large doses of juniper berries may cause catharsis, and repeated large doses may be associated with convulsions and renal damage.[2]

Kidney irritation from juniper oil is examined in one report, that relates this effect to 1-terpinen-4-ol content.[29]

Because the berries are known to exert their diuretic effect by irritating the renal tissue, products containing juniper should be used with caution by all and should never be used by those with reduced renal function. Safer and more effective diuretic and carminative drugs exist. The oil can induce gastric irritation and may induce diarrhea. Therefore, its use is limited to low concentrations (less than 0.01%) as a beverage flavor.

Juniper tar has an oral lethal dose of 8014 mg/kg in the rat.[2]

SUMMARY: Junipers are evergreen trees found widely in the northern hemisphere. The dried ripe fruit is commonly used as a flavoring in foods and alcoholic beverages, particularly gin, and in cosmetics and perfumes. Juniper berries and their extracts have been used with some success as diuretics. Juniper may have some promise in diabetic treatment, but further study is necessary. Juniper has an extensive toxicology profile, and therefore must be used with caution.

PATIENT INFORMATION — Juniper

Uses: Juniper berries have long been used as a flavoring for beverages and as a seasoning for cooking. It is also used as a diuretic and in the management of bronchitis and arthritis.

Side Effects: Skin and respiratory allergic reactions, potentially carcinogenic DNA damage and, in large doses, convulsions and renal damage. Use is limited to low concentrations. Juniper should not be ingested by pregnant women.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "J" MONOGRAPHS
    JUNIPER

"K" MONOGRAPHS

KAOLIN

DATE OF ISSUE: APR 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Kaolin, hydrated aluminum silicate

COMMON NAME(S): Heavy or light kaolin, China clay, bolus alba, porcelain clay, white bole, argilla [1]

SOURCE: Kaolin is a hydrated aluminum silicate. It is a naturally occurring clay that is prepared for pharmaceutical purposes by washing with water to remove sand and other impurities.

HISTORY: Kaolin has been used commercially and medicinally for hundreds of years. It is currently found in the manufacture of pottery, bricks, cement, plastering material, color lakes (insoluble dyes) and insulators. It is also used in pharmaceutical preparations as a filtering agent to clarify liquids. When applied topically, it serves as an emollient and drying agent. When ingested, it acts as an adsorbent to bind gastrointestinal toxins and to control diarrhea.

Kaolin has been added to dusting powders and is used as a tablet excipient. Kaolin is also utilized in a variety of automated laboratory chemistry tests, including the determination of activated coagulation time (ACT)[2] and in the serodiagnosis of tuberculosis, using the kaolin agglutination test (KAT). [3]

CHEMISTRY: Kaolin has the approximate chemical formula of $H_2 Al_2 Si_2O_8 (H_2O)$. It is a white or yellow-white powder that has a slightly oily feel to the touch. It is insoluble in water.[1] Light kaolin is the preferred material for use in pharmaceutical preparations. The finely divided particles of kaolin yield a very large surface area that adsorbs a wide variety of compounds.

PHARMACOLOGY: When given orally, kaolin (especially light kaolin) adsorbs substances from the gastrointestinal tract and increases the bulk of feces. [4] Therefore, antidiarrheal preparations containing kaolin have been used in the treatment of enteritis, cholera and dysentery. Kaolin preparations, however, have no intrinsic antibacterial activity and should not be used as the sole treatment in infectious diarrheas. A dose of 15 to 60 g is typically administered to adults to assist in the control of diarrhea.

TOXICOLOGY: Because kaolin actively adsorbs a wide variety of substances to its surface, it should not be administered with drugs that may adhere (ie, digoxin, lincomycin, phenothiazines, etc).[4] This is a particular concern when formulating new dosage forms, in that it must be assured that the kaolin diluent does not reduce the bioavailability of the active drug substance. [4]

Kaolin is highly insoluble and is not absorbed systemically. Therefore, it is not generally associated with severe toxicity.

Inhalation of nonfibrous silicate compounds such as kaolin may predispose miners to pulmonary diseases. [5]

SUMMARY: Kaolin is a widely used natural mineral that finds its most common pharmaceutical application as an adsorbent in antidiarrheal preparations. Kaolin is believed to exert it effects by adsorbing toxins that may have initiated the diarrheal episode by providing bulk to the stool. Kaolin may adsorb certain drugs, thereby reducing their bioavailability.

PATIENT INFORMATION — Kaolin

Uses: Kaolin is used internally to control diarrhea and topically as an emollient and drying agent.

Side Effects: Kaolin may adsorb certain drugs and reduce their bioavailability.

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "K" MONOGRAPHS
  KAOLIN

KARAYA GUM

DATE OF ISSUE: MAR 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Sterculia urens* Roxb. Family: Sterculiaceae. The gum may also be obtained from *S. villosa*, *S. tragacantha* or other species of *Sterculia*.[1]

COMMON NAME(S): Karaya, sterculia, Indian tragacanth, Bassora tragacanth, kadaya, mucara, kadira, katila, kullo [2,3,4,5]

BOTANY: The Sterculia is a soft wooded tree that grows to approximately 30 ft. It is native to India and Pakistan and grows there almost exclusively, where it is cultivated for karaya production. All parts of the tree exude a soft gum when injured. Karaya gum is produced by charring or scarring the tree trunk and removing a piece of bark or by drilling holes into the trunk. The gum seeps from the scars and is collected, washed and dried. The tree bears a star-like fruit and flowers bloom from February to March.[3]

HISTORY: The use of karaya gum became widespread during the early 20th century, when it was used as an adulterant for tragacanth gum. However, experience indicated that karaya possessed certain physiochemical properties that made it more useful than tragacanth; furthermore, karaya gum was less expensive. Today the gum is used in a variety of products to provide bulk, including cosmetics, hair sprays and lotions. [6] The bark is astringent and has been used traditionally. [3]

CHEMISTRY: The quality of karaya gum depends on how well impurities have been removed. Food-grade gum is usually a white to pinkish gray powder with a slight vinegar smell.[2] Pharmaceutical grades of karaya may be almost clear or translucent.[3]

Karaya gum is the least soluble of the commercial plant exudates but it absorbs water rapidly and swells to form viscous colloidal solutions even at low concentrations (1%).[2] When used in higher concentrations in water (up to 4%), karaya forms gels or pastes. Unlike other gums, karaya swells in 60% alcohol, but remains insoluble in other organic solvents. Karaya may absorb up to 100 times its weight in water.[2]

The polysaccharide component of karaya has a high molecular weight and is composed of residues containing galacturonic acid, beta-D-galactose, glucuronic acid, L-rhamnose and other residues.[1,2,3]

Because the gum is partially acetylated, upon degrading it may release acetic acid. [2]

PHARMACOLOGY: Karaya gum is not digested, nor is it absorbed systemically. Medicinally, it is used primarily as a bulk laxative [7] and as an adhesive for dental fixtures and ostomy equipment.[4] The gum has been used as a base for salicylic acid patches. [8] Karaya gum is essentially inert and is not associated with any pharmacologic activity per se. Some preliminary studies suggest that gums may normalize blood sugar and plasma lipid levels, [9] but this has not been well investigated with karaya gum.

The demulcent properties of the gum make it useful as an ingredient in lozenges to relieve sore throat. [3] A protective coating of karaya gum applied to dentures has been shown to reduce bacterial adhesion by 98%.[10]

TOXICOLOGY: Karaya gum is generally recognized as safe for internal consumption. Widespread experience with the product throughout the US and Europe has not been associated with any significant adverse experiences. [11]

SUMMARY: Karaya gum finds widespread use in the food and pharmaceutical industries. Its ability to absorb large amounts of water make it useful in the production of gels and as a bulk laxative. The gum has not been associated with any significant toxicity and is essentially inert when ingested.

PATIENT INFORMATION— Karaya Gum

Uses: Karaya gum is used in cosmetics and food, and in pharmaceuticals as a laxative and adhesive.

Side Effects: Karaya gum is generally recognized as safe.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KARAYA GUM

KAVA

DATE OF ISSUE: JAN 2003

REPLACES MONOGRAPH DATED: DEC 1999

SCIENTIFIC NAME(S): *Piper methysticum* Forst.f. Family: Piperaceae (black peppers)

COMMON NAME(S): Kava, kawa, kava-kava, awa, yangona, kawain, kavain

BOTANY: Kava is the dried rhizome and roots of *P. methysticum*, a large shrub widely cultivated in many Pacific islands from Hawaii and Tahiti to New Guinea. [1] It has large, heart-shaped leaves and is propagated exclusively by root cuttings. It is thought to be derived from the wild species *P. wichmannii* C. DC.[2] Many cultivars of kava are recognized. The comparative chemistry and ethnopharmacology have been studied in detail and 121 named cultivars from 51 islands have been grouped into 6 chemotypes.[3,4,5]

HISTORY: The kava beverage is prepared from the roots of the plant, which are chewed or pulverized and then steeped in water. The cloudy mixture is filtered and served at room temperature. Kava has been an important part of Pacific island ceremonial cultures for many centuries, with elaborate rituals attending its consumption.[6] Traces of kava extract on archaeological artifacts from Fiji have been identified by mass spectrometry. [7] Its main use has been to induce a relaxed state in the participants in a kava ceremony, facilitating discussion and interaction.

CHEMISTRY: An 1886 monograph on kava[8] stimulated research and isolation of the kava lactones, the primary bioactive constituents of kava root. The 6 major kava lactones are as follows: Kawain, dihydrokawain, methysticin, dihydromethysticin, yangonin, demethoxyyangonin, [9] which occur in varying proportions in different cultivars. The structures of the kava lactones were first elucidated in the 1930s, [10] although many of the pure compounds were first isolated in the 19th century. They were later synthesized in both racemic and optically pure forms.[11,12,13] Full nuclear magnetic resonance (NMR) assignments have been made for the kava lactones.[14] While the kava lactones are characteristic of *P. methysticum*, individual kava lactones occur in other plant families (ie, Lauraceae, Gesneriaceae, Zingiberaceae).[15] A process for the commercial production of kava extract has been patented,[16] and the use of supercritical fluid extraction of kava lactones from the root has been demonstrated.[17] Many methods have been developed for the analysis of kava lactones. These include the following: Thin layer chromatography, [18] gas chromatography,[19] high-performance liquid chromatography (HPLC),[20,21,22] gas chromatography-mass spectrometry (GC-MS),[15,23,24,25] chiral HPLC,[26] HPLC-MS,[27] micellar electrokinetic chromatography.[28] The metabolism of the kava lactones has been studied in humans,[29] while the uptake of kava lactones into mouse brain also has been studied.[30] The latter study found elevated brain levels of kawain when the whole resin was administered, compared with kawain alone. This supported the observation that the total kava resin has greater pharmacologic effect than the sum of the individual kava lactones, presumably because of saturation of common metabolic pathways utilized by these compounds.

Other constituents of kava include 2 chalcones, flavokawains A and B,[31] that were postulated to cause a dermopathy seen in heavy kava users.[32] The patent claims production of an extract with very low chalcone content.[16] Several minor alkaloids also have been isolated from kava roots[33] and leaves.[34]

PHARMACOLOGY: Chewing kava causes numbness in the mouth caused by a local anesthetic action of the kava lactones. In addition, it produces a mild euphoria characterized by feelings of contentment and fluent and lively speech. Higher doses may lead to muscle weakness, especially in the legs, although some observers relate this to sitting for long periods during the kava ceremony rather than to kava itself. Very high doses may induce a deep sleep. Kava lactones, especially kawain, have been shown to have modest anticonvulsant activity in electroshock and metrazol models. [35]

The molecular mechanism of action of kava lactones and kava is not entirely clear. Kava lactones at concentrations from 0.1 to 100 mcM were found to enhance the binding of bicuculline to the GABA receptor by only 20% to 30%. [36] Another study found weak displacement of diazepam from rat brain membranes by kava lactones but no effect on binding of GABA or of baclofen.[37] The observation that strychnine-induced convulsions are effectively antagonized by several kava lactones supports a possible effect on the glycine receptor. [38] Kava extract and methysticin also were found to protect rats against ischemic brain damage, although several kava lactones were not active in this model.[39] This might modulate antagonism of the excitatory amino acids glutamate and aspartate. Inhibition of uptake of norepinephrine, but not serotonin, by kava lactones at high doses was observed. [37] No effect on dopamine or serotonin levels was found in a chronic experiment with kava lactones in rats.[40]

A somewhat more persuasive mechanism involves kava lactone inhibition of various neuronal sodium channels. Patch clamp experiments with voltage-gated sodium channels of rat hippocampal neurons found that kava lactones could rapidly and reversibly lower peak amplitudes of sodium currents. [41] A noncompetitive inhibition of the binding of batrachotoxinin benzoate to voltage-gated sodium channels by kava lactones was demonstrated in saturation binding experiments. [42] Less potently, kava lactones blocked veratridine-activated sodium channels, but had no effect on glutamate release from brain slices. [43] In rat brain synaptosomes, kava lactones appeared to interact with voltage-dependent sodium and calcium channels. [44] High concentrations of synthetic kawain were found to relax evoked contractile activity in a guinea pig ileum preparation, showing that smooth muscle also is affected by kava lactones. [45] A fluorescently labeled kawain derivative was studied using fluorescence correlation spectroscopy and found to bind specifically and saturably to cultivated human cortical neurons. [46]

Neurophysiological studies of sleep-wakefulness in cats showed decreased muscle tone, marked changes in EEG, and decreased duration of wakefulness and increased sleep with kava. Involvement of the amygdala and other limbic structures of the brain was deduced. [47] These effects were distinct from those of tricyclic antidepressants and benzodiazepines.

Kawain showed an antithrombotic effect on platelets, dose-dependently blocking platelet aggregation, adenosine 5´-triphosphate (ATP) release and synthesis of prostaglandins at high micromolar concentrations.[48] Despite a reputation as an antimicrobial agent in urinary tract infections, kava extracts showed very minimal antifungal and no antimicrobial or antiviral activity. [49]

The pharmacokinetics of kava lactones have been elucidated to some extent. In rats, dihydrokawain was completely excreted within 48 hours, primarily through urinary excretion of hydroxylated metabolites.[50] Bile and feces did not appear to be important routes of excretion, although lactones such as kawain with poorer oral absorption than dihydrokawain were found unchanged in feces.[50] The octanol-water partition coefficient for yangonin is 1500; thus, these compounds are quite nonpolar and water-insoluble; this accounts in part for their poor oral absorption. [50] Because the metabolites of kava lactones are different in humans than in rats,[29] the pharmacokinetics also may differ. Kinetics of entry of kava lactones into mouse brain after intraperitoneal injection have been studied, and kawain and dihydrokawain were rapidly taken up and quickly eliminated within several minutes, while yangonin and desmoethoxyyangonin were more slowly incorporated and eliminated.[30]

Concerns about impaired performance under the influence of kava have motivated several studies in humans. One study found insignificant decreases in cognitive function when using kava, with only the extent of body sway showing an increase.[51] Subjects' rating of intoxication under kava was low to moderate, while respiration, heart rate, and blood pressure were unaffected. Kava lowered arousal rating without affecting the stress rating, although the decrease was not statistically significant.[51] Another small study of 12 patients compared kava with oxazepam in their effect on behavior and event-related potentials in a word recognition task. While oxazepam produced pronounced negative effects on performance, no effects were seen with kava. [52] A study of reaction time by the same authors concluded that kava may increase attention slightly, in contrast to oxazepam, which impaired attention. [53] Kawain in electroencephalogram (EEG) studies showed mild sedation at high doses (600 mg) but not at lower doses (200 mg).[54] Kava had no effect on alertness and long-term memory in a further trial.[55] Minor changes in vision and balance were detected with kava in a single subject.[56]

Clinical studies on kava have produced evidence of substantial efficacy in mild to moderate anxiety. Several investigations have been reviewed in comparison with other CNS-active herbal products.[57] Kawain was compared with oxazepam in a double-blind study of 58 patients and was found to be equally effective and safe. [58] Over 4 weeks, kava extract progressively reduced anxiety compared with placebo in 60 patients with no reported side effects. [59] Menopause-related anxiety was successfully treated with kava extract in an 8-week study of 40 women, with rapid onset of efficacy.[60] A 12-week study also found improvement in menopausal symptoms; however, poor compliance in the placebo group confounded interpretation.[61] A longer 25-week, double-blind, placebo-controlled study of 101 patients with anxiety disorders found that Hamilton Anxiety Scale (HAMA) scores decreased faster than with placebo.[62] A similar 4-week study found kava extract effective using both HAMA and Clinical Global Impression Scale (CGI) scores.[63] All of the preceding trials were conducted in Germany.

The first US study of kava in anxiety was reported at a conference but has not been published. It found similar therapeutic effects of kava extract under double-blind, placebo-controlled conditions.[64] A combination of kava and hormone replacement therapy for menopause symptoms was undertaken in Italy over 6 months. Kava with hormone therapy accelerated the improvement in anxiety scores over single treatments alone.[65]

Positive results in a sleep study involving 12 patients were found with kava extract WS 1490, as measured by EEG, electromyography, and subjective measures. No adverse effects on REM sleep were found.[66] A clinical study of kava's ability to moderate cardiac symptoms in generalized anxiety disorder found that it improved baroreflex control (BRC) of heart rate, but not respiratory sinus arrhythmia, and improvement in BRC was associated with overall clinical improvement in kava-treated patients.[67]

The transition from benzodiazepines to kava extract WS 1490 in treatment of anxiety was monitored in a 5-week study involving 40 patients. While symptoms of benzodiazepine withdrawal were not controlled by kava, anxiety was reduced, and symptoms were less after kava treatment than during benzodiazepine therapy. [68] A meta-analysis of clinical trials of kava extracts in anxiety has been conducted. Seven trials met the acceptance criteria for inclusion and found kava superior to placebo in the treatment of anxiety.[69]

TOXICOLOGY: Kava's actions are potentiated by alcohol and by benzodiazepines (eg, alprazolam), although this well-known interaction is poorly documented in the clinical toxicology literature.[70,71] Heavy consumption of kava has long been known to produce a scaly skin rash similar to pellagra; however, supplementation with niacin did not reverse the condition.[72] Cessation of kava use causes reduction or disappearance of the dermopathy. It was suggested that the flavokawain pigments were responsible for this toxicity;[32] despite the lack of any scientific proof, these pigments are commonly removed in the production of commercial extracts.[16] Poor nutritional status and other general adverse effects were seen in an Australian aboriginal community where (nontraditional) kava consumption was very heavy. [73] Disturbances in visual accommodation also have been described.[56]

A string of reports of fulminant hepatic failure have been made in Europe and the United States in which kava has been implicated. [74,75,76] Despite the fact that the incidence of such adverse events appears to be very low, on the order of 1 per million doses consumed, [74] authorities in Germany, Switzerland, France, Ireland, and the United Kingdom have removed kava products from the market.[77] The German action has been protested by members of the Commission E as unwarranted.[78] The FDA, as well as Australian and Canadian authorities, have issued warnings to consumers and health care workers on the potential for liver damage from kava products.[79] A definite link has not been determined between kava and the observed severe cases of hepatotoxicity; interactions between kava and prescription or OTC drugs have not been ruled out at this time. Caution would dictate that patients with any predisposition to liver problems should avoid use of kava. A systematic review of kava safety issues has been published.[80] The incidence of hepatotoxicity is clearly too low to have been detected in previous clinical trials. [81]

SUMMARY: Kava root is approved for conditions of anxiety, stress, and restlessness by the German Commission E, and also is monographed in the *British Herbal Pharmacopoeia* (vol. 2) and in the *WHO Monographs on Selected Medicinal Plants* (vol. 2). Kava has long been a popular drink in many South Pacific islands, used socially and ceremonially. Kava lactones are the chemical principles responsible for its mild sedative effects, which are additive with those of alcohol or benzodiazepines. Dosage of kava lactones in clinical studies has been in the range of 100 to 200 mg/day, corresponding to 1.5 to 3 g of ground root. Heavy use can cause a scaly skin rash. Disturbances in visual accommodation also have been described. [56] Serious concerns have been raised about its potential for severe liver toxicity; however, such episodes appear to be rare. Reviews of its chemistry and pharmacology are extensive. [1,8,32,82,83,84,85,86,87]

PATIENT INFORMATION— Kava

Uses: Kava has mild sedative effects and is used for nervous anxiety, stress, and restlessness.

Interactions: Kava appears to potentiate the CNS effects of benzodiazepines (eg, alprazolam).

Side Effects: Heavy kava use can cause visual disturbances and a scaly skin rash. Rare cases of severe liver toxicity also have been reported.

Dosing: Dosage of kava lactones in clinical studies has been in the range of 100 to 200 mg/day, corresponding to 1.5 to 3 g of ground root.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KAVA

KH-3

DATE OF ISSUE: OCT 2003

REPLACES MONOGRAPH DATED: MAY 1991

SCIENTIFIC NAME(S): Procaine HCl

COMMON NAME(S): KH-3, Gerovital H3, GH-3, GeroVita

HISTORY: Although procaine HCl is a pure synthetic drug, its use as one of the active ingredients in KH-3 is marketed by many commercial Web sites as a "natural" approach to reversing or delaying the aging process. KH-3 was developed in Germany in the 1960s and was popularized by Romanian and other Eastern European researchers.[1] Procaine-containing products are available over-the-counter and by mail order in the US and parts of Europe.

These products have been administered parenterally and orally for their effect on the overall aging process and for the treatment of cerebral atherosclerosis, progressive dementia, arthritis, hair loss, hypertension, and sexual dysfunction.

CHEMISTRY: Chemical name is 2-diethylaminoethyl 4-aminobenzoate hydrochloride. Preparations are based primarily on the pharmacologic effects of procaine HCl and are often marketed as mixtures of procaine, buffers (eg, benzoic acid, potassium metabisulfate), analgesics, and nutritional supplements. [2] One preparation from Germany contains procaine, hematoporphyrin to aid absorption of procaine, magnesium carbonate, sodium hydrogen phosphate, potassium HCl, and other compounds. Most products contain approximately 2% procaine HCl. Studies have shown that the biotrophic treatment with Gerovital H3 has a strong influence on glucose-6-phosphate dehydrogenase with a tendency to diminish the thermolabile fractions. [3]

PHARMACOLOGY: Procaine has been used for decades as a local anesthetic and antiarrhythmic. The compound has a number of pharmacologic characteristics, including an ability to decrease membrane excitability and alter membrane ionic transmission. Procaine is hydrolyzed rapidly to inactive compounds by plasma enzymes.[2] Procaine is poorly absorbed and quickly metabolized following oral administration; therefore, it is primarily used by injection. Hematoporphyrin is added to some oral preparations and is said to inhibit intestinal hydrolysis of procaine. There is no evidence that pharmacologic levels of procaine are attained in the brain or other target organs following oral administration of KH-3 or other products.

Numerous studies also have been conducted to evaluate the efficacy of procaine HCl or commercially available mixtures of this compound for the treatment of elderly patients with a variety or organic diseases. [4] The effect of Gerovital H3 on psychologic and physiologic functions was assessed on geriatric patients (mean age, 73) in a placebo-controlled, double-blind study. Patients received either a 5 mL injection or placebo IM 3 times/week for the first 6 weeks. The dose was doubled to 10 mL per injection during the second 6 weeks. Objective rating scales included interpersonal functioning, cognitive ability, psychiatric symptoms, and urine and blood chemical findings. The study results indicated that Gerovital H3 had no ameliorative effect on either psychologic or physiologic functioning. [5]

The results have been conflicting but generally indicate these compounds are ineffective in the treatment of any disease. As early as 1977, a comprehensive review of the use of procaine in over 100,000 patients found no evidence for its efficacy. [6] Of 8 studies published prior to 1980, 6 found no effect. [2]

Antidepressant activity: Although controversial, some authors suggest that procaine may act as an inhibitor of monoamine oxidase, thereby relieving depression. [4]

One study found slight mood improvement in depressed elderly patients. [2] Although a slight antidepressant activity was considered possible in 1 study, [6] it was suggested this may have accounted for the occasional reports of improvement in complaints related to the musculoskeletal, cardiovascular, and GI symptoms.

Anticholesterol activity: Reports of the effect of procaine on blood cholesterol levels are inconsistent, with some studies showing a reduction in cholesterol and others showing little beneficial effect. [7]

TOXICOLOGY: Procaine HCl is generally contraindicated in patients with known hypersensitivity to the drug or related compounds. The drug should not be administered to patients taking concurrent anticholinesterase medications (eg, neostigmine). Furthermore, because of the lack of clinical trial data, procaine HCl should not be used during pregnancy.

Procaine may inhibit the bacteriostatic action of sulfonamides. [2] Reports have described heartburn, migraine, and systemic lupus erythematosus following treatment with KH-3. No adverse events have been reported in other studies. [2]

SUMMARY: Procaine HCl has been available for several decades in preparations designed for the amelioration of chronic diseases associated with aging. Although a number of reports have described its use, these reports generally have been poorly designed, and their results have been inconclusive. There is no valid evidence for a pharmacologic effect of these compounds in the elderly.

PATIENT INFORMATION — KH-3

Uses: Without much supporting clinical trial data, KH-3 has been credited with inhibiting diseases of aging and may have antidepressant activity.

Side Effects: Published reports have described heartburn, migraine, and systemic lupus erythematosus. KH-3 is contraindicated in patients with known hypersensitivity to the drug. Furthermore, because of the lack of clinical trial data, KH-3 should not be used during pregnancy.

Disease-State Concerns: KH-3 is contraindicated in patients with myasthenia gravis (ie, progressive muscular weakness) and systemic lupus erythematosus (theoretical risk of this condition being induced by procainamide). [2,8]

Drug-Interaction Concerns: KH-3 may antagonize the antibacterial effect of sulfonamides through para-aminobenzoic acid competition. Prolonged neuromuscular blockade may occur with concurrent use of KH-3 with succinylcholine. [8] KH-3 is potentially contraindicated in patients taking anticholinesterase and anticholinergic agents.[8]

Dosage Concerns: Although not supported by clinical trial data, dosage regimens marketed by commercial Web sites include: (a) 100 to 200 mg capsule daily by mouth; (b) 100 to 200 mg capsule daily by mouth for 1 month, then no drug for 1 week, then repeat the cycle.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KH-3

KHAT

DATE OF ISSUE: MAR 2002

REPLACES MONOGRAPH DATED: MAR 1993

SCIENTIFIC NAME(S): *Catha edulis* Forsk. Family: Celastraceae (moonseed)

COMMON NAME(S): Khat, qut, chaat, chat, kaht, tchat, qaad, jaad, miraa, Kus es Salahin, Tchaad, Tschut, Tohat, Tohai, Gat, Qat

BOTANY: Khat is a tall plant (2.7 to 3.7 m) with a natural distribution limited to East Africa and the Arabian Peninsula (Kenya, Yemen, and Ethiopia). It grows best at high elevations, and its tender twigs and leaves are harvested almost year-round. Freshly harvested khat is wrapped in leaves and exported by air to neighboring African countries.

HISTORY: One of the most common forms of drug use and abuse in many East African nations involves chewing parts of the khat plant. Khat use has increased steadily over the last 50 years and has become a problem of significant social and medical importance. Because of its social acceptability and euphoriant effects, khat chewing often plays a dominant role in celebrations, meetings, marriages, and other gatherings. Khat use even has been prevalent in the Somali military. It has been issued to soldiers in their daily rations with the intention of inhibiting their need for food and sleep, as well as increasing their aggression. [1]

The amount of khat chewed per user is 100 to 200 g of leaves and stems over 3 to 4 hours. The tender leaves and stems, which lose their potency 1 day after harvest, are chewed and the juice is swallowed.[1] Khat has a sweet taste and an astringent action.[2] Large amounts of liquids are consumed while chewing because of the dryness induced by the plant.

Khat leaves have been used in traditional medicine for the treatment of depression, fatigue, hunger, obesity, and gastric ulcers.

CHEMISTRY: Studies of the chemical constituents of this plant date to the late 1800s, when European investigators isolated the alkaloid fraction "katin." It had a stimulating effect on the frog heart and caused dilation of the frog pupil. Katin was later renamed cathine and was identified as (+)-norpseudoephedrine (also designated S(-)-alpha-aminopropiophenone).[3] This amphetamine-like compound has been isolated from the genus *Ephedra*, the biologic effects of which are, in many respects, similar to those of khat. The cathine content of dried khat leaves ranges from 0.1% to 0.2%.[4] Cathine has ~ 1/10 the stimulant activity of d-amphetamine. It decreased food intake and increased locomotor activity in rat studies. The compound has been confused with d,1-norephedrine in the literature, although the 2 compounds differ in pharmacologic properties.[5]

Cathinone (alpha-aminopropiophenone) has been isolated in variable quantities from fresh leaves. This compound is a more powerful stimulant than cathine and generally considered to be the most important component; however, it is unstable in the presence of oxygen, and decomposes within a few days of picking or if the plant is dried,[6] making fresh leaves the best source of cathinone.[7] For maximum potency, khat must be picked in the morning and chewed that afternoon.[8] The red variety of khat, considered superior by users, contains more cathinone than the white type. Fresh khat leaves (100 g) contains ~ 36 mg cathinone, 120 mg norpseudoephedrine, and 8 mg norephedrine.[9] More than 30 other minor compounds (eg, cathinine, cathidine, eduline, ephedrine) have been isolated from khat leaves. Khat contains khatamines (phenylpropyl and phenylpentenylamines) in amounts that vary according to the origin, type, and quality of the product. [10] Khat leaves and twigs contain large amounts of tannins (up to 14% of dry weight). One hundred grams of fresh khat contains 36 mg cathinone, 120 mg norpseudoephedrine, and 8 mg norephedrine.[11] After oral administration, 22% to 52% of synthetic cathinone is excreted in 24-hour urine samples, the principal metabolites being aminoalcohols. S-(-)-cathinone is metabolized primarily to R/S-(-)-norephedrine, and R-(+)-cathinone is metabolized primarily to R/R-(-)-norpseudoephedrine.[12]

PHARMACOLOGY: The subjective effects of khat include euphoria, intellectual efficiency, and alertness in most subjects, while others report only dysphoria and mild sedation. The expression of these effects appears to be affected by environmental factors.[13]

CNS effects: In studies of skeletal muscle, (-)-cathinone and d-norpseudoephedrine antagonized the actions of physostigmine but not those of d-tubocurarine, suggesting that the 2 compounds have a direct action on the neuromuscular junction independent of cholinergic and adrenergic transmission. [14] In the toad heart, a khat extract produced a dose-dependent chronotropic effect and increased the amplitude of the ventricular action potential with acute treatment. Chronic treatment had the opposite effect. These results are related to the catecholamine-releasing effects of the extract. [15]

The psychotropic effects of khat are caused by the amphetamine-like compounds, of which cathine is found in highest concentration. The stimulating effects of khat are somewhere between caffeine and amphetamine. Although amphetamine and cathinone act on different regions of the brain, they both share common pharmacologic effects, including an interaction with the dopaminergic pathways.[16] D1-type dopamine receptors, studied in rats, have been implicated in mediating the reinforcing effects of cathinone.[17]

Central stimulation by khat is manifested by euphoria, increased alertness, garrulousness, hyperactivity, excitement, aggressiveness, anxiety, elevated blood pressure, and manic behavior, effects that have been verified in a double-blind trial of a single dose of khat. [18] This period of stimulation lasts for ~ 3 hours.[9] A depressive phase, including insomnia, malaise, and a lack of concentration, almost always follows. True psychotic reactions occur with much less frequency than with amphetamines. This is most likely because of the self-limiting dose of khat, which does not permit blood levels of the active compounds to rise high enough for toxic psychosis to occur. However, paranoid (typically persecutory) delusions have been seen. [19]

Physical dependence to khat does not occur, and the mental depression, sedation, and social separation that may follow withdrawal are a rebound phenomenon rather than an abstinence syndrome. When studied in rats that self-administer cathinone IV, results show that it was self-administered for its reinforcing properties. [17] The psychic dependence that occurs is less than that with amphetamines but still suffices to make daily use of khat the norm. Development of tolerance to the effect of cathinone is more rapid than to that of amphetamine, and there is a cross-tolerance between the effects of cathinone and amphetamine.[3]

Cardiovascular effects: Cardiovascular effects occur within 15 to 30 minutes after ingestion, suggesting absorption of active principles through the oral mucosa. Effects include tachycardia, palpitations, and increased systolic and diastolic blood pressure. These effects can persist up to 4 hours after the onset of chewing. [20]

Chronic use of khat has been implicated as a contributing factor to hypertension in young adults; spontaneous improvement follows cessation of use. Other physiological effects include increased respiratory rate, hyperthermia, sweating, pupil dilation, and decreased intraocular pressure.

GI effects: GI side effects are often encountered with khat use. The stomatitis, esophagitis, and gastritis noted in chronic users are most likely because of the presence of the strongly astringent tannins. Two separate studies in healthy volunteers showed that chewing khat slows whole gut transit time, possibly caused by the sympathomimetic action of cathinone.[21,22] Daily khat chewing has been found to be associated with a high prevalence of *Helicobacter pylori*.[23] One report has noted an exceptionally high rate of periodontal disease in Yemeni males who chewed khat. [24] A more recent report states that khat use is associated with some temporomandibular joint dysfunction and keratosis of the buccal mucosa.[25]

Constipation is perhaps the most common GI symptom of khat use and is caused by the tannins and the sympathomimetic effects of the alkaloids. The relationship between khat use and constipation is so strong that when a ban was imposed on khat in Aden in 1957, the sales of laxatives decreased 90% but returned to the original levels soon after the ban was lifted.[4] Hemorrhoidal disease has been linked to khat chewing in a study in Yemen. The pathogenesis by which khat induces hemorrhoids includes the following: Chronic constipation, straining during defecation and micturation, and prolonged sitting (during a khat chewing session). Many of these patients with chronic hemorrhoids need to have a hemorrhoidectomy.[26]

GU effects: Chewing khat leaves results in reduction in maximum and average urinary flow rates, presumably because of the sympathomimetic action of cathinone on the bladder neck.[27]

Norpseudoephedrine has been found in breast milk from mothers who use khat and in the urine of at least 1 infant of such a mother. Until research into health hazards is completed, use of khat by lactating mothers is discouraged.

Endocrine and metabolic effects: Khat has little effect on blood sugar levels. Although hypoglycemia has been noted in rabbits after SC injections of khat leaf extracts, no changes in blood sugar were found in 15 healthy males after khat ingestion.[28] Interviews of 7500 khat users in Somalia[29] did not reveal any beneficial effect of khat in diabetic patients. The overall effect of khat on diabetic patients is deleterious. Its appetite-suppressant effect leads to the omission of meals; the uncooperative khat user is less likely to follow dietary advice, and the consumption of sweetened beverages while using khat aggravates hyperglycemia.[30] Anorexia is a socially important effect of khat abuse. The WHO implicates khat in a vicious cycle of khat use, destitution, hunger, anorexia, malnutrition, and digestive troubles.

Experimental therapeutic use: In experiments with albino rats, a flavonoid fraction isolated from khat at a dosage of 200 mg/kg, reduced paw edema induced by carrageenan and cotton-pellet granuloma. The substance had an anti-inflammatory activity comparable with that of oxyphenbutazone.[31]

Social notes: In his review of the use of khat in Somalia, Elmi[28] warns that "the pleasant stimulation obtained when chewing khat induces many to abuse the drug. This may have damaging effects from a social and economic point of view. Some people may spend a great part of their earnings on khat, thus failing to ensure for themselves and their families important and vital needs. Excess of khat chewing may lead to family disintegration. The chewer often shows irritability and spends much of the time away from home. These facts and the failure of sexual intercourse after chewing may endanger family life. For some countries where khat imports account for the loss of a sizable portion of the national income, there may be a serious economic balance of payments problem." In an interview with Somalis living in England, up to 90% would rather see their children use khat as opposed to alcohol or cigarettes.[6]

A study in Butajira, Ethiopia, where khat usage is legal, showed that 80% of chewers used khat to gain a good level of concentration for prayer, facilitate contact with God, and prevent them from doing bad things. Muslim religion, smoking, and a low income showed strong association with daily khat consumption.[32,33]

Khat use is tolerated in the Netherlands and Great Britain, but is prohibited in the US, France, Switzerland, and Sweden.[9,20,34]

A study in Scotland of 16 to 25 year olds attending a rave showed that khat is one of the drugs of choice when attending one of these dance events. A marketing leaflet states that khat is said to produce "feelings of euphoria, increased libido, talkativity, excitement, loads of energy, and a big khat smile." Khat juice is made by blending the plant with water and lemon and filtering the resulting mixture and is sold by the glass or as a tincture (alcohol extracted active ingredients).[35]

Methcathinone (also referred to as "cat"), is structurally and pharmacologically related to cathinone and methamphetamine and is a popular drug of abuse in Russia and parts of the US. According to addicts, methcathinone is more potent and addictive than other psychostimulants, with a long-lived intoxicating effect of up to 6 days.[17,36]

INTERACTIONS: Khat chewing/ingestion has been shown to delay or decrease absorption of amoxicillin and especially ampicillin. Investigations of the chemical and biological effects of khat indicate that the tannins present in khat leaves are most likely responsible for the observed effects on these antibiotics. It is therefore recommended that ampicillin and amoxicillin be taken 2 hours after the khat chewing session is completed.[37]

TOXICOLOGY: Severe adverse effects have been associated with khat use: Migraine, cerebral hemorrhage, MI, and pulmonary edema have been described, particularly in older and predisposed individuals. A case report of a 56-year-old patient with diffuse abnormality in the deep white matter of both cerebral hemispheres suggested a rapidly progressive leukoencephalopathy that was likely precipitated by khat use.[38] Anaphrodisia is reported frequently by men during khat use. Although libido initially may be increased, a loss of sexual drive, spermatorrhea, and subsequent impotence soon follow. However, 72% of female users in one survey reported increased sexual desire, followed by an improvement in sexual performance in 78% of the respondents.[28]

Khat chewing has been associated with duodenal ulcer. This effect can be because of the stress that follows khat chewing, the amphetamine-like action of cathine, increased presence of *H. pylori*, or insecticides and chemicals used for growing the khat plant.[23]

In vitro studies have demonstrated that a chloroform extract of khat leaves is cytotoxic in cultures of KB, 1BR.3, and XP2B1 mammalian cells. This cytotoxicity appears to be because of inhibition of de novo RNA synthesis affecting all the cell strains tested; KB cells possessed some resistance to the toxicity.[39] The tannins found in khat leaves have been shown to thicken the mucosa of the oropharynx and esophagus and also may be carcinogenic.[40] Oral cancers in certain regions of Saudi Arabia have been found to occur mainly among patients who had been chronic khat chewers.[41] Esophageal and gastric carcinoma have been attributed to khat chewing and water-pipe smoking in men and women in Yemen.[40] Khat-chewing men living in the area of the horn of Africa were studied and were found to have an increased risk of oral carcinoma, especially when accompanied by alcohol and tobacco consumption.[42]

Data from *Allium cepa* root tips suggest that (-)-cathinone is responsible for teratogenic and mutagenic effects of khat because it caused clumping and condensation of chromosomes, sticky metaphases, and anaphasic bridges.[43] Animal studies indicate that cathinone can depress testosterone levels, degenerate testicular tissue, and decrease sperm count and motility.[44] In a study of 65 khat addicts compared with 50 nonkhat addicted subjects, statistically significant differences were detected between the semen parameters of the 2 groups. These parameters included semen volume, motility index, sperm count, sperm motility, and percentage of normal spermatozoa, all of which were lower among the addict group. Long-term addicts also showed severe ultrastructural deformation in comparison with the nonkhat addicted subjects.[45]

Studies of full-term human newborns have shown that khat use by the mother is associated with lower birth weight,[46] but no differences in the rates of stillborns or congenital malformations were observed.[47] A study of guinea pigs suggests that (+)-norpseudoephedrine in khat may reduce placental blood flow, impairing fetal growth.

A report of 2 cases has described bilateral optic atrophy in 2 khat users who consumed amounts larger than usual. This may have been an idiosyncratic reaction to khat.[48] Khat-induced anorexia causes a deficient nutritional state that favors infections. Tuberculosis is a particular threat because the chewed residues of the leaves are ejected by spitting and the water pipe is used collectively during a khat session.[9]

Hepatic cirrhosis of unknown etiology has been noted in khat users; poor diet and the potentially hepatotoxic effects of khat tannins may be contributing factors. Two case reports of *Fasciola hepatica* infection have been attributed to contaminated khat chewing. Human fascioliasis usually occurs from ingesting contaminated watercress, water, or liver. Khat grows especially well in moist conditions and could become contaminated with metacercariae, thus leading to fascioliasis.[49,50]

SUMMARY: Khat is a plant product produced and consumed in East Africa and the Arabian Peninsula. Chewed for its euphoric effects, khat does not induce physical dependence. However, it does induce psychological dependence and can cause serious physical and psychological side effects. Active ingredients found in khat are similar to amphetamine. Khat is exported worldwide and may represent a serious economic problem, with considerable social costs, for users. Khat use has been seen at raves.

Khat consumption should be considered when addressing health-related topics in patients from communities that advocate its use.[6,19]

PATIENT INFORMATION — Khat

Uses: Khat leaves are chewed for stimulant and euphoriant effects and are used to treat obesity and prevent hunger in areas with meager food supplies. Some users experience dysphoria and sedation. Khat is prohibited in the US, France, Switzerland, and Sweden.

Interactions: Khat chewing interferes with the absorption of the antibiotics ampicillin and amoxicillin. Consult the health care provider if prescribed these antibiotics and continuing to chew khat.

Side Effects: Khat may cause oral and gastric cancer, cerebral hemorrhage, MI, duodenal ulcers, hypertension, testicular degeneration, low birth-weight infants, and a variety of other severe effects including addiction and the attendant ills.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KHAT

KINETIN

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): N6-furfuryladenine, N-(2-furanylmethyl)-1H-purin-6-amine, 6-furfurylaminopurine

COMMON NAME(S): Kinetin

BOTANY: Kinetin, a cytokinin and plant hormone, is a cell division factor found in plant parts and yeast. [1] Kinetin has also been detected in freshly extracted DNA from human cells.[2]

HISTORY: Plant hormones, or cytokinins, were named for their ability to stimulate cell division (cytokinesis). [3] The first known cytokinin was a component of coconut milk. This was used as a standard additive to plant tissue cultures in the lab because of its ability to make plants divide. Cytokinins were eventually isolated from coconut milk, immature organs of corn, and various other sources.[4] Studies dating back to the mid-1950s describe the structure and synthesis of kinetin specifically. [1]

Kinetin has been advertised as an antiaging product for wrinkled skin treatment. *Kinerase* is a cream/lotion containing a 0.1% kinetin concentration. [5]

CHEMISTRY: Cytokinins are N6-substituted adenine derivatives.[6] The furfuryl moiety of kinetin is reported to originate from furfural, a primary oxidation product of the deoxyribose in DNA.[7] N6-furfuryladenine has electrochemical properties. Electrochemical assignments have been confirmed from kinetin using mass-spectrometric analysis.[2]

Studies have reported the following: Isolation of kinetin from autoclaved water slurries of DNA, structure determination, and physiologic activity at high dilutions in the presence of auxin.[1]

PHARMACOLOGY: Cytokinins function as essential growth hormones, which can influence cell growth and differentiation in plant and non-plant tissues. [6,7] Kinetin can be formed in vivo, neutralizing harmful properties of hydroxyl radical reaction products. This is a defense mechanism in response to oxidative stress of cells. [8] Degradation of sugar residues in DNA is a major route of this cellular damage.[7] Kinetin-activated, major nucleolar organizer regions in basal, equatorial, and near-apical tissue of onion (leaf base) suggest it to be a regulator. [9] Single-celled yeast, *Saccharomyces cerevisiae*, used as a model, demonstrated spore formation at micromolar concentrations of kinetin.[6] Another report finds kinetin to delay aging and prolong lifespan of the fruitfly *Zaprionus paravittiger*.[10] Addition of kinetin in a culture medium of human cells can delay and offset aging characteristics such as growth rate and cell size. [11] The amount of DNA in the nucleii of the fibroblast cells increased in the presence of kinetin from human skin.[12]

The skin care product *Kinerase* claims to be a "nature-identical" plant growth factor, which "delays and improves unwanted changes in appearance and texture of photodamaged skin." It allegedly reduces wrinkles and improves skin texture, telangiectasia, and mottled hyperpigmentation. Results are typically seen in 4 to 6 weeks. Product literature compares *Kinerase* with the prescription cream *Renova* (0.05% tretinoin), finding *Kinerase* to be superior to *Renova* parameters by patient self-assessment at a 24-week period. There was an incidence of side effects using *Kinerase* vs *Renova* (eg, erythema, peeling, burning, and stinging).[5]

TOXICOLOGY: Computer literature searches found no information on toxicology of kinetin. The makers of *Kinerase* claim its use is associated with virtually no skin irritation, no thinning of the skin, no restrictions in pregnant or nursing women, no restrictions on duration of use, etc. The product is reportedly hypoallergenic and noncomedogenic and has no known interactions with drugs or other products.[5]

SUMMARY: Kinetin is a cytokinin, a plant hormone, with the ability to influence cell growth and differentiation in plant and non-plant tissues. It has gained some popularity with the introduction of the product *Kinerase*, which supposedly improves wrinkles, skin texture, and color. Very low incidence of adverse effects have been reported in studies with use of the product. Further research in human clinical trials are warranted.

PATIENT INFORMATION — Kinetin

Uses: Kinetin functions as an essential growth hormone, which can influence cell growth and differentiation. It can delay and offset aging characteristics such as cell growth rate and size. It is claimed to reduce wrinkles and improve skin texture, telangiectasia, and mottled hyperpigmentation, although there is limited information to support this.

Side Effects: There is a very low incidence of side effects when used topically. Common side effects include erythema, peeling, burning, and stinging..

Dosing: There is no available information on appropriate human doses of this plant growth hormone.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
      KINETIN

KIWI FRUIT

DATE OF ISSUE: SEP 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Actinidia chinensis*Planchon. Family: Actinidiaceae

COMMON NAME(S): Kiwi fruit, Chinese gooseberry, China gooseberry

BOTANY: The kiwi is native to eastern Asia, but today is widely cultivated for its fruit. Major producers of the kiwi fruit include New Zealand and Italy, although a significant harvest is obtained from other temperate countries including France and Israel. The bisexual plant grows as a trained vine and is often cultivated as an ornamental.[1]

HISTORY: The kiwi fruit has been used in China as the basis for a flavorful wine. It has a long tradition of use as a fruit beverage.

CHEMISTRY: An enzyme inhibitor and a proteolytic enzyme have been isolated from the kiwi fruit. A glycoprotein inhibitor specific for pectin methylesterase has been isolated from the fruit.[2] This enzyme inhibitor is ineffective against other polysaccharide-degrading enzymes such as polygalacturonase and amylase.

The proteolytic enzyme, actinidin, is derived from the kiwi fruit. [3] The nucleotide sequence of this enzyme has been established.[3,4,5] The proteolytic activity of actinidin is similar to, but not identical to, that of papain. Kiwi fruit juice has been used in some cultures as a traditional meat tenderizer.

Kiwi fruits have high concentrations of vitamin C, and the serotonin concentration of the fruit is approximately twice that of tomatoes and one-third that of bananas. [6] Ingestion of kiwi fruits, therefore, can increase urinary 5-hydroxyindoleacetic acid excretion and may interfere with laboratory analyses for this serotonin by-product.

PHARMACOLOGY: Kiwi fruit has no inherent pharmacologic activity. However, the action of the proteolytic enzymes can result in activity that may lead to toxic events (see Toxicology).

One study reported the effects of a kiwi fruit-based drink supplement given to athletes training in hot environments. [7] In athletes riding a Monark ergometer, the mean work time to exhaustion was longer (149 min) compared to placebo (120 min), and the work load was larger (947 KJ vs 833 KJ) ($p < 0.001$). The kiwi-based drink supplement resulted in an expansion of blood volume; hematocrit increased significantly after exercise in athletes taking placebo, but did not change significantly in those consuming the supplement. Furthermore, based on the urinary excretion of vitamin C, it appeared that the vitamin C status of supplemented athletes improved compared to placebo. The drink was found to be "fragrant, tasty, refreshing and thirst quenching," and it did not appear to have any side effects.

TOXICOLOGY: The enzymatic components appear to be largely responsible for the toxicities associated with kiwi fruit. These events are typically manifested as food allergies.[8] This hypersensitivity manifests as oral/buccal reactions that occur a few minutes after ingesting the fruit. [9] More severe reactions, including dysphagia, vomiting and urticaria, have occurred immediately following ingestion of the fruit. [10]

Contact urticaria has also been reported. [11]

SUMMARY: The kiwi fruit is a widely cultivated, popular fruit throughout the world. It serves as the base for flavorful juices. It contains a proteolytic enzyme that has been used as a traditional meat tenderizer, but which may also be responsible for an increasing number of allergic events to the fruit.

PATIENT INFORMATION— Kiwi Fruit

Uses: Kiwi fruit is used as food, meat tenderizer and basis of a "sports drink."

Side Effects: Some experience severe allergic reactions immediately after consumption.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KIWI FRUIT

KOMBUCHA

DATE OF ISSUE: AUG 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Yeast/bacteria fungal symbiot

COMMON NAME(S): Kombucha tea, kombucha mushroom, Manchurian tea, Combucha tea, Spumonto, Tschambucco, Teekwass, Kwassan, Kargasok tea, "Fungus" Japonicus, Manchurian "fungus, "Dr. Sklenar's kombucha mushroom infusion, Champagne of life, T'Chai from the sea

BOTANY: Kombucha is not a fungus or a mushroom, but rather a gray, pancake-shaped patty that grows up to six inches in diameter. The patty is placed in a mixture of black tea and sugar to ferment. Technically, the fermentation becomes a mixture of yeast and bacteria (ie, *Bacterium xylinum*, *Bacterium gluconicum*, *Acetobacter ketogenum* and *Pichia fermentans*).

HISTORY: Kombucha tea has grown rapidly in popularity over the past year and has been touted as a miracle cure for a wide variety of illnesses, ranging from memory loss to premenstrual syndrome.[1]

The name kombucha is derived from the Japanese in that it is brewed in a seaweed (kombu) tea (cha).[2] In Western countries, the product is typically propagated in black tea. Users float growing spores on the surface of brewed, sweetened black tea. The mycelium double in mass approximately every week. The mass is then divided and the new portion is propagated on a new tea media. In this manner, kombucha mycelium can be propagated at a rapid rate for commercial distribution. Units of the fungus can sell for $50 each.[2]

As the growth matures, it ferments the beverage slightly. This fermented tea is drunk for its purported medicinal properties. Drinking fermented teas has long been popular in Eastern countries, and the use of this particular mycelial growth may date back several centuries.

Despite extravagant claims for its pharmacologic activity, some experts believe that the tea fulfills the FDA criteria identifying a *fraudulent* product, including: reference to non-US medical studies, an appeal to a person's vanity, ancient origins and alleged cures for a wide variety of ailments.[1] Some of these claims include curing cancer, rheumatism, aging and intestinal disorders.

CHEMISTRY: The fermentation process induced by kombucha is said to produce substantial amounts of glucuronic acid, which is normally synthesized by the body.[1] Fermentation products may also include alcohol (0.5%), hyaluronic acid, chondroitin-sulfate acid, mukoitin sulfate, heparin, lactic acid[3] and usnic acid.[1]

PHARMACOLOGY: There is no good evidence to support the pharmacologic claims for kombucha. Because kombucha tea is a product of bacterial fermentation, it may contain compounds that affect the bacterial flora of the gut.

One report on Dr. Sklenar's kombucha mushroom infusion (1960s) as a cancer therapy indicated that there was no solid medical data available on its usefulness in cancer treatment.[4]

Screening of "Kargasok tea" (kombucha tea) for anorexia and obesity has also been reported, but not validated.[5]

TOXICOLOGY: Cases of nausea and allergic responses have been reported. No kombucha-related deaths have occurred, although Iowa health officials have reported the first suspected death linked to the tea.[6] Regulatory agencies are investigating the possibility that kombucha may be a source of bacterial pathogens.[2] In one case, an 83-year-old person with multiple health problems drank 0.5 cup of a kombucha mixture for a 3-week period. Upon examination, laboratory results indicated AST/MLT greater than 2000 IU/L, lactate dehydrogenase peaking at 4000 IU/L and a prothrombin time over 25 seconds. The APAP (acetaminophen) level was "trace."[3]

SUMMARY: Kombucha is a popular natural product that is used to ferment tea. However, it is not approved by the FDA for medical purposes. Kombucha tea is covered widely in the popular press. The fermented liquid is purported to have a wide variety of medicinal properties, but there is no good evidence supporting any clinically relevant pharmacologic activity. No significant adverse events have been associated with drinking the fungal tea, although one suspected death linked to it has been reported.

PATIENT INFORMATION — Kombucha

Uses: There is no good evidence to support the pharmacologic claims for kombucha.

Side Effects: The fermented tea associated with kombucha has been suspected as fatal in one user.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KOMBUCHA

KUDZU

DATE OF ISSUE: NOV 1999

REPLACES MONOGRAPH DATED: JUN 1994

SCIENTIFIC NAME(S): *Pueraria lobata* (Willd) Ohwi. Also known as *P. thunbergiana*. Family: Leguminosae. Other species include the following: *P. mirifica* (Thailand herb known as kwaao khruea, used for hormonal content),[1] *P. tuberosa*DC (also studied for hormonal effects),[2,3] and *P. thomsonii* Benth.[4]

COMMON NAME(S): Japanese arrowroot, kudzu vine[5], ge gen (Chinese)

BOTANY: Kudzu is a fast-growing vine native to the tropics of China and Japan. It has been used as fodder and as a ground cover crop. Because it produces long stems that can attain 20 m in length and extensive roots, it has been used to control soil erosion. The plant was introduced into the US where it has become established and proliferates particularly in the moist southern regions. It is in the southern regions that it grows vigorously and is now considered a pest. The leaves of the plant contain 3 broad oval leaflets with purple flowers and curling tendril spikes. [6]

HISTORY: Although kudzu has been widely recognized as a ground cover and fodder crop in the Western world, the plant has a long history of medicinal use in Asian cultures. As far back as the 6th century BC, Chinese herbalists have used the plant for muscular pain and for the treatment of measles. [6] Kudzu is cited in botanical herbals from Japan, China, and Fiji.[7] The Chinese have also used extracts of the plant to treat alcoholism.[6,8]

CHEMISTRY: Numerous reports are available identifiying chemical constituents of various plant parts of kudzu.[9,10,11] Flavonoid, isoflavonoid, and isoflavone content have been identified in kudzu roots and flowers.[12,13,14,15,16,17,18] A report discusses kudzu as an excellent food source for both genistein and daidzein, 2 anticancer isoflavones.[19] Oleanene-type triterpene glycosides, termed "kudzu saponins," have been isolated from the plant as well.[20,21]

Analysis of isoflavonoid aglycones and their glycosides has been performed.[22] Robinin in kudzu leaf has also been reported.[23] Other constituents reported include daidzin, formononetin, biochanin A, puerarin, and plant sterols.[6,8,24,25,26] In addition, morphological and anatomical identification of kudzu have been performed.[27]

PHARMACOLOGY: Pharmacokinetic studies on urinary and biliary metabolites of kudzu have been performed in rats.[28,29]

Kudzu has gained attention because the isoflavones contained in the root have been found to be reversible inhibitors of the enzyme alcohol dehydrogenase. Derivatives of these compounds are also potent inhibitors of aldehyde dehydrogenase. Both of these enzymes are required for the normal metabolic degradation of alcohol and its byproducts.[25]

In one controlled study, an extract of kudzu reduced alcohol consumption in Syrian Golden hamsters, which are bred for their desire for alcohol. After establishing baseline intakes of water and a 15% ethanol solution, animals were injected with crude kudzu extract, daidzein or daidzin for 6 days. In each group, the volume of ingested alcohol solution decreased by = 50% during the treatment phase. Alcohol consumption returned to pretreatment levels after the study was stopped. This in vivo activity is likely because of the inhibition of enzymes that metabolize alcohol.[30] Isoflavones daidzin and daidzein were later determined to account for this suppression of ethanol intake.[31] In animal experimentation, these same compounds have also decreased blood alcohol levels, and shortened alcohol-induced sleep.[32,33] Certain saponins from kudzu have also demonstrated in vitro liver protective effects when tested in rat hepatocytes.[34,35]

Traditional Chinese medicine still employs kudzu for treatment of muscular aches and pain, such as neck pain and stiffness and upper back problems.[6] It is also a traditional remedy for gastritis, dysentery, and the flu.[26] *P. lobata*and *P. omeiensis* have significantly inhibited induced fever in rats.[36]

Kudzu's beneficial effects on heart disease and related disorders have been documented. Plant extracts increased cerebral blood flow in arteriosclerosis patients,[6] decreased oxygen consumption by myocardium, exerted spasmolytic activity,[26] and have caused relaxation in induced contractions in cat vascular smooth muscle.[37] Kudzu has been used in the treatment of hypertension,[38] arrhythmia,[39] ischemia,[36] angina pectoris, and migraines.[26] At least one report is available discussing one kudzu glycoside and its antioxidant acitivity.[40]

Related species *P. mirifica* and *P. tuberosa* have been studied for their contraceptive effects.[6] One of these reports investigates *P. mirifica* for birth control in pigeons.[41]

TOXICOLOGY: Kudzu has been used as a medicinal herb for centuries without any reported toxic side effects.[25] However, the safety profile of the plant and its extracts has yet to be defined through systematic pharmacologic screens. The Chinese Materia Medica, through pharmacological and clinical experimentation, has been published to establish safety information for just under 4700 known specimens used in traditional medicine of which kudzu is discussed.[38] Acute toxicity of 4 species of *Pueraria* has been comparatively studied.[36]

SUMMARY: Kudzu is a fast-growing plant native to Asia that has been naturalized to the southern US. It has been used as a ground cover and for fodder and in Asian medicine for the management of alcoholism. Several compounds in kudzu root can inhibit enzymes involved in alcohol metabolism, thereby inducing a reduction in alcohol consumption in animal models. Kudzu is also used for muscular aches, heart disease, and related disorders. Its toxicity profile is low. More clinical studies in humans are needed to verify its wide use in numerous medical conditions.

PATIENT INFORMATION— Kudzu

Uses: Kudzu has been used as a ground cover, fodder, and medicinal herb especially for treating alcoholism. It is also used for muscular aches, heart disease, and related disorders.

Side Effects: No known toxic effects; safety undefined.

Dosing: Kudzu root has been studied at a dose of 2.4 g/day in alcoholism.[42]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "K" MONOGRAPHS
    KUDZU

"L" MONOGRAPHS

L-ARGININE

DATE OF ISSUE: FEB 2001

REPLACES MONOGRAPH DATED: N/A

COMMON NAME(S): L-arginine

SOURCE: Amino acids are the major components of protein. Animal and plant products contain several amino acids, including arginine. Some of these sources are meats, milk, and eggs.[1] The physiologically active form, L-arginine, is the natural product obtained by hydrolysis of proteins. In the laboratory, arginine can be precipitated from gelatin hydrolysate. L-arginine also can be synthesized from L-ornithine and cyanamide in aqueous solution in the presence of $Ba(OH)_2$.[2] Because L-arginine can be synthesized endogenously from L-citrulline, it is classified as a nonessential amino acid in adults. However, in children and in certain conditions (eg, trauma, infection), L-arginine synthesis may become compromised and then may be considered "semi-essential."[3]

HISTORY: L-arginine is commonly sold as a health supplement claimed to be capable of improving vascular health and enhancing sexual function in men.

PHARMACOLOGY: Nitric oxide is produced by a variety of animal and human cells and is involved in many physiological and pathophysiological processes.[4] Nitric oxide is a free radical, generated from L-arginine by the enzyme nitric oxide synthase.[5] L-arginine supplementation to raise nitric oxide levels has been suggested to be beneficial in many areas.

Nutritional/Metabolic/Immunostimulatory: Arginine is classified as a nonessential amino acid but may become essential in stressful situations, including periods of growth (during childhood or pregnancy) or trauma to the body (eg, severe sepsis, wound healing, liver disease).[6,7,8] L-arginine is a human growth stimulant and has been used in bodybuilding.[9] In jaundiced rats, L-arginine supplementation demonstrated anabolic and immunostimulatory properties.[10] Anabolic actions also can be confirmed in many studies concerning L-arginine supplementation and improved wound healing,[4,11,12,13] including healing of burns,[14] tendons,[5] GI tract,[15] and bone.[16] One mechanism suggested may be because of the enzyme arginase, which produces a favorable environment for fibroblast and collagen production.[17] L-arginine has also exhibited protective effects in spinal cord injury in animals[18] and in cortical impact injury in rats.[19] In another report, exogenous L-arginine produced nitric oxide, resulting in a decrease of hepatic ischemia/reperfusion injury.[20]

Cardiovascular health: Many cardiovascular diseases originate in the vascular endothelial cells, which, if unhealthy, can cause vasoconstriction, inflammation, thrombolytic activity, and cell proliferation. These abnormalities are due in part to enhanced degradation of nitric oxide. By having increased concentrations of L-arginine available to maintain nitric oxide, it may improve certain vascular disease states.[21,22,23] Several articles are available on this topic and include the following findings: 1) Increased flow-induced vasodilation in isolated guinea pig hearts was dependent on L-arginine to maintain nitric oxide concentrations;[24] 2) Coronary blood flow was restored after L-arginine was administered in diabetic dogs;[25] 3) L-arginine produced nonstereo-specific peripheral vasodilation and improves endothelium-dependent vasodilation in coronary heart disease (CHD) patients;[26] 4) Patients with peripheral artery disease experienced a 150% improvement in walking distance with L-arginine supplementation of 8 g twice daily for 14 days;[27] 5) An intermediate compound of L-arginine was found to be reduced in plasma concentrations of patients with cardiovascular risk factors, including impairment of endothelial function;[28] 6) L-arginine has improved cardiac performance in severe congestive heart failure (CHF) patients;[29] 7) CHD patients with angina demonstrated improvement after L-arginine supplementation,[30] as have angina patients who experienced improved exercise tolerance with L-arginine.[31] In one clinical trial, oral L-arginine therapy was ineffective in improving nitric oxide bioavailability in coronary artery disease (CAD) patients.[32]

L-arginine also has been beneficial in similar disease states including hypertension and hypercholesterolemia. It has enhanced vasodilation and has lowered systolic blood pressure in rats.[33,34,35] According to one report, L-arginine supplementation in humans significantly lowered blood pressure in 6 patients.[36] Certain mechanisms in this area have been investigated, suggesting that nitric oxide-mediated vasodilator tone is deficient in hypertension[37] and salt-sensitive patients with mild essential hypertension reduce the ability of L-arginine to produce nitric oxide in vascular endothelium.[38] Nitric oxide possesses antithrombotic and antiatherosclerotic actions in the vasculature. A report on hypercholesterolemic rabbits demonstrated a direct inhibitory effect on leukocyte adhesion from L-arginine. This effect was found to be beneficial in cardiovascular health, to slow the development of atheromatous lesions, to reduce vascular superoxide anion production, and to improve endothelium-dependent relaxation.[39] In human microvascular endothelial cells, nitric oxide (with L-arginine substrate) regulates tissue factor as well, reducing endotoxin and cytokine-induced expression of tissue factor.[40]

L-arginine supplementation in other vascular disease states has been beneficial. L-arginine's ability to increase nitric oxide availability has improved transplantation diabetes, renal disease, and other perfusion-type injuries. IV infusion of L-arginine into animals undergoing liver transplantation improved cardiac output, liver blood flow, and pulmonary vascular resistance, and reduced portal hypertension and reperfusion injury.[41,42] L-arginine supplementation to piglets with chronic hypoxia-induced pulmonary hypertension has increased nitric oxide production.[43]

The substrate for nitric oxide synthesis by the endothelium is limited in diabetes but can be overcome with L-arginine supplementation.[44] L-arginine counteracts lipid peroxidation, reducing damage to the blood vessels.[45] Hyperglycemia in patients with type 2 diabetes causes hemodynamic changes (eg, reduction of blood pressure), which can be reversed by L-arginine.[46] Endoneurial ischemia in animals may be improved by L-arginine.[47] L-arginine also may play a role in insulin resistance.[48]

L-arginine is a precursor for polyamines required for proliferative responses characteristic of many renal diseases. It is also the nitric oxide precursor that is a vasodilator in the endothelium, which is beneficial in reducing intraglomerular pressure and disease.[49] L-arginine has been proven effective in nephrosclerosis and progressive renal failure.[50] L-arginine's ability to raise nitric oxide levels relaxes bladder muscle spasms, as well, and controls the pain in interstitial cystitis.[51]

Relaxation of cavernous smooth muscle in the penis requires nitric oxide synthesized by L-arginine. This suggests that L-arginine may be beneficial in erectile dysfunction. In rats, increased nitric oxide concentrations demonstrated erectile response and altered vascular tone, suggesting possible benefit in men with Peyronie disease.[52] In humans, it has been advertised that L-arginine in the form of dietary supplements improves sexual performance in men. However, in a clinical, controlled, crossover study no statistical difference in impotence scores was found in 32 patients administered 3 × 500 mg L-arginine/day vs placebo.[53]

Other effects of L-arginine include increasing quantity and cytotoxic capability of lymphokine activated and natural-killer T-cells in breast cancer.[54] Another source suggests that individuals with genital herpes should decrease their intake of arginine (while increasing lysine). Arginine assists herpes simplex in multiplying, while lysine breaks down arginine.[55]

TOXICOLOGY: Parenteral administration of L-arginine in high doses has caused metabolic acidosis including elevated potassium levels due to effects on intra- and extracellular potassium balance.[3] Oral administration of L-arginine in humans has not caused any major adverse effects. L-arginine may exacerbate sickle cell crisis. Doses up to 30 g/day are well tolerated, with infrequent reports of nausea and diarrhea.[56] No adverse effects were reported with 9 g/day L-arginine over 6 months.[30] Arginine may trigger onset of herpes infection, although there is no solid evidence to confirm this.[56]

SUMMARY: L-arginine is the physiologically active form of the nonessential amino acid arginine. However, it may become "essential" in stressful situations,

including growth periods or wound healing. L-arginine plays an important role in healing by providing a favorable environment for fibroblast and collagen production. In addition, L-arginine increases nitric oxide concentrations (low concentrations are typical of cardiovascular disease). L-arginine has been beneficial in cardiovascular diseases (eg, CHD, hypertension, renal disease, diabetic vascular disease). It has become popular because of claims that it improves erectile dysfunction, but human studies have not yet confirmed this effect. In standard dosages, L-arginine appears to have little or no adverse effects.

PATIENT INFORMATION— L-arginine

Uses: L-arginine has been beneficial in several cardiovascular diseases. It plays an important role in healing and increases nitric oxide concentrations.

Side Effects: L-arginine has few reported side effects. Nausea and diarrhea have been reported infrequently. Parenteral administration at high doses has caused metabolic acidosis or electrolyte alterations.

Dosing: L-arginine has been studied at oral doses of 6 to 17 g/day for a variety of conditions. [32,57,58,59,60]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    L-ARGININE

L-THEANINE

DATE OF ISSUE: SEP 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Gamma-ethylamino-L-glutamic acid[1]

COMMON NAME(S): L-theanine, *Suntheanine*[1]

BOTANY: Black, oolong, and green tea are produced from the leaves of *Camellia sinensis*. *C. sinensis* is native to eastern Asia and is a member of the Theaceae family. This evergreen shrub or tree grows to over 9 m in height and is pruned from 60 cm to 1.5 m for cultivation. Its dark green, serrated-edged leaves are alternate and oval, while its white and fragrant blossoms appear singly or in clusters. [2]

HISTORY: Second only to water, tea is one of the most widely consumed beverages in the world. With the exception of a mushroom (eg, *Xerocomus badius*) and certain species belonging to genus Camellia(*C. japonica* and *C. sasanqua*), L-theanine is a unique amino acid found only in the tea plant. L-theanine was approved in Japan in 1964 for unlimited use in all foods (including chocolates, soft drinks, herb teas), except infant foods. It also provides a unique *umami* (brothy or savory) taste and flavor to green tea infusion.[1,2,3,4] L-theanine has been used in cosmetics to moisturize the skin. [5]

CHEMISTRY: L-theanine was discovered in 1949 and constitutes 1% to 2% of the dry weight of tea leaves. It exists only in the free (nonprotein) form. Taiyo Kagaku Co. Ltd., Japan, has developed an enzymatic method to manufacture synthetic L-theanine (*Suntheanine*).[1,2,3]

PHARMACOLOGY: L-theanine's mechanism of action has not been fully elucidated.

Recent literature searches of peer-reviewed scientific studies are mostly associated with theanine. The results specifically associated with L-theanine are discussed below.

Relaxing effect: L-theanine is able to cross the blood-brain barrier and most research has focused on its relaxing effect. Brain waves were measured in 50 high-anxiety and low-anxiety human volunteers after the oral administration of 50 to 200 mg of L-theanine. L-theanine promoted the generation of alpha-brain waves, an index of relaxation, and induced a relaxed but nondrowsy state in the volunteers. Emission intensity of the alpha-brain waves was determined to be dose-dependent.[1,6]

Immune system functioning: L-theanine may provide natural resistance to microbial infections and perhaps even tumors. In a recent pilot study, 11 healthy non-tea drinking volunteers were asked to consume approximately 600 mL/day of black tea for either 2 or 4 weeks. Another 10 healthy, non-tea and non-coffee-drinking volunteers were asked to drink 5 to 6 cups per day of instant coffee. The tea group consumed approximately 1.3 mmol/day of L-theanine. Cell samples from the volunteers on the tea regimen indicated that the brief exposure to the tea's L-theanine, which is turned into ethylamine in the liver, initiated immunologic memory. When bacteria were introduced to the ethylamine-exposed cells, these cells multiplied 10-fold, producing larger amounts of T-cells that fought the bacteria. Cells not exposed to tea did not attack the invading antigens. The first line of defense against many types of bacterial, viral, fungal, and parasitic infections is gamma-delta T-cells in the blood. The researchers of this study suggest further isolating and refining L-theanine from tea to use it as a drug to boost the infection defense of the body.[7]

TOXICOLOGY: Toxicology profile is based primarily on historical data from consumption of L-theanine in green tea by consumers. The LD_{50} of L-theanine is 5 g/kg. Mutagenicity and acute and subacute toxicity tests have failed to show toxicity of the synthetic L-theanine product *Suntheanine*.[1]

SUMMARY: L-theanine helps promote a calming and relaxing effect and may also boost natural resistance to microbial infections and perhaps even tumors. An enzymatic method to manufacture synthetic L-theanine on an industrial scale has been developed, and this nutraceutical ingredient is being extensively marketed in over 50 food products in Japan. Approval as a food additive is being sought in the US.

PATIENT INFORMATION — L-theanine

Uses: L-theanine may help relieve stress by inducing a relaxing effect without drowsiness. It may also boost natural resistance to microbial infections and perhaps even tumors. Limited information is available to support these claims.

Side Effects: L-theanine is enzymatically synthesized by Taiyo Kagaku Co. Ltd., Japan and is extensively marketed in over 50 food products (eg, chocolate, soft drinks, herb teas) in Japan. Thus far, it has not resulted in any reported adverse reactions.

Disease-State Concerns: None. Avoid use in patients with known hypersensitivity reactions to L-theanine.

Dosage Concerns: Based on the alpha-wave study, a dose of 50 to 200 mg may provide a relaxation effect. No dosage of L-theanine is suggested for enhanced immune system functioning; however, volunteers in a pilot study consumed approximately 600 mL of tea a day.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    L-THEANINE

LABRADOR TEA

DATE OF ISSUE: NOV 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Several Ledum species have been used medicinally including *L. groenlandicum*, *L. latifolium, Jacq.*, and *L. palustre*, L. Family: *Ericaceae*.

COMMON NAME(S): Labrador tea, James tea, Marsh tea, Wild rosemary and Continental tea

BOTANY: *L. groenlandicum* is a short (0.3 to 1.9 m high), aromatic, evergreen shrub common to North America, primarily found in Greenland and Canada, where it thrives in wet, peaty soils. It has bright-green, 2.5 to 7.6 cm alternate leaves with a leathery dorsal surface, and a rust colored, hair-like underside. The leaves curl inward and have a bluntly pointed tip. The small (12 mm), white, bell-shaped, scented flowers grow from slender stalks in terminal clusters. The fruit is a many seeded capsule.[1,2,3]

HISTORY: Labrador Tea (*L. latifolium, Jacq.*) is named after the swamps of Greenland and Labrador, where it grows in profusion. During the American Revolution, it was one of the several herbs used as a pleasant-tasting substitute for commercial tea. Germans once added the leaves to their beer to make it more intoxicating. Although Labrador tea is found as far south as Wisconsin and Pennsylvania, it is listed as rare and could become an endangered species. Medical literature gives full credit to Labrador tea use in folk medicine, though it has been rarely studied clinically. It has been used for coughs, chest ailments, headache, kidney, rheumatisim, diarrhea, sore throat and malignancies.[1,2,3,4]

CHEMISTRY: Reported constituents of *L. latifolium* include tannic acid, arbutin, resin, and mineral salts.[2] Leaves contain 0.3% to 2.5% volatile oil, including ledum camphor (ledol), palustrol, (a stearopten), with valeric and volatile acids, ericolin, and ericinol.[4]

PHARMACOLOGY: The leaves of the *L. groenlandicum* have been used as an astringent. They were once used to treat dysentery and diarrhea.[2] It is also said to be very useful in coughs and colds, as well as bronchial and pulmonary infections. A tea can be prepared by adding 1 teaspoonful of dried leaves to one cup of boiling water.

A stronger decoction has been recommended externally for itching and redness from skin ailments. Homeopaths have used Labrador tea for various ailments such as insect bites and stings, acne, prickly heat, varicella and wounds. Homeopathic use also includes asthma, hand and foot pain, gout, rheumatism, ear inflammation, tinnitus and tuberculosis.[3] Other references discuss use of the leaves by Koreans to treat female disorders.[4] It is rarely used today as it once was used historically.[2]

TOXICOLOGY: Labrador tea has narcotic properties. Evidence suggests that excessive use of the tea may cause delirium or poisoning.[2] Labrador tea contains andromedotoxin, more recently designated as grayanotoxin. This toxic diterpene causes symptoms of intoxication, such as slow pulse, lowering of blood pressure, lack of coordination, convulsions, paralysis and death.[5] It is apparently safe in a weak tea solution, but should not be made too strong.[6]

SUMMARY: Labrador tea is an aromatic evergreen, native to Greenland and Canada. It has been used in folk medicine for upper respiratory ailments, and by homeopaths for skin infections and asthma. It contains grayanotoxin which causes symptoms of intoxication and can lead to paralysis and death in high concentrations. Further clinical investigation is welcome in order to assess more of the potentially useful properties of Labrador tea.

PATIENT INFORMATION — Labrador Tea

Uses: Labrador tea has been used historically and folklorically for a variety of ailments ranging from skin complaints to malignancies. It can be made safely into a weak tea, but care must be taken not to make concentrations too high. A tea for coughs, colds, bronchial infections and pulmonary infections can be made by adding one teaspoonful of dried leaves to one cup of boiling water.

Side Effects: Labrador tea has narcotic properties. If taken in concentrations that are too high, it can cause symptoms of intoxication that can lead to paralysis and death. If Labrador tea is to be used, be sure to take only in small doses with weak concentrations.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "L" MONOGRAPHS
  LABRADOR TEA

LAMINARIA

DATE OF ISSUE: OCT 2003

REPLACES MONOGRAPH DATED: MAY 1992

SCIENTIFIC NAME(S): *Laminaria digitata* (L.) Lamour or *L. bracteata Ag*. (*L. japonica* Aresch). Family: Laminariaceae

COMMON NAME(S): Kelp, brown algae, laminaria, horsetail, sea girdles[1]

BOTANY: The marine kelps derived from *Laminaria* species are found primarily in the cold waters of the North Atlantic and North Pacific oceans.

HISTORY: Laminaria for cervical dilation is used in the form of "tents." A tent is any material, usually hygroscopic (readily absorbs water), which is placed in a canal or chamber to maintain the opening or cause dilation.

Laminaria tents are made from the dried stems of *Laminaria* seaweeds. When dried and rounded into a stick-like shape, the tent is approximately 6 cm (2.5 inches) long with a diameter of 0.3 to 0.5 cm. A strong thread is attached to one end and a collar prevents its migration into the uterus. The stem is hygroscopic and can swell to 3 to 5 times its original diameter within 12 to 24 hours. Other natural products have been used in the past as tents, including sponges, dried corn stalks, slippery elm bark, and tupelo wood.[2] The use of laminaria became popular in the 1800s; hollow laminaria tents were developed to improve uterine drainage, and laminaria coated with wax was designed to release antiseptics as it melted.

Tents fell into disuse because of complications caused by infections. This was especially evident in tents derived from land plants because of the inability to sterilize *Clostridium* spores (the causative agents of tetanus, botulism, and gas gangrene). Although laminaria from the ocean contains relatively nonpathogenic bacterial contaminants, polluted waters and poor packaging extended the problems of infections related to its use. However, with the advent of ethylene oxide and gamma irradiation sterilization techniques, interest in laminaria tents returned.

L. bracteata Ag. (*L. japonica* Aresch) is commonly used in soup, candy, and sushi, and eaten with rice or as a salad. The plant is harvested as kombu in the Far East and is cultivated in China, Korea, and Japan.[3]

CHEMISTRY: Laminarin (laminaran) is a polysaccharide found in *Laminaria* sap. Soluble and insoluble forms are found in algae.[4,5] Kelp (of which *Laminaria* is one species) are rich in algin, a high molecular weight polysaccharide that forms viscous colloidal solutions or gels in water. This property has led to the use of kelp derivatives as bulk laxatives.[6] The constituents of *Laminaria* also include iodine, potassium, magnesium, calcium, and iron.[7,8,9]

PHARMACOLOGY

Cervical ripening: When inserted into the cervix, laminaria tents absorb surrounding moisture and gradually swell to a diameter of approximately one-half inch. While most of the swelling occurs in the first 4 to 6 hours, it may continue for up to 24 hours. Since this is a gradual process, the patient rarely notices pain. At the same time, the cervix is induced to ripening (becoming soft and flexible). The effect is often limited to local cervical ripening; however, stimulation of the cervix can induce labor.

The mechanism of action may be similar to that of a foreign body that, when inserted into the cervical canal, disturbs the normal chorioamniotic balance and initiates a cascade of prostaglandin synthesis. This in turn has myometrial-contracting and cervical-ripening effects.[10] The authors of one paper suggest the activity of laminaria may be because of its high levels of the prostaglandin precursor arachidonic acid;[11] however, evidence of this purported activity could not be found in a recent review of the scientific literature. Cervical dilation may also be the result of partial placental detachment induced by laminaria.[12]

Laminaria tents have been used to dilate narrow cervixes prior to dilation and curettage (D & C) and diagnostic procedures;[13] to provide relief from cervical stenosis; to ripen the near-term or term cervix, especially in primagravidas; to facilitate labor;[14] to induce labor at term with the adjunctive use of prostaglandins,[15]; and to induce first trimester abortions.[16] Laminaria tents have been inserted before the placement and removal of intrauterine devices and have been used to facilitate the placement of therapeutic radium within the uterus.[2]

The effectiveness of laminaria in dilating the cervix and inducing labor has been evaluated in a number of clinical trials. In 1 study, the effectiveness of laminaria on the preinduction ripening of the cervix was compared with untreated control patients. Although laminaria was effective in reducing the duration of induction, there was no difference in the incidences of cesarean births. Endometritis occurred in 15 of 25 mothers treated with laminaria and 3 of 28 in the control group ($P < 0.05$). Furthermore, 5 of 25 neonates from the laminaria group had bacterial sepsis compared with none of the controls ($P < 0.05$). Three of the 5 septic neonates died.[10]

In another study, 28 of 32 women were successfully induced with laminaria compared with 4 of 32 untreated controls ($P < 0.001$). The mean induction-to-delivery time was shorter (121/3 hours vs 21/2 days) in the laminaria group.[14]

A randomized study involving 175 women between 16 to 20 weeks of gestation compared the abortifacient efficacy of vaginal prostaglandin E_2 suppositories (PGE_2), PGE_2 + *L. japonica*, and PGE_2 + *Laminaria japonica* + concurrent treatment with intracervical PGE_2 gel. Abortion rates were higher in the *Laminaria* groups; however, no significant statistical difference was noted among the 3 groups. Reported side effects included pain and fever. No statistical significance was attained in accessing pain scores among the 3 groups. However, a statistically significant increase in febrile morbidity was noted with use of *Laminaria* ($P = 0.002$).[17]

Other Pharmacologic Properties: Seaweeds of the species *Laminaria* have other pharmacologic properties. Laminarin, a complex polysaccharide, has antilipemic activity when partially sulfated and exerts anticoagulant activity similar to that of heparin when sulfated more extensively. The basal parts of the blades of L. *japonica* and L. *angustata* have been used as a hypotensive agent (ne-kombu) in Japanese folk medicine. Chemical analysis of the blades suggests that histamine and the amino acid laminine may be responsible for this hypotensive effect.[18,19] Alginate-containing algae and kelp have been shown to reduce the absorption of radioactive strontium in both animals and man and are used in the management of radioactive intoxications.[20]

TOXICOLOGY: A review of the findings from the early studies with laminaria suggests that it may be associated with a risk of neonatal and maternal infection. One manufacturer recommends swabbing the cervical canal with a suitable lubricant and antibacterial agent prior to inserting the tent, then packing the canal with antibacterial gel. The follow-up of 17 women who had laminaria tents inserted for the induction of abortion and who then decided to continue the pregnancy found no evidence of infection at term.[21]

The spontaneous uterine contractions that may accompany the use of laminaria have been implicated in the induction of fetal hypoxia and subsequent intrauterine death.[15] Fetal activity should be monitored closely. Other potential problems with the use of laminaria include difficulty removing the tent, breaking the tent during removal,[22] or rupturing the cervical wall and subsequent infection. Blood loss does not appear to increase following the use of laminaria tents in first trimester abortions.[23]

Although laminaria tents possess many qualities of an ideal cervical dilator (eg, easy to insert/remove, slow expansion, painless dilation), persistent problems of infection and cervical injury have spurred the search for alternate types of dilators. Synthetic laminaria tents prepared from hydrophilic polymers provide increased levels of structure stability.[24] Synthetic tents have efficacy similar to that of prostaglandin E_2 tablets.[25]

SUMMARY: Laminaria tents are effective in stimulating the dilation of the cervical canal and in ripening the cervix at term. Their effectiveness in facilitating labor is variable. Clinical studies suggest that laminaria tents may increase the incidence of maternal and neonatal infections. Cervical injuries have also been reported. Other

pharmacologic properties of laminaria derivatives include hypotensive activity, anticoagulant properties, and the ability to limit the absorption of radioactive strontium.

PATIENT INFORMATION— Laminaria

Uses: Laminaria has been used as a hygroscopic cervical dilator and inducer of labor. Other reported activity includes hypotensive and anticoagulant properties and absorption of radioactive strontium. However, an increased risk of infection in neonate and mother as well as a potential increase in mortality in the neonate may limit its use.

Side Effects: Laminaria may cause or contribute to maternal and neonatal infection. Patients in clinical studies have reported pain and fever. Use is contraindicated during pregnancy. Use may also be contraindicated in patients taking medications for hyperthyroidism because of the plant's iodine content.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LAMINARIA

LARCH

DATE OF ISSUE: OCT 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Larch (*Larix*) species include: *L. dahurica* L., *L. decidua* Mill (*L. europaea*), *L. eurolepis* Gord., *L. gmelinii*, *L. kaempferi* , *L. laricina*Koch., *L. leptolepis* (Sieb. et Zucc.) Gord., *L. occidentalis* Nutt., and *L. sibirica ledeb.* Family: Pinaceae.

COMMON NAME(S): Larch, Larix, Mongolian Larchwood (*L. dahurica*)

BOTANY: Larch trees are deciduous conifers. One example, *L. decidua*, grows to 50 m and has needle-like leaves and small, light brown cones. [1]

HISTORY: Larch trees were said to have been introduced into Great Britain in 1639 and cultivated there since the early 19th century. The tree is grown mainly for its timber, but the inner bark and resin are also used. [1] Arabinogalactan constituents from certain *Larix* species have gained popularity because of their ability to enhance the immune system.[2]

CHEMISTRY: Arabinogalactans are present in species *L. dahurica* and *L. occidentalis*.[3,4,5] Arabinogalactans are long, densely branched, highly molecular polysaccharides found throughout the plant kingdom and in some microbial systems. They are abundant in the genus *Larix* and are most often covalently linked to pectin and protein.[2,3] The powdered extract from the pine bark of the western larch tree, for example, is 98% arabinogalactan. This substance has a pine odor, a sweet taste, and is easily soluble in water.[2] All arabinogalactans isolated thus far from *Larix*, are the 3,6-beta-D-galactan type.[3] The extract is harvested from already fallen trees, otherwise a waste product from the lumber industry. A benefit of this natural polymer is that it possesses great uniformity. Batch variation is not a problem among larch trees that it is with other natural products. [2] Arabinogalactans from *L. occidentalis* have been isolated, characterized, and purified as discussed in one report.[5] Properties of arabinogalactans from *L. dahurica* have been documented as well, finding a homogeneous product with very narrow molecular weight distribution.[3]

Other constituents from *Larix* have been identified. *Larix* flavonoids from various species have been analyzed, including flavanones (naringenin, hesperitin, hesperidin), flavones (apigenin, vitexin), and flavonols (kaempferols, quercetins, isorhamnetins, myricetins, and syringetins). [6] *L. decidua* contains lignans, resins, and volatile oil (mainly alpha- and betapinene and limonene). [1] 18-nor-abietatrienes and diterpenes, including abietane-type diterpenes (eg, 7alpha,15-dihydroxyabieta-8,11,13-trien-18-al), have been isolated from species *L. kaempferi*.[7,8] Phenolics (flavonoids) from *L. leptolepis* have been reported.[9] Resin constituent diterpene from *L. europaea*has been documented.[10]

PHARMACOLOGY: Arabinogalactan displays moisture retention, flavor encapsulation, film-forming capabilities, and desirable viscosities for a pleasant feeling in the mouth as both a natural and functional food ingredient. [2] Also, its role as a dietary fiber and its solubility properties make arabinogalactan an important polysaccharide. Its properties may be influenced by different side chain moieties on the molecule. [3]

Arabinogalactan's role as an immune-boosting phytochemical has gained popularity. It has been reported to stimulate macrophages and other immune system components better than echinacea, although echinacea contains some arabinogalactans. Arabinogalactans have also been reported to increase the release of interferons, tumor necrosis factors, and interleukins, all of which are known to enhance immune function. Liver metastases in animals have been inhibited by arabinogalactans.[2] Human peripheral blood mononuclear cells and other cell lines have shown enhancement of natural killer cytotoxicity against certain tumor cells when pretreated with arabinogalactans extracted from *L. occidentalis*.[11]

Arabinogalactan has properties that make it an ideal carrier to deliver agents to hepatocytes via the asialoglycoprotein receptors. Of radiolabeled arabinogalactans, 52.5% (4 mg/kg) were identified in the livers of rats receiving IV injection. [4] Arabinogalactan is highly bound to this receptor in both in vitro and in vivo experimentation. In one study, it was reported that those arabinogalactans with a lower molecular weight may be more desirable for hepatic drug delivery than others. [5] In another study, arabinogalactan conjugated with the antiviral vidarabine was effective in suppressing serum viral DNA titers in woodchucks infected with the hepatitis virus. [12]

Arabinogalactan has also been reported to exhibit anti-inflammatory actions, and it may enhance vascular permeability. [2]

L. laricina inhibited xanthine oxidase, thereby reducing uric acid formation, in a study of plant remedies used for gout. This was the greatest inhibition seen among the 26 species from 18 families that were evaluated.[13]

Larchwood (*L. decidua*) also possesses astringent and diuretic actions. Its antiseptic actions may be useful in treating cystitis, respiratory infections, and wounds. [1]

TOXICOLOGY: There is no apparent allergy or toxicity to larch-derived arabinogalactans. [2] Arabinogalactan produced no adverse reactions in single IV doses administered to mice at 5000 mg/kg or at repeated doses in rats for 90 days at 500 mg/kg/day. [4] One source advises caution with the use of *L. decidua* in patients suffering from kidney disease.[1]

SUMMARY: Larch is a genus of conifers that has many species. It has gained popularity because of its high yield of the polysaccharide arabinogalactan from certain species, which has been reported to enhance the immune system. Arabinogalacten attains high concentrations in the liver, making it ideal to deliver agents there. Species *L. laricina* may be helpful in treating gout. *L. decidua* possesses antiseptic actions. No toxicity has been reported from larch arabinogalactans. Use *L. decidua* with caution in patients with kidney disease.

PATIENT INFORMATION— Larch

Uses: Arabinogalactan, present in some larch species, has been reported to stimulate the immune system, to exhibit anti-inflammatory actions, and may enhance vascular permeability. Larchwood possesses astringent and diuretic actions. Its antiseptic actions may be useful in treating cystitis, respiratory problems, and wounds.

Side Effects: No adverse effects have been reported with use. Use with caution in patients with kidney disease.

Dosing: The balsam of larch is used at a concentration of 10% to 20% in gels and ointments for colds and fevers. No clinical trials have been published addressing its safety or efficacy.[14]

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "L" MONOGRAPHS
  LARCH

LATHYRUS

DATE OF ISSUE: JUN 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Various species of *Lathyrus*, most commonly *L. sativus* (chickling vetch or chick-pea), *L. odoratus* (sweet pea), *L. cicera* (flat-podded vetch), *L. hirsutus* (caley pea), *L. sylvestris*(everlasting pea), *L. clymenum* (spanish vetchling), *L. incanus* (wild pea) and *L. pusillus* (singletary pea). Family: Leguminosae [1,2]

COMMON NAME(S): Chickling vetch, chick-pea, sweet pea, flat-podded vetch, caley pea, everlasting pea, spanish vetchling, wild pea, singletary pea and others, depending on species

BOTANY: *Lathyrus* is a widespread genus with species that grow throughout the world.

HISTORY: The *Lathyrus* species are generally cultivated for food, fodder and as ornamentals. For example, flowers of the sweet pea, *L. odoratus* (not to be confused with the common garden pea, *Pisum* spp.), are cultivated for their color and fragrance. The seeds of the *Lathyrus* species are commonly eaten by large populations in India, parts of Africa, France, Italy, Spain and other countries. [1] *L. sativus* is used to prepare unleavened Indian bread and is sometimes eaten raw as pasteballs or cooked.[1] However, ingestion of certain species, particularly *L. sativus*, *L. cicera*and *L. clymenum*, can result in a toxic syndrome known as neurolathyrism. This disease has been recognized for more than a century in Europe, Africa and Asia; most commonly in Asia. Because of the potential for public health problems, the sale of *L. sativus* has been banned in many states in India; despite these efforts, distribution persists. [1] Lathyrism remains a common problem among grazing animals in some countries.

CHEMISTRY: A variety of compounds with potential neurotoxic effects have been identified and are discussed below. Other compounds isolated from seeds of the *Lathyrus* species include phytates, divicine and a mixture of alkaloids. The lack of vitamins A, B and C from these seeds may enhance the neurotoxic potential. [1]

PHARMACOLOGY: Lathyrism appears to be the result of toxicity caused by several compounds, including beta-N-oxalyl-L-alpha,beta-diaminopropionic acid (ODAP) and beta-aminopropionitrile (BAPN).

ODAP is a neurotoxin that is associated with the animal and human neurotoxic manifestations of the disease neurolathyrism. BAPN induces skeletal abnormalities in animals; this compound and related compounds appear to be responsible for osteolathyrism (damage to the skeleton), which has not been observed in man. BAPN induces osteolathyrism and angiolathyrism (damage to the blood vessels) without inducing neurotoxic effects. [3] *L. odoratus* is more commonly associated with osteolathyrism than other species[1] and a separate term, odoratism, has been proposed for this syndrome.

TOXICOLOGY: Osteolathyrism, evidenced by skeletal deformities and aortic rupture, has been induced in rats given a 50% diet of sweet peas or diets containing 0.1% to 0.2% BAPN.[1] The toxicity appears to be related to structural defects in collagen induced by the *Lathyrus* toxins.

Neurolathyrism occurs in many animal species, but some (eg, the squirrel monkey) appear to be particularly resistant to the toxic effects of *Lathyrus*.[4] Human neurolathyrism remains a significant public health problem in India, particularly among the poor for whom *L. sativus* forms the main part of the diet. The disease generally occurs when a diet consisting of one-third to one-half *L. sativus* seeds in consumed for 3 to 6 months. Muscular rigidity and spasticity, weakness, paralysis of leg muscles, weak pulse, shallow breathing, convulsions or death may occur.[1,5,6] Prolonged neurotoxicity lasting more than 40 years, characterized by poor central motor coordination and reduced nerve conduction in the lower limbs, has been observed in persons suffering from the effects of neurolathyrism. [7]

There does not appear to be a common mechanism for the mode of action of the neurolathyrogens. Some propose that these compounds may affect glutamine concentrations or activity in the central nervous system. [1]

Pyramidal tract involvement has been observed in primates fed beta-N-oxalylamino-L-alanine (BOAA), a potent neuroexcitatory amino acid found in chickling peas and an inhibitor of glutamate.[8] Others have proposed that the neurotoxin may function as a zinc carrier and that cerebral zinc deficiency may play a role in the disease.[9]

Several procedures have been used in an attempt to deactivate the toxin prior to ingestion. Typically, these involve soaking seeds in water, followed by steaming or sun drying. Roasting the seeds at high temperatures for 20 minutes also seems to help destroy the neurotoxic factors. These procedures, however, only destroy 80% to 85% of the toxin.[1]

Preliminary findings suggest that treatment with the centrally acting muscle relaxant tolperisone can significantly reduce the spasticity in neurolathyrism. [10]

SUMMARY: Seeds of many *Lathyrus* species play an important role as foodstuffs and animal fodder throughout much of the developing world. Unfortunately, numerous species of these plants contain toxic compounds that can induce severe neurotoxicity in both animals and man when ingested at high levels for prolonged periods. This toxic syndrome is rare in Western countries, but remains common in Asia and may be observed in Asian immigrants to Western countries. No effective therapy is available for this toxicity.

PATIENT INFORMATION — Lathyrus

Uses: Some *Lathryus* species are eaten.

Side Effects: Some species are neurotoxic.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LATHYRUS

LAVENDER

DATE OF ISSUE: AUG 1998

REPLACES MONOGRAPH DATED: DEC 1996

SCIENTIFIC NAME(S): Several Lavandula species have been used medicinally, including *L. angustifolia* Mill. (syn. *L. officinalis* Chaix. and *L. spica*L.), *L. stoechas*, *L. dentata*, *L. latifolia* and *L. pubescens* Decne. Family: Lamiaceae

COMMON NAME(S): Aspic, lavandin (usually refers to particular hybrids), lavender, spike lavender, true lavender

BOTANY: Lavender plants are aromatic evergreen sub-shrubs that grow to about 3 feet high. The plants are native to the Mediterranean region. Fresh flowering tops are collected, and the essential oil is distilled or extracts are obtained by solvent extraction. [1] The plant has small blue or purple flowers. The narrow leaves are fuzzy and gray when young and turn green as they mature.[2] Lavender is cultivated extensively for use as a perfume, potpourri and as an ornamental.

HISTORY: Lavender has long found a role in folk medicine. The plant has been used as an antispasmodic, carminative, diuretic and general tonic. Extracts have been used to treat conditions ranging from acne to migraines.[1] Although the plant has been known to increase bile flow output and flow into the intestine, its greatest value is not in the treatment of biliary conditions. [2] Lavender has been used quite extensively as an antidiabetic agent in parts of Spain and is included in some commercial herbal antidiabetic preparations.[3] Fresh leaves and flowers are applied to the forehead to relieve headaches and to joints to treat rheumatic pain. The vapors of steamed flowers are used as a cold remedy.[4] Chileans drink the tea to induce or increase menstrual flow. [5]

Lavender is usually administered in the form of an infusion, decoction or oil and is either taken internally or applied topically for relief of neuralgia. Today, lavender oil and extracts are used as pharmaceutical fragrances and in cosmetics. Spike lavender oil is often used in soaps because it is inexpensive but of lower quality than true lavender oil. Lavandin oil, lavender absolute (an extract) and spike lavender oil are used in concentrations of up to 1.2% in perfumes. [1] Small amounts (0.002% to 0.004%) of the oil are used to flavor food.

Lavender's versatility is seen in its various applications as a fragrance in perfumes, bath and shower products, hair care products, toiletry soaps, detergents, typical formulations, synthetic derivatives and production figures. [6]

CHEMISTRY: Lavender flowers contain between 1% to 3% essential oil.[7] Lavandin hybrids contain a higher volatile oil content, but its composition is extremely variable. The oil is a complex mixture of more than 150 compounds, the most abundant of which are linaloyl acetate (30% to 55%), linalool (20% to 35%), cineole, camphor, beta-ocimene, limonene, caproic acid, caryophyllene oxide and tannins (5% to 10%). [1,7] However, the relative amounts of these compounds can vary widely between species.[8,9] Perillyl alcohol, a distillate of *L. angustifolia* has been shown to exert anticancer effects.[10] Several articles on lavender are available, discussing analysis methods,[11,12,13] enantiomeric purity and distinctiveness, [14,15,16] variety deviation,[17,18,19,20] essential oil quality, [21,22] GC retention indices,[23] and lavender content in perfumes.[24]

PHARMACOLOGY: One report investigated the effects of lavender oil aromatherapy for insomnia and concluded that it is comparable to hypnotics or tranquilizers.[25] Lavender aromatherapy has also been utilized to increase mental capacity and diminish fatigue, [26] and to improve mood and perceived levels of anxiety.[27] Oils of different lavender species yield different results. [28] The German Commission E Monograph lists among lavender's uses, to be helpful for restlessness and difficulties in sleeping. [7] Lavender EEG studies, which have shown various alpha wave responses to different odors, can be used for psychophysiological response evaluation.[30] Spike lavender oil has a spasmolytic effect on animal smooth muscle. These effects are consistent with the pharmacologic activities of many other common volatile oils. In mice, lavender oil exhibits CNS depressant activity, characterized by anticonvulsant activity and a potentiation of chloral hydrate-induced sleep. Another report on aromatherapy finds "exposure time-dependent" decreases in motility in mice after inhalation of lavender fragrance. This helps to confirm folk remedies such as herbal pillow use to facilitate rest or minimize stress in people. [29]

The infusion and suspension of *L. stoechas* cause hypoglycemia in normoglycemic rats, reaching maximum activity 30 minutes after administration.[3] Further studies with *L. dentata* and *L. latifolia* have found the active hypoglycemic components to be partially water soluble. Furthermore, the extracts were not active in rats with alloxan-induced diabetes, indicating the need for intact pancreatic cells for a pharmacologic effect to occur. The active components have not been chemically classified.[31]

There is little direct evidence to support the use of lavender oil as a choleretic or for the treatment of GI disorders. A Bulgarian report discusses choleretic and cholagogic action of Bulgarian lavender oil. [32] Many volatile oils also may share these common actions. One of lavender's uses listed in the German Commission E Monograph includes helping in functional disorders of the upper abdomen with irritable stomach and intestinal disorders of nervous origin. Its effects are both calming and antiflatulent.[7]

Extracts of lavender are used in Europe as insect repellents. This effect appears to be related to compounds in the volatile oil. [33]

A study of percutaneous absorption of lavender oil in massage found that within 5 minutes after application, main constituents of the oil were detected in the blood. After this rapid absorption, most of the lavender oil was excreted within 90 minutes.[34]

Another report evaluated the role of lavender oil as a bath additive to relieve perineal discomfort after childbirth. When compared with placebo and synthetic oil, analysis of daily discomfort scores show less discomfort between days 3 to 5 with true lavender oil use. [35]

Herbal research finds perillyl alcohol, a compound distilled from lavender (also found in cherries, mint and celery seeds) to possess anticancer activities. [10] This monoterpene is being tested in clinical trials to study its role in cancer chemoprevention and therapy. [36,37]

A variety of mechanisms are proposed to explain perillyl alcohol's chemopreventative and chemotherapeutic effects. One such mechanism is that it promotes "apoptosis," a self-destructing ability the cell has when its DNA is severely damaged. In cancer, these cells lack this self-destructing ability, resulting in abnormal cell growth.[10] In one report, liver tumor formation was not promoted by perillyl alcohol, but its growth was inhibited by this apoptosis mechanism by enhancing tumor cell loss.[38] In another report, the rate of apoptosis was more than 6-fold higher with perillyl alcohol treated pancreatic adenocarcinoma cells than in untreated cells. [39]

Another proposed mechanism of monoterpenes is inhibition of post-translational isoprenylation of cell growth-regulatory proteins (such as Ras). [40] Perillyl alcohol has inhibited in vivo prenylation of specific proteins in one report, [41] and has altered RAS protein synthesis and degradation in another. Interfering with these pathways can regulate malignant cell proliferation. [42] Monoterpene-treated rat mammary tumors have been remodeled and redifferentiated to more benign phenotypes.[40] Perillyl alcohol treatment resulted in 70% to 99% inhibition of "aberrant hyperproliferation," a late occurring event preceding mammory tumorigenesis in vivo. [43]

Other cancers where perillyl alcohol has been effective include: murine melanoma growth suppression in vitro and in vivo; [44] pancreatic carcinoma in hamsters;[45,46] colon carcinogenesis in rats;[47] mammary cancer in rats;[40,48] liver tumors in rats;[38] and lung cancer in rats.[10]

With such promising results from animal studies, human clinical trials are under way to treat patients with breast, ovarian and prostate cancers. Results are not yet available.[10]

Besides anticancer effects, perillyl alcohol has been used orally in rabbits to reduce vein graft intimal hyperplasia. [49] It was also found to suppress hepatic HMG-CoA reductase activity, a rate limiting step in cholesterol synthesis, lowering serum cholesterol. [50]

TOXICOLOGY: Lavender oil exhibited a low order of toxicity when administered subcutaneously to animals. Although lavender absolute has been reported to be a skin sensitizer, no human phototoxicity has been reported. Lavender and lavandin oil have been reported to be nonirritating and nonsensitizing to human skin. [1]

However, three reports discuss allergic contact dermatitis from lavender oil and fragrance. [51,52,53] These examples are few, probably because the oil is used in small quantities in foods and cosmetics and has not been associated with major toxicity during normal use. The German Commission E Monograph lists no known side effects or contraindications.[7]

One report in mice observes an interaction between a 1/60 dilution of lavender oil, and pentobarbital, where sleeping time is increased. [54]

SUMMARY: Lavender is an aromatic plant that has been used in herbal medicine for centuries. It has been known to exhibit CNS depressant activity and is used for insomnia or to relieve anxiety and stress. It may also be helpful in GI disorders to reduce sugar and cholesterol levels and aid in grafting surgery. Lately, lavender compound perillyl alcohol is being studied for its promising effects in cancer prevention. Lavender has a low toxicity profile.

PATIENT INFORMATION — Lavender

Uses: Therapeutic: Antispasmotic, carminative, antidiabetic agent, restlessness and insect repellant. Nutritional: Food flavoring agent.

Interactions: May increase or potentiate the CNS depressant effects of sedative-hypnotics.

Side Effects: Allergic contact dermatitis.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LAVENDER

LECITHIN

DATE OF ISSUE: SEP 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): 1,2-diacyl-sn-glycero-3-phosphatidylcholine

COMMON NAME(S): Lecithin, lecithol, vitellin, kelecin, granulestin

SOURCE: Lecithin is found in many animal and vegetable sources including beef liver, steak, eggs, peanuts, cauliflower, and oranges. [1] Commercial sources for lecithin can come from soybeans, egg yolk, or brain tissue.[3,4] Some commercial lecithin and lecithin supplements contain between 10% and 35% phosphatidylcholine.[1]

HISTORY: Lecithin originated from the Greek "Lekithos." Lecithin is used today to treat liver ailments, hypercholesterolemia and neurologic diseases. [1,2] It is also used in the food processing industry.[3,5] Lecithin is a common compound found in cells of all living organisms, its presence being required for proper biological function.[6]

CHEMISTRY: Lecithin is a phospholipid mixture of acetone insoluble phosphatides consisting mainly of phosphatidylcholine, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol combined with various other substances including fatty acids and carbohydrates. [2] Lecithin is the common name for a series of related compounds called phosphatidylcholines.[5] Lecithin is defined chemically as a mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid (eg, soybean lecithin contains 4% stearic, 11.7% palmitic, 9.8% oleic acids, along with others). Lecithins also contain phosphorous and nitrogenous (eg, choline) compounds.[5]

Physical properties of lecithin can vary depending upon acid value. It is a waxy mass at acid value 20 and a thick pourable fluid at acid value 30. The color is white when freshly made but turns yellow to brown in air. It is an edible and digestible surfactant and emulsifier. [3]

PHARMACOLOGY

Use: Lecithin is used as an emulsifying and stabilizing agent in the food (eg, margarine, chocolate production), pharmaceutical, and cosmetic (eg, creams, lipsticks, conditioners) industries.[2,3,5]

Pharmacological use of lecithin primarily includes treatments for hypercholesterolemia, neurologic disorders, and liver ailments.

Hypercholesterolemia: Lecithin seems to possess beneficial properties in reducing cholesterol levels and controlling or preventing atherosclerosis. However, studies done in the late 1970's to early 1980's provide insufficient clinical or epidemiologic evidence to entirely support its positive effects against atherosclerosis. Although other studies from this time appear promising and have found results such as "18% cholesterol reduction," or "lowered cholesterol levels along with changes in lipid metabolism," no study is reliable with respect to atherosclerosis progression. [5]

Four months of soybean lecithin administration was found to reduce total serum lipids, cholesterol, and triglycerides in 21 hyperlipidemic patients. [6] The mechanism appears to be enhancement of cholesterol metabolism in the digestive system.

Neurology: Variable results occur using lecithin supplementation for treatment of neurologic disorders.

Lecithin is a good source of choline for treatment in dementias. [2] Phosphatidylcholine is thought to be a precursor for acetylcholine (Ach) synthesis. [5] Choline increases the accumulation of Ach within the brain. Ach is important for many brain functions including memory, so increasing concentration of this neurotransmitter can result in improved memory.[1] Positive effect on long-term memory has been demonstrated after administration of 35 g lecithin for 4 to 6 weeks. [5] However, another report shows no improvement from lecithin in memory disorders when taken in 30 mg/day dosages.[7]

Lecithin supplementation has also been studied in Alzheimer's disease, starting with memory difficulties. Three of 7 Alzheimer's patients receiving 25 g lecithin showed improvement in learning ability (coinciding with peak choline levels). [8] Combination tacrine and lecithin therapy conducted in a 32-patient double-blinded trial yielded poor results.[9] In a multicenter study, this combination did not improve mental status in 67 Alzheimer's patients. [10]

Ach deficiencies are also associated with other neurological disorders including tardive dyskinesia, Huntington's chorea, Friedreich's ataxia, myasthenia gravis, and other brain atrophies. In 2 patients with tardive dyskinesia, lecithin administration reduced abnormal movements. Ten cases of Friedreich's ataxia were also improved by lecithin supplementation.[11] One study failed to show any beneficial response in 12 patients with Friedreich's ataxia taking 25 g lecithin daily. [12]

Liver: In Germany, a product called *Essentiale*, (phosphatidylcholine) is marketed for liver disorders including acute and chronic hepatitis, cirrhosis, diabetic fatty liver, and toxic liver damage. Documentation supporting these claims have been authorized by the BGA (the German equivalent of the FDA). One report describes supplementation with phosphatidylcholine and how it protects against alcoholic cirrhosis in baboons. [1]

Other: Lecithin has also modified the immune system, activating specific and nonspecific defense systems in 20 patients receiving 1 teaspoonful 3 times daily for 30 days.[13] Another report discusses gallstone dissolution in 2 of 7 patients treated with lecithin and oral cholic acid. One patient experienced stone size reduction. [14]

TOXICOLOGY: Adverse effects generally have not been associated with lecithin as a nutritional supplement. [5] Some studies had no observable side effects, as well.[4,6,11] Six of 12 patients complained of anorexia and nausea when taking 25 g lecithin daily; one of these patients also noted excessive salivation. [12] Gastrointestinal side effects and hepatitis were experienced from the study in Alzheimer's patients taking both tacrine and lecithin. [10] One report in rats observes biochemical alterations and impaired sensorimotor development in offspring of rats fed a diet including 5% crude lecithin, suggesting its consumption is inadvisable during pregnancy.[5]

SUMMARY: Lecithin is a phospholipid mixture naturally occurring in nervous tissue and certain plants. It is used for its emulsifying properties in the food, pharmaceutical, and cosmetic industries. Pharmacological use of lecithin includes treatment for hypercholesterolemia, neurologic disorders, and liver ailments, all with variable to poor results. Toxicity profile appears to be low, with some exceptions. Its use in crude form is not recommended during pregnancy.

PATIENT INFORMATION — Lecithin

Uses: Lecithin is used for its emulsifying properties in the food, pharmaceutical, and cosmetic industries. Pharmacological use of lecithin includes treatment for hypercholesterolemia, neurologic disorders, and liver ailments. It has also been used to modify the immune system by activating specific and nonspecific defense systems.

Side Effects: Adverse effects are usually not associated with lecithin. However, there have been reports of anorexia, nausea, increased salivation, other GI effects, and hepatitis. Use during pregnancy is not recommended.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LECITHIN

LEECHES

DATE OF ISSUE: APR 1995

REPLACES MONOGRAPH DATED: APR 1989

SCIENTIFIC NAME(S): *Hirudo medicinalis* L. Phylum: Annelida

COMMON NAME(S): Fresh water leech, medicinal leech

HISTORY: The medicinal uses of leeches date back to more than two centuries before Christ. The 19th century heralded the widespread use of leeches for "bloodletting," a practice that grew so quickly that by the 1830s a leech shortage arose in France requiring the importation of more than 40 million Mexican leeches. [1] The last 45 years have seen a resurgence in the use of leeches, particularly as adjuncts in post-surgical wound healing procedures.

THERAPEUTIC USES: Medicinal leeches are used to stimulate the flow of blood at post-operative surgical sites, a procedure that has been claimed to increase the success of tissue transplants, reduction mammoplasty and the surgical reattachment of amputated extremities.[2]

The application of leeches to the area immediately surrounding the surgical wound temporarily reestablishes venous blood flow, thereby allowing the nutritive perfusion of the wound site by fresh blood. Blood stasis is a major contributor to unsuccessful reconstructive surgery. It is believed that if sufficient blood flow is maintained at the site until permanent adequate natural perfusion is established, the affected tissue has a significantly improved survival rate.

After attaching to the site, leeches secrete compounds that reduce blood viscosity; they also draw from 20 to 50 ml of blood from each bite. The leeches provide the drainage needed to permit decongestion and to preserve tissue viability until normal venous flow is established (about 5 to 7 days after the surgery). [3]

Application method: Leeches obtained from commercial breeders are easily maintained in a chlorine-free salt solution at 10°C to 20° C. Under such conditions, leeches can survive for up to 18 months.

Patients undergoing leech therapy should be administered a broad-spectrum antibiotic such as an aminoglycoside or third-generation cephalosporin to prevent infection by *Aeromonas hydrophilia*, which is found in the leech gut.[4,5] This is of particular importance considering that wild species are being investigated and that these leeches have been reported to contain a variety of potentially pathogenic bacteria. [6] In one study, blood from collected African leeches tested positive for HIV and hepatitis B, and leeches bought in German pharmacies contained up to 11 species of bacteria; viruses and protozoans have been shown to survive for months in the gut of the leech and as such, the leech should be considered a vector for infectious diseases. [7]

In practice, the area is washed well and covered by gauze or transparent dressing with a precut 1 cm hole to reveal adhesion site. The leech is then placed near the site. The biting end of the leech is generally the smaller of the two ends and moves in a "searching" fashion. [4] If attachment does not occur readily, the leech can be induced by pricking the skin with a pin to draw a drop of blood or the area can be dabbed with a sugar solution. The bite has been described as virtually painless or similar to a mosquito bite. A detailed description of the application technique has been outlined by Abrutyn. [8]

One leech is applied from 2 to 4 times a day for up to a week.[9] Feeding is complete in about 20 minutes, at which time the leech drops off. The feeding may suffice the leech for months. Removal of the leech may be hastened by applying solutions of salt, vinegar, a match or a local anesthetic, but the leech should not be forcibly removed. Bleeding from the attachment site usually continues for several hours. [10] Reuse of leeches is discouraged to minimize cross-infection.

PHARMACOLOGY: Medicinal leeches have an anterior and posterior sucker; within the anterior sucker is a y-shaped mouth with marginal teeth for biting. Following attachment, the leech secretes hirudin, a selective thrombin inhibitor, which enhances bleeding and prevents coagulation.

Hirudin was first described more than a century ago. It has recently been identified as a 65-amino acid peptide with antithrombokinase activity. Therapeutic studies of hirudin have been limited by its low natural yield, but the compound has recently been produced in quantities by recombinant gene techniques. [11,12] Recombinant hirudin binds very efficiently with thrombin, thus low doses are needed to inhibit venous thrombosis in animals. Extracts from leeches have been marketed as a cream for topical application, but their efficacy is unproven.

Recombinant hirudin has been used successfully in the treatment of Kasabach-Merritt Syndrome which leads to loss of circulating platelets and fibrinogen. Paradoxically, low-dose subcutaneous hirudin normalized fibrinogen and platelet activity. [11]

In addition to hirudin, leeches secrete a vasodilator, a hyaluronidase, a collagenase and two fibrinases (one disrupts clots, the other atherosclerotic plaque). The compound calin has also been isolated from leeches. By binding to collagen to interfere with the platelet-collagen interaction, this inhibitor of von Willebrand factor causes an antithrombotic effect in vitro and in hamster models.[13,14] There is conflicting evidence as to whether an anesthetic is secreted.

A number of studies have confirmed that the use of medicinal leeches improves venous drainage of wound sites in patients who have undergone reattachment surgery after amputation.[15,16] The ability of leeches to improve blood flow across congested surgical flaps has been documented using Doppler laser perfusion monitoring in pigs. Within one hour of applying leeches, blood flow through the surgical area increased 142% at surface probes and 491% at implanted probes. The average change for untreated control flaps was 6%.[1]

One study, however, found no changes in ipsilateral activated partial thromboplastin or prothrombin times when leeches were applied to an intact hand. [17] These findings suggest that significant systemic or local anticoagulation is not likely to occur and the risk of interference with other therapies may be small.

Salivary extracts of the giant leech (*Haementeria*) interfere with the metastatic growth of lung tumors.[2]

TOXICOLOGY: Leeches may draw up to 50 ml of blood per feeding. Repeated leeching may decrease hemoglobin levels dramatically. Drops of 1 to 2 gm% during a 5-day course are common. Decreases of up to 7 gm% have been observed following a 6-day course and required tranfusion therapy. [9] Following removal of leeches, the wound site will continue to bleed for up to 4 hours.

Several reports have documented severe wound and systemic infections caused by *Aeromonas hydrophila* (a Gram negative rod) harbored by leeches, and *Providentia* has been isolated in transport water.[18]

Local allergic reactions and anaphylaxis have been reported. [10] A unique case of nasal bleeding was reported in Spain, where a man was found to have a leech in his nostril. It is believed that the leech was transmitted through water from a rural drinking fountain. [19]

SUMMARY: Leeches have been used medicinally for centuries and interest in their use continues today. They are used most widely in post-surgical wound management. Although their use is not painful, it has been associated with severe anemia and systemic infections. The clinical development of hirudin and other leech-derived anticoagulant compounds may eventually supplant the use of leeches. Experience with the leech continues to grow and to become well documented.

PATIENT INFORMATION— Leeches

Uses: Leeches have been used for bloodletting, wound healing and stimulating blood flow at post-surgical sites.

Side Effects: Allergic reactions, anaphylaxis and infection, possibly even with hepatitis and HIV, may develop.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEECHES

LEMON

DATE OF ISSUE: APR 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Citrus limon* (L.), family *Rutaceae*

COMMON NAME(S): Lemon

BOTANY: The lemon tree is an evergreen, growing to over 6 m in height. Its toothed leaves are light green. The citrus fruit (lemon) is small, green to yellow in color, and oval in shape. Unlike other citrus varieties, the lemon tree bears fruit continuously. The plant is cultivated in Mediterranean and subtropical climates worldwide. [1,2]

HISTORY: The lemon originated in southeast Asia, probably in India or southern China. Its history is sometimes unclear because of the confusion with the similarly appearing "citron," a closely related species. The lemon was thought to have been depicted in Roman artwork as early as the first century A.D. [2] Other sources state that the fruit was first grown in Europe in the second century A.D.[1]

In the 1600s, physicians became aware that daily intake of lemon juice would prevent outbreaks of scurvy among sailors on long sea voyages. Scurvy is a vitamin deficiency disease characterized by muscle wasting, inability of wound healing, bruising, and gum deterioration. [3] English ships were required by law to carry enough lemon or lime juice for each sailor to get 1 ounce daily, earning them the nickname "limeys."[3]

The California lemon industry began after the Gold Rush of 1849. From 1940 to 1965, production increased. Today, California and Arizona are the major lemon producers, making the US a major source ahead of Mexico and Italy.

More than 50% of the US lemon crop is processed into juice and other drink products. The peel, pulp, and seeds are also used to make oils, pectin, or other products. Lemon juice has long been used as a diuretic, diaphoretic, astringent, tonic, lotion, and gargle. [2]

CHEMISTRY: Citrus fruits in general contain sugars, polysaccharides, organic acids, lipids, carotenoids (responsible for color), vitamins, minerals, flavonoids, limonoids (causing bitterness), and volatile components.[4,5]

The lemon is a good source of potassium (145 mg/100 g of fruit), bioflavonoids, and vitamin C (40 to 50 mg/100 g, twice as much as oranges). [1,2] The isolation of vitamin C from lemon juice has been performed.[6] Calcium (61 mg) is also present, along with vitamins A, B_1, B_2, and B_3. The fruit is also low in calories, containing 27 Kcal/100 g.[1,2,7]

Other constituents of lemon include volatile oil (2.5% of the peel), limonene (= 70%), alpha-terpinene, alpha-pinene, citral, coumarins, mucilage, pectins, and bioflavonoids (mostly from pith and peel).[1] Flavonoids eriocitrin and hesperidan have been evaluated. [8] When purchasing supplements for bioflavonoid benefits, it is also important to note content. Low-cost powdered lemon (and other citrus fruit) peels contain only 1% to 2% flavonoids, where standardized products contain 10% to 90% flavonoids. The percentage may not be stated on the label. [9] Adulteration of lemon juice has been reported.[10]

PHARMACOLOGY: Pharmacologically, the lemon is also important for its nutritional value. Vitamin C is necessary to sustain the body's resistance to infection and heal wounds. The potassium content in the fruit is useful to offset the potassium loss caused by blood-pressure lowering drugs in some patients. [11] In addition, lemon juice may increase iron absorption as described in a report of 234 women.[12]

Lemons also play a role as antioxidants. German studies in the late 1980s related this effect to the peel. [3] Bioflavonoids eriocitrin and hesperidan reduced oxidative stress in diabetic rats.[8] The pectin fiber and lemon oil also possess antioxidant properties. [11]

Lemons have anticancer properties illustrated in animal and human studies. [7,11] Citrus fruit intake is inversely related to cancer rates, especially stomach cancers. Vitamin C blocks formation of carcinogenic nitrosamines, after consumption of nitrites or nitrates (ie, in smoked food). [11]

The pectin component in lemons, because of the hydrophilic properties, acts to thicken gastric contents, regulating transit. This is useful to treat both vomiting and diarrhea.[13] Pectin also lowers blood cholesterol and aids in prevention of cardiovascular disease. [3,11,13] Bioflavonoids strengthen the inner lining of the blood vessels, including veins and capillaries. This is important for treatment of varicose veins, easy bruising, arteriosclerosis, or bleeding gums. [1]

Lemon's role as an antimicrobial agent has been reported. The volatile oil is said to be both antiseptic and antibacterial. [1] It has inhibited growth of *Aspergillus* mold in 1 report.[14] The juice has been evaluated as a natural biocide to disinfect drinking water. [15] Lemon juice also has sterilized rabies-virus-contaminated areas, to inactivate the virus in patients bitten by affected dogs. [16] The lemon has also been useful for infections, fevers, colds, flu, sore throat, gingivitis, and canker sores. It is also a liver and pancreas tonic.[1]

Skin ailments have also benefitted from lemons. It has been externally used for acne, fungus (ringworm and athlete's foot), sunburn, and warts. [1] One study reports lemon juice in the treatment of keloid, a scarring condition. [17] Application of lemon juice, once thought to have faded tattoos in conjunction with sunlight exposure, was disproven in another report.[18]

Once digested, lemon (despite its acidity) has an alkaline effect in the body, rendering it useful in such conditions as rheumatism, arthritis, and gout, where acidity is a negative contributing factor.[1]

Other actions of lemon preparations include sedative effects in fish, [3] increasing citrate levels inexpensively as therapy in patients with hypocitraturic calcium nephrolithiasis,[19] and behavior modification.[20,21,22,23,24]

TOXICOLOGY: The erosive effects of lemon juice on tooth enamel have also been evaluated.[25,26,27,28] One study finds loss of gloss, alteration in enamel color, and irregular dental tissue loss upon morphological analysis. [28]

SUMMARY: The lemon is an important and versatile fruit, dating back to the first or second century A.D. It contains many important vitamins including vitamin C, a necessary factor in preventing infection and healing wounds. Lemon's effects as an antioxidant and antitumor agent have been reported. The pectin component is also beneficial, aiding in cardiovascular health. Lemons also play important roles as antimicrobials, for skin ailments, and in GI health. Toxicology includes erosive effects on tooth enamel.

PATIENT INFORMATION — Lemon

Uses: Lemon has been used in food preparations and the agricultural industry to gel and stabilize foods. Important for its nutritional value, lemon possesses vitamin C, which is necessary to sustain the body's resistance to infection and heal wounds. Lemon also contains antioxidant, anticancer, hydrophilic, and antimicrobial

properties.

Side Effects: Toxicology reports include erosive effects on tooth enamel.

Dosing: No dosage information is available on the medicinal use of lemon or lemon oil.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEMON

LEMON BALM

DATE OF ISSUE: FEB 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Melissa officinalis* L. Family Lamiaceae (Mints)

COMMON NAME(S): Lemon balm, balm, melissa, sweet balm

BOTANY: Lemon balm is a low perennial herb with ovate- or heart-shaped leaves that have a lemon odor when bruised. The small yellow or white flowers are attractive to bees and other insects. It is indigenous to the Mediterranean region and western Asia, and widely naturalized in Europe, Asia, and North America. The leaves are harvested before flowering and used medicinally.

HISTORY: Lemon balm has been used in herbal medicine since the times of Pliny, Dioscorides, Paracelsus, and Gerard. The name "melissa" corresponds to the Greek word for bee, while "balm" is a contraction of balsam. The plant has found both culinary and medicinal uses, with the principal historical medicinal uses being carminative, diaphoretic, and antipyretic.

CHEMISTRY: Lemon balm leaves contain 0.2% to 0.3% of a lemon-scented essential oil similar to lemon grass. Major mono- and sesquiterpenes include geranial, neral, b-caryophyllene, b-caryophyllene oxide, linalool, citronellal, nerol, and geraniol. [1,2] R(+)-methyl citronellate is characteristic of melissa oil and distinguishes it from lemon grass oil.[3] Flavonoids,[4] oleanane, and ursane triterpenes[5] also have been isolated from the plant. Major nonvolatile constituents are caffeic acid and its di- and trimeric derivatives, including rosmarinic acid and melitric acids A and B. [6]

PHARMACOLOGY: Lemon balm's traditional medicinal use was as a sedative and antispasmodic. This activity was formerly attributed to the volatile oil. However, the lyophilized hydroalcoholic extract, which does not contain the volatile oil components, has sedative activity in several mouse models when given intraperitoneally.[7] This extract also was active in an acetic acid writhing analgesia assay but not in the hot plate test. The volatile oil of the plant had much weaker activity or was inactive in the same assays.

Lemon balm has antiviral activity against a variety of viruses, including herpes simplex virus (HSV) and HIV-1. The activity has been attributed to caffeic acid and its di- and trimeric derivatives as well as to tannins. [8,9] A clinical trial of a cream formulation of melissa extract demonstrated evidence of activity against HSV cold sores.[10]

Another use of melissa has been in Graves' disease, in which the thyroid is abnormally activated by thyroid-stimulating immunoglobulin (TSI). Freeze-dried extracts of melissa bound thyrotropin and prevented it and the Graves' TSI from activating its receptor, [11,12,13,14] although with less potency than the extracts of *Lithospermum officinales*, *Lycopus virginicus*, and *Lycopus europaeus*. In all cases, the activity was traced to caffeic acid oligomers such as rosmarinic acid and lithospermic acid. Auto-oxidation of the caffeic acid derivatives to ortho-quinones was postulated to be important for the biological activity.

Rosmarinic acid has also been found to inhibit the C3 and C5 convertase steps in the complement cascade. [15,16,17] This action may play a role in the anti-inflammatory action of melissa extract, because the action was observed both in vitro and in vivo in rats with oral administration of the compound.

TOXICOLOGY: The antithyroid activity of melissa extract mentioned above is weak enough that it does not present a serious safety concern in patients without Graves' disease. The topical use for herpes cold sores has not produced any reports of dermal toxicity. Melissa extract was not found to be genotoxic in a screen of several medicinal plants. [18]

SUMMARY: Lemon balm may be of use as a topical agent for cold sores, and it appears to have potential use as a mild sedative. No side effects have been reported.

Lemon balm is approved in the German Commission E monographs for nervous sleeping disorders and functional GI complaints. It is also monographed in ESCOP F-2, WHO vol. 2, and BHP vol. 2.[19] An AHP monograph is in progress.

PATIENT INFORMATION — Lemon Balm

Uses: Lemon balm has been used for Graves' disease as a sedative, antispasmodic, and a topical agent for cold sores.

Side Effects: No side effects have been reported.

Dosing: Crude lemon balm herb typically is dosed at 1.5 to 4.5 g/day. A standardized preparation of lemon balm extract, *Euvegal forte*(Spitzner Arz.) contains 80 mg lemon balm leaf extractb and 160 mg valerian root extract, given 2 or 3 times/day as a sleep aid.[20,21] A 1% extract cream also has been studied as a topical agent for herpes.[22]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEMON BALM

LEMON VERBENA

DATE OF ISSUE: JAN 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Aloysia triphylla* (L'Her.) Britt. Formerly described as *A. citriodora* (Cav.) Ort., *Verbena citriodora* Cav., *V. triphylla*, *Lippia citriodora* (Ort.) HBK Family: Verbenaceae

COMMON NAME(S): Lemon verbena, louisa

BOTANY: Lemon verbena is an aromatic plant native to Argentina and Chile.[1] It is a deciduous plant that is commonly cultivated in the tropics and Europe. It is grown commercially in France and North Africa. The plant grows to 3 meters and is characterized by the presence of fragrant, lemon-scented narrow leaves. It bears small white flowers in terminal panicles.[1]

HISTORY: Lemon verbena has been used as a medicinal plant for centuries, having been touted for use as an antispasmodic, antipyretic, carminative, sedative and stomachic. The leaves and flowering tops are used in teas and as beverage flavors. Its fragrance is used in perfumery. Although the plant is grown as an ornamental, it requires shelter during cold periods. [1]

CHEMISTRY: An essential oil, which is present in small quantities (0.42% to 0.65%), is extracted from the leaves by steam distillation. [2] Known as oil of verbena, it contains a variety of fragrant compounds including citral (35%), methyl heptenone, carvone, l-limonene, dipentene and geraniol. [1,2] Because the pure oil can be expensive, it is sometimes adulterated with distillates from other plants.

PHARMACOLOGY: The essential oil is said to be acaricidal and bactericidal. An alcoholic leaf extract has been reported to have antibiotic activity in vitro against *Escherichia coli*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*, although it had no antimalarial activity. A 2% emulsion of the oil has been reported to kill mites and aphids.[2]

A component of the related plant, *Verbena officinalis*, has been reported by Chinese investigators to have antitussive activity. [3]

TOXICOLOGY: Lemon verbena generally is recognized as safe for human consumption and for use as a flavor in alcoholic beverages. Contact hypersensitivity has been associated with members of the related *Verbena genus*.

SUMMARY: Lemon verbena is a fragrant plant that finds use in the preparation of teas. Extracts of the plant are used in fragrances and to flavor beverages. No significant toxicity has been associated with the plant.

PATIENT INFORMATION — Lemon Verbena

Uses: Lemon verbena is used in teas, flavorings, fragrances, antispasmodics, carminatives, sedatives and stomachics.

Side Effects: Some individuals may experience contact hypersensitivity.

Dosing: Lemon verbena is used as a digestive aid in doses of approximately 5 g/day; however, there are no clinical studies to substantiate the safety or efficacy of this dose.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEMON VERBENA

LEMONGRASS

DATE OF ISSUE: SEP 2000

REPLACES MONOGRAPH DATED: OCT 1989

SCIENTIFIC NAME(S): *Cymbopogon citratus*(DC.) Stapf. *Andropogon citratus* DC, *A. schoenathus*. *C. flexuosus*, *A. flexuosus*. Family: Poaceae (Gramineae), Grass.

COMMON NAME(S): Lemongrass. *C. citratus*, is known as Guatemala, West Indian, or Madagascar lemongrass. *C. flexuosus*, is known as cochin lemongrass, British Indian lemongrass, East Indian lemongrass, or French Indian verbena.

BOTANY: *Cymbopogon* is a tall, aromatic perennial grass that is native to tropical Asia. *C. citratus* is cultivated in the West Indies, Central and South America, and tropical regions. The linear leaves can grow up to 90 cm in height and 5 mm wide. Freshly cut and partially dried leaves are used medicinally and are the source of the essential oil.[1,2]

HISTORY: Lemongrass is one of the most widely used traditional plants in South American folk medicine. It is used as an antispasmodic, analgesic, for the management of nervous and GI disorders, to treat fevers, and as an antiemetic. In India, it is commonly used as an antitussive, antirheumatic, and antiseptic. It is usually taken by ingesting an infusion made by pouring boiling water on fresh or dried leaves. Lemongrass is an important part of Southeast Asian cuisine, especially in Thai food and has been used in flavoring. In Chinese medicine, lemongrass is used in the treatment for headaches, stomachaches, abdominal pain, and rheumatic pain.[3]

CHEMISTRY: Fresh *C. citratus* grass contains about 0.4% of volatile oil.[3] The oil contains 65% to 85% of citral (a mixture of 2 geometric isomers, geraniol and neral). Citral is used as a flavoring to fortify lemon oil and in perfumes and colognes for its lemon scent.[4] Accumulation of citral in certain lemongrass leaf structures has been studied.[5] The yield of essential oil and citral content in the plant has been evaluated.[6] Certain citral isolated from *C. citratus*from Laguna was found to be of good quality with 93.7% purity.[7] GC analysis in 1 report finds geraniol and neral, along with related geraniol, geranic acid, and nerolic acid.[8]

Other compounds found in the oil include myrcene (12% to 25%), diterpenes, methylheptenone, citronellol, linalol, farnesol, other alcohols, aldehydes, linalool, terpineol, and more than a dozen other minor fragrant components.[1,4,9,10,11] Reports concerning chemical analyses of *C. citratus* specific to country of origin are available, finding some similarities to the above components. Philippine lemongrass has been found to contain alpha and beta pinene, limonene, phellandrene, and others,[12,13] findings of 21 components such as anisaldehyde, cinnamaldehyde, catechol, and hydroquinone from certain fractions of this species from Bangladesh,[14] and various constituents from this species and others (including *C. winterianus*, *C. jwarancusa*) from China[15] and Morocco.[16]

Other species' chemical components have been reported. *C. flexuosus* grass contains ˜ 0.5% volatile oil, which in some strains contains up to 85% citral. However, many strains have a higher concentration of geraniol (50%) with citral (10% to 20%) and methyl eugenol as minor components. Yet another type of East Indian lemongrass is reported to contain no citral but up to 30% borneol.[1,3] In 1 report analyzing essential oil samples, *C. jwarancusa* contains 70% piperitone; *C. distans*, 40% piperitone; *C. matrini*, geranol, and geranyl acetate; *C. tortius*, Me eugenol; *C. caesius*, 30% carvone.[15]

Nonvolatile components of *C. citratus* consist of luteolins, homo-orientin, chlorogenic acid, caffeic acid, P-coumaric acid, fructose, sucrose, octacosanol, and others.[17] Flavonoids luteolin and 6-C-glucoside have also been isolated.[18] One study reports high concentrations of cobalt.[19]

PHARMACOLOGY: Lemongrass has been widely used in South American traditional medicine. A report of Guatemalan use lists lemongrass as a popular medicinal plant.[20] Brazilian folk medicine uses the plant for nervous conditions or GI disturbances.[21] Traditional Indian medicine employs lemongrass for fever, infection, and sedation.[1] Other uses include as an astringent, fragrance in beauty products, food flavoring, and treatment for skin conditions, muscle pain, infections, fever, colitis, and indigestion.[1,2] However, effectiveness of lemongrass has not been sufficiently evaluated to help substantiate these claims.

The general lack of pharmacologic activity of oral doses of lemongrass have been substantiated in humans. Volunteers who took a single oral dose or 2 weeks of oral intake of the tea showed no changes in any hematologic or urinary tests, or in EEG or ECG tracings. Some subjects showed mild elevations of direct bilirubin and amylase levels, but none were accompanied by any clinical manifestations. The hypnotic effect was further investigated in 50 volunteers who ingested a tea prepared under double-blind conditions 3 nights 3 to 5 days apart. The parameters tested (sleep induction time, sleep quality, dream recall, reawakening) did not show any effect of lemongrass compared with placebo. Furthermore, 18 patients with documented anxiety traits showed no differences in their anxiety scores after taking a single 150 ml dose of lemongrass tea under double-blind conditions.[21]

A peripheral, dose-dependent, analgesic effect was found in studies including rat paw testing, which may explain certain "sedative" folk uses of the plant.[22] Similarly, when rats were fed the 20% decoction, rat paw edema was inhibited by 19% vs control; however, indomethacin inhibited the edema by 59%. The study concluded that the antirheumatic effects of lemongrass after oral administration were too weak to be considered of any clinical usefulness.[23]

Antimicrobial effects: Several reports demonstrating the antimicrobial effects of lemongrass are available discussing its activity against animal and plant pathogens, gram-positive and gram-negative bacteria, and fungus.[24] Constituents geraniol (alpha-citral) and neral (beta-citral) were found to possess these antibacterial effects in 1 report.[25] The citral content in the oil greatly affected the antibacterial actions as shown in another report testing fresh oil against oils up to 12 years old.[26] Some organisms inhibited by lemongrass oil include *Acinetobacter baumanii*, *Aeromonas veronii*, *Candida albicans*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Serratia marcescens*, *Staphlycoccus aureus*, and *Proteus mirabilis*.[27,28] One mechanism of action explained in a report evaluating lemongrass oil and its antibacterial effects on *E. coli* determined that the oil elicits morphological alterations on the host, including filamentation, inhibition of septum formation, production of bulging, abnormal shaping of cells, as well as cell lysis, all of which deter bacterial growth.[29]

Antifungal effects: Antifungal effects of the oil have been studied as well, and include actions against such dermatophytes as *Trichophyton mentagrophytes*, *T. rubrum*, *Epidermophyton floccosum*, and *Microsporum gypseum*.[30] In a 13-oil study, lemongrass oil was found to be among the most active against human dermatophyte strains, inhibiting 80% of strains, with inhibition zones greater than 10 mm in diameter.[31] Other studies report lemongrass actions against keratinophilic fungi,[32] ringworm fungi,[33,34] and food storage fungi.[35] Lemongrass oil is discussed as being effective as an herbicide[36] and an insecticide[37,38] because of these naturally occurring antimicrobial effects.

Anticarcinogenic effects: There are also numerous reports demonstrating the anticarcinogenic (or antitumor) properties of lemongrass. Edible plants (including lemongrass), in general, are discussed.[39,40] Active compounds in lemongrass include d-limonene and geraniol.[41] Essential oil from *C. citratus* leaves and constituent citral were both proven to be toxic against P388 mouse leukemia cells.[42,43] Another report finds the plant extract to possess antimutagenic properties against certain *S. typimurium* strains.[44] Lemongrass extract also inhibits DNA adduct formation in rat colon.[45] Another report on aflatoxin-albumin adduct formation influenced by the plant finds no alteration in this area.[46] A Japanese patent application discusses how constituent geraniol markedly inhibits Epstein-Barr virus.[47] Oil of *C. citrans* possessed high antiradical power, as well as some antioxidant activity.[48]

Other effects: Other reported effects of lemongrass include a 1975 report on fever reduction,[49] dose-related hypotensive effects in rats, weak diuretic actions,[50] and myrcene's ability to induce antinociception in mice.[51]

TOXICOLOGY: Lemongrass is "Generally Recognized As Safe" (GRAS) in the US.

Topical application of lemongrass has rarely led to an allergic reaction. Two cases of toxic alveolitis have been reported from inhalation of the oil. [2] No laboratory test abnormalities were noted after ingestion of lemongrass tea. Oral doses equivalent to 208 times the normal human dose did not potentiate the sleep-time of sodium pentobarbital in mice.[22,52] An infusion of lemongrass given orally to rats for 2 months in doses up to 20 times the corresponding human dose did not induce any toxic effects. The tea did not affect male rats in any way. Similarly, female rats showed no abnormality in the estrus cycle, nor did doses interfere with fertility, pregnancy, or the development of the offspring. No external malformations were noted in the pups. The authors concluded that the lack of toxicity and pharmacologic activity made lemongrass a valuable placebo.[53] Achara, an herbal tea made from dried lemongrass leaves, was found to be atoxic.[54] Substance beta-myrcene was found not to be genotoxic in another report.[55] Aqueous extracts of the plant used as an insecticide led to some mitotic abnormalities in *Allium cepa* root tips grown in these extracts, which may have implications in humans.[56] In addition, constituent beta-myrcene was found in reports to interfere with cytochrome P450 liver enzymes, suggesting possible toxicities.[57,58,59]

Lemongrass should not be used in pregnancy because of uterine and menstrual flow stimulation. [60]

SUMMARY: Lemongrass is widely used in South American folk medicine for analgesia, nervousness, and GI disorders. In India, it is used for inflammation and as an antiseptic. Lemongrass is also used as a food flavoring and fragrance in beauty products. The plant possesses marked antibacterial and antifungal effects, as well as anticarcinogenic actions. Lemongrass is generally considered to be of low toxic potential, but may alter certain liver enzymes.

PATIENT INFORMATION— Lemongrass

Uses: Lemongrass is used as a fragrance and flavoring, and in folk medicine as an antispasmodic, hypotensive, anticonvulsant, analgesic, antiemetic, antitussive, antirheumatic, antiseptic, and treatment for nervous and GI disorders and fevers. Because there is little human evidence to support its effectiveness in an oral dosage, lemongrass may be considered a placebo.

Side Effects: Lemongrass is considered to be of low toxicity. Constituent beta-myrcene was found to interfere with cytochrome P450 liver enzymes, suggesting possible toxicities.

Dosing: No information is available on dosage in the medicinal use of lemongrass oil.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEMONGRASS

LENTINAN

DATE OF ISSUE: MAY 1997

REPLACES MONOGRAPH DATED: OCT 1989

SCIENTIFIC NAME(S): *Lentinula edodes* (Berk.) Pegler, synonymous with Tricholomopsis edodes Sing.

COMMON NAME(S): Shiitake, snake butter, pasania fungus, forest mushroom, hua gu

BOTANY: Lentinan is a polysaccharide derived from the vegetative parts of the edible Japanese Shiitake mushroom. It is the cell wall constituent extracted from the fruiting bodies or mycelium of *L. edodes* (Berk.). The mushroom is synonymous with *Cortinellus edodes* (Berk.) *S. Ito* and *Imai, Armillaria edodes* (Berk.) *Sacc.*and *Cortinellus shiitake* (Takeda) Henn.[1] The light, amber fungi are found on fallen broadleaf trees, such as chestnut, beech or mulberry. They have decurrent, even or ragged gills, a stem, and are covered with delicate, white flocking.[2] Shiitake mushrooms are commonly sold in food markets in the Orient and are now widely available in the United States, Canada and Europe.

HISTORY: Lentinan is a complex polysaccharide that has been found to possess immunostimulating antitumor properties. Lentinan was isolated from edible Shiitake mushrooms that have been used in traditional oriental cooking and herbal medicine. Shiitake has been renowned in Japan and China as both a food and medicine for thousands of years. It is now commonplace throughout the world. Extracts of these mushrooms are now being incorporated into over-the-counter dietary supplements designed to improve the status of the immune system.

CHEMISTRY: Lentinan is found in very low concentrations in fresh Shiitake mushrooms. In one study, 200 kg of fresh mushrooms yielded 31 g of lentinan (0.02%). Lentinan is a water-soluble beta-1,3 glucan polysaccharide characterized by beta-1,6 branched glucan linkages. At least five additional polysaccharides have been isolated from *L. edodes*.[1] Lentinan is a high molecular weight polysaccharide in a triple helix structure, containing only glucose molecules with mostly (1-3)-ß-D-Glucan linkages in the regularly branched main chain with two ß (1,6)-D-glucopyranoside branchings for every five ß-(1,3)-glucopyranoside linear linkages. [2]

PHARMACOLOGY: The antitumor activity of lentinan has been recognized for almost 30 years. Because a number of naturally occurring polysaccharides had previously been found to have antitumor activity, lentinan was considered for detailed evaluation. In addition to antitumor activity, lentinan also possesses immune-regulatory effects, anti-viral activity, antimicrobial properties and cholesterol-lowering effects. The pharmacology available on lentinan is vast. The following is a brief outline of key aspects.

Antitumor Activity: When administered by intraperitoneal (IP) injection to mice implanted with Sarcoma 180, lentinan showed striking antitumor activity. Ten daily doses as low as 1 mg/kg/dose resulted in tumor growth inhibition of 95% to 100% depending on the strain of mouse tested. Although one other polysaccharide fraction from *L. edodes* inhibited tumor growth, most other fractions were devoid of activity.[1]

In rats with a model of colon cancer, lentinan was found highly effective in extending their lifespan. When treated with five IP injections 2 days apart, (2 mg/kg), 11 of 20 rats were found to be tumor-free at autopsy on day 42 of the study. Furthermore, lentinan significantly increased the lifespan of carcinomatous rats. In the control group, 50% of the rats lived 42 days compared with 70 days in the treated group. Four of 10 treated rats were still alive on day 210 of the study while all of the controls had died by day 70.[3]

Therapeutic effects of lentinan in the GI tract have been noted. A case study reports reduced primary tumor size, in a 63-year-old patient treated with lentinan combination therapy. Metastasis disappeared, and only mild thrombocytopenia occured as a side effect. [4] Lentinan used as an agent for post-operative adjuvant therapy was investigated in GI patients with stages II to IV cancer. Stage IV patients had higher lymphocyte counts than control patients, suggesting lentinan's immuno-potentiating efficacy in advanced GI cancer.[5] Another study reports lifespan prolongation in stomach cancer patients, using lentinan combination therapy. [6] Other successful chemotherapies using lentinan include: CDDP and 5-FU, [7] mitomycin and 5-FU,[3] cisplatin with radiation[8] and interleukin 2.[9] Another study involving gastric cancer describes how lentinan causes marked development of reticular fibers related to anti-tumor effect and enhanced interstitial response. [10] Intracavitary injection of lentinan is a useful treatment for malignant effusions in gastric carcinoma patients. [11] Resistance to lentinan chemoimmunotherapy is also reported.[12]

Lentinan's effects in other cancers have also been reported. In prostatic cancer, lentinan 2 mg weekly in combination with Tegafur was evaluated. A five year average survival rate of treated patients was 43% compared with 29% in the control group. [13] Another report referred to the safety and efficacy of lentinan post-treatment with surgical therapy in 33 breast cancer patients. [14] Lentinan has also been evaluated in cervical cancer patients. [15,16,17]

Another study has reported effective results for lentinan in metastasis inhibition. [19] In combination therapy with IL-2, lentinan exhibited a synergistic effect against induced fibrosarcoma in mice.[19] The same combination again in mice had similar results against lung metastases. [20]

Survival rates using lentinan therapies have increased. One study reports 129 days vs. 49 days in malignant ascites and pleural effusion patients given lentinan 4 mg/week for 4 weeks.[21] A four-year follow-up survey of stomach cancer patients reports survival at 1, 2 and 3 years, with few reported side effects. [6]

Immune System Effects: Although not directly cytotoxic, beta-1,3 glucan has been shown to enhance natural protective immunity. When administered IP to mice with implanted tumors, lentinan effectively increased the activity of cytotoxic peritoneal exudate cells. [22] Kurokawa, et al draws a similar conclusion when reporting direct action of lentinan on tumor cells in mice by scanning electron microscopy. Lentinan contributes to antitumor immunity enhancement, but not to direct killing activity against tumor cells.[23] Evidence suggests that lentinan preferentially acts on T-cells and may enhance T-helper cell function. Furthermore, lentinan augments natural killer cell activity and activates macrophages. [24] Lentinan also triggers production of interleukin 1 by a direct action on macrophages or indirectly by augmenting colony stimulating factor.[25] Many other studies are available where lentinan is found to improve immune function by stimulating T-cell/killer cell/monocyte production,[5,9,11,26,27,28,29,30,31] increasing natural cell-mediated cytotoxicity, [32] stimulating production of acute-phase transport proteins, [33] affecting lymphocyte and enzyme concentrations[34] and activating complement.[35]

Anti-viral Activity: Lentinan has antiviral activity and has been found to protect against encephalitis caused by the intranasally infected vesicular stomatitis virus in mice.[36] Lentinan enhances AZT's effects when used in combination against HIV for in vitro studies. [37] Additional discussion of lentinan's mechanism against HIV is reported in an article by the same authors.[38]

Antimicrobial Properties: Tsujinaka, et al report that rabbits with induced septic insult without lentinan treatment had low platelet counts, elevated bilirubin and creatinine. In lentinan-treated septic animals, platelet counts did not decrease, and elevation of plasma bilirubin and creatinine levels were less prominent. Findings suggest a modified septic process by administration of lentinan. [39] Host resistance against microbial infection by lentinan is reviewed in another report by Kaneko, et al.[40]

Cholesterol-Lowering Effects: The compound lentinacin has been shown to reduce cholesterol levels in rats by 25% after 7 days of oral administration in a dose as low as 0.005% of feed intake.[41] Other compounds isolated from Shiitake have also been shown to lower blood cholesterol and lipids as well. [42]

TOXICOLOGY: The Shiitake mushroom is edible and has not been associated with toxicity. In animals, lentinan shows little toxicity. In mice, the LD-50 is greater than 1,500 mg/kg (IP). In a phase I study conducted in 50 patients with advanced cancer, minor side effects were observed in 3 patients; in a study of 185 patients, 17 experienced minor adverse reactions.[3] Animal studies have been remarkable for lack of significant toxicity. [1] Few toxic effects are mentioned in two reports of lentinan

use.[43,44]

SUMMARY: Lentinan is a polysaccharide derived from the edible Shiitake mushroom. It is found to have anti-tumor, immune-regulatory, anti-viral, antimicrobial and cholesterol-lowering effects. Studies show little toxicity associated with lentinan's use.

PATIENT INFORMATION — Lentinan

Uses: Lentinan is proving to be a valuable component in cancer and infection treatments. It has also demonstrated cholesterol-lowering and immune-regulatory properties.

Side Effects: Lentinan is derived from the Shiitake mushroom, which is edible and is not generally associated with side effects. Lentinan side effects are rarely reported.

Dosing: The isolated polysaccharide lentinan from shiitake culture has been used IV at doses of 2 to 10 mg on a weekly schedule as adjunctive therapy in HIV as well as cancer, primarily in Japan.[45]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LENTINAN

LETTUCE OPIUM

DATE OF ISSUE: MAY 2003

REPLACES MONOGRAPH DATED: NOV 1991

SCIENTIFIC NAME(S): Lettuce opium is a product obtained from the milky white sap of *Lactuca virosa* L. (wild lettuce) and *L. sativa var capitata* L. (garden lettuce) but related species are sometimes used. Family: Compositae

COMMON NAME(S): Wild lettuce, German lactucarium, garden lettuce, lettuce opium, strong-scented lettuce, green endive, acrid lettuce, greater prickly lettuce.

BOTANY: Widely cultivated, lettuce opium flowers from July to September. This biennial herb grows to 1.8 m. The large leaves can attain lengths of 0.46 m. The stalks are rich in a milky-white sap that flows freely when the stems are broken.

HISTORY: Lettuce opium has been used in folk medicine for indications ranging from aiding circulation to treating swollen genitals. In Europe, it is used as a substitute for opium in cough mixtures.[1] In homeopathy, a tincture has been used for laryngitis, bronchitis, asthma, cough, and urinary tract infections. [2] The juice of the stem covering yields a medicinal extract known as thridace, the use and efficacy of which is widely disputed. [3]

In Chinese medicine, lettuce preparations have been widely used. The dried juice has been recommended as a topical wound antiseptic and the seeds have been used as a galactogogue (to increase the flow of milk in nursing mothers). It has been claimed that the flowers and seeds are effective in reducing fevers. [4] More recently, lettuce opium products have been marketed as legal highs or narcotic substitutes intended to be smoked alone or in combination with marijuana to enhance potency and flavor.[5] Its analgesic and sedative attributes seem more based on fiction than fact.

CHEMISTRY: Some confusion exists regarding the nomenclature of the products derived from *L. virosa* and related plants. Flowering lettuce plants contain large amounts of a milky-white sap, which has a bitter taste and strong opiate-like odor. When the juice is collected and is exposed to air, it turns a brownish color. This substance is called lactucarium, a mixture of compounds to which the touted narcotic properties of the product have been ascribed. Lactucarium has been reported to contain approximately 0.2% lactucin, a sesquiterpinoid lactone. Additionally, the mixture contains a volatile oil, caoutchouc, mannitol, and lactucerol (taraxasterol) (approximately 50%). Lactucerin, also found in the latex, is the acetyl derivative of taraxasterol, a widely distributed triterpene. [4,6]

Reports that lactucarium contains hyoscyamine have been refuted.[7] A report that *L. virosa* contains N-methyl-beta-phenylethylamine[8] also has been refuted.[5]

PHARMACOLOGY: A variety of legal, alternate "hallucinogenic" products containing lettuce opium have been available on the market. Brand names of such products include Lettucine, Black Gold, Lettucene, Lettuce Hash, and Lopium. These products contain a lettuce derivative or lactucarium and are smoked in pipes or heated in small bowls, and the vapors are inhaled. These extracts are sometimes combined with damiana distillates, African yohimbe bark, or catnip distillates. The hallucinogenic effect is usually mild and appears to be related to the degree of user expectation. There is no pharmacologic basis for the purported hallucinogenic effects of lettuce opium.

Lettuce leaf cigarettes have been marketed as nicotine-free tobacco substitutes. Support for such alternatives has been variable because of slow acceptance of the unique flavor and the lack of a nicotine-induced kick.

Phytochemical and biological screening of several *Lactuca* species indicates that the genus has no antimicrobial activity, slight antitumor activity, and can produce gross CNS effects in mice.[9,10] However, the *Lactuca* species has resistance to viruses, bacteria, and fungi (*Bremia lactucae*).[11]

While lactucin and lactucopicrin have been reported to have depressant and sedative activity on the CNS, these compounds are chemically unstable; commercial lactucarium contains little, if any, of these.[12] Latex of *L. sativa* has been shown to inhibit the growth of *Candida albicans* in vitro.[13] Extracts of *L. sativa* resulted in hypotension when administered to dogs.[5]

TOXICOLOGY: No reports of clinically important adverse effects caused by smoking lettuce opium have been reported. However, a possible association exists between lettuce ingestion and a localized oral allergic reaction. [14]

Three young adult drug users became ill with fevers, chills, abdominal pain, flank and back pain, neck stiffness, headache, leucocytosis, and mild liver function abnormalities after injecting wild lettuce opium and valerian root. However, all 3 patients recovered within 3 days. [15]

SUMMARY: Lettuce opium is an antiquated folk remedy with little value in modern medicine. The hallucinogenic effect of lettuce opium and other lettuce derivatives has not been substantiated. The effects appear to be more psychological rather than physiological and are proportional to the user's expectations.

PATIENT INFORMATION — Lettuce Opium

Uses: Lettuce opium has been used as a topical antiseptic, as folk medicine to ameliorate a variety of conditions, and as a narcotic substitute or enhancer. It is also a mild sedative and hypnotic. There is little evidence to support its use for any indication.

Side Effects: Lettuce opium contains sesquiterpene lactones; thus, oral ingestion may be associated with allergic reactions.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LETTUCE OPIUM

LEVANT BERRY

DATE OF ISSUE: AUG 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Anamirta cocculus* Wight & Arn. Also described as *A. paniculata*, *Menispermum cocculus*, *M. lacunosum*, *Cocculus suberosus* and *C. lacunosus*. Family: Menispermaceae.

COMMON NAME(S): The levant berry goes by a large number of synonyms including fish killer, fishberry, hockle elderberry, Indian berry, louseberry and poisonberry. The dried fruit is called "cocculus fructus" or "cocculus indicus" in commercial trade. [1]

BOTANY: The levant berry is a climbing woody shrub that is native to India, Burma and other parts of Malaysia. It has wide thick leaves and rootlets that ooze a white milky latex. The fragrant flowers produce U-shaped seeds. The fruit dries to a bitter, nearly black wrinkled shape. [1]

HISTORY: The fruits are gathered from the wild and sun-dried for export. In India, the leaves are inhaled as a snuff to relieve malaria, and the leaf juice is used in combination with other natural products as a vermifuge.[1] Extracts of the plant are applied topically for lice, but the toxic nature of the components (in particular picrotoxin) make this a dangerous use, especially when the skin is abraded or irritated. Although picrotoxin had been considered an official remedy for epilepsy at the turn of the century in the US, it is no longer used for this treatment because of severe toxicity. It had found use as a stimulant for the management of morphine poisoning.[1]

CHEMISTRY: The fruit flesh contains the nontoxic alkaloids menispermine and paramenispermine. [1] The seed, however, contains the bitter, toxic principle picrotoxin (1.5% to 5.0%).[2,3] This compound can be separated into picrotoxinin, an oxygenated sesquiterpene derivative, and picrotin. The tasteless compounds anamirtin and cocculin are also present along with a fixed oil (11% to 24% of the seed). [1] The seed is also rich in fatty acids.

PHARMACOLOGY: Picrotoxin in doses of 0.3 mg to 0.6 mg has been used to manage epilepsy and in slightly higher doses to manage night sweating. [1] Picrotoxin continues to find use in experimental models of central nervous system stimulation, but its use in medicine has largely been abandoned in the US and Europe.

TOXICOLOGY: Picrotoxin stimulates the central nervous system and is a gastrointestinal irritant. [1] High doses can cause salivation, vomiting, purging, rapid shallow respiration, palpitations or heart slowing, stupor, loss of consciousness and death. the lethal dose is approximately 30 mg/kg body weight.

In some societies, ground whole dried fruits have been used to kill birds or dogs and to stupefy fish and game. A seed paste is applied to arrow tips by some jungle tribes.[1]

SUMMARY: The levant berry is not widely used in the US and Europe, but remains a popular folk remedy in Asia and adjacent regions. The berry contains the toxic principle picrotoxin and should not be ingested or applied topically to abraded skin.

PATIENT INFORMATION — Levant Berry

Uses: Levant berry is used to relieve malaria, treat lice, stun or kill fish and game, and manage epilepsy.

Side Effects: Levant berry should not be used on abraded skins or ingested. It is potentially lethal.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LEVANT BERRY

LICORICE

DATE OF ISSUE: FEB 1998

REPLACES MONOGRAPH DATED: JUL 1989

SCIENTIFIC NAME(S): *Glycyrrhiza glabra* L., *G. uralensis*, *G. palidiflora* Family: Leguminosae

COMMON NAME(S): Licorice, Spanish licorice, Russian licorice

BOTANY: *Glycyrrhiza glabra* is a 4- to 5-foot shrub that grows in subtropical climates having rich soil. The name glycyrrhiza is derived from Greek words meaning "sweet roots." It is the roots of the plant that are harvested to produce licorice. Most commercial licorice is extracted from varieties of *G. glabra*. The most common variety, *G. glabra var. typica* (Spanish licorice), is characterized by blue flowers, while the variety *G. glabra var. glandulifera* (Russian licorice) has violet blossoms. Turkey, Greece and Asia Minor supply most commercial licorice.

HISTORY: Therapeutic use of licorice dates back to the Roman empire. Hippocrates and Theophratus extolled its uses, and Pliny the Elder (23 A.D.) recommended it as an expectorant and carminative. Licorice also figures prominently in Chinese herbal medicine as a "drug of first class" — an agent that exerts godly influence on the body and acts to lengthen life. Licorice is used in modern medicinals chiefly as a flavoring agent that masks bitter agents, such as quinine, and in cough and cold preparations for its expectorant activity. Most recently, a sample of historic licorice from 756 A.D. was analyzed and was found to still contain active principles even after 1200 years.[1]

CHEMISTRY: Licorice root contains a variety of chemical agents including ammonia and oleanane triterpenoids. However, it is for the glycoside glycyrrhizin that the root is cultivated. The amount of glycyrrhizin varies from 7% to 10% depending on growing conditions. The root also contains various starches and sugars, among them glucose, mannose and sucrose. Raggi, et al have published an HPLC method to compare the bioavailability of glycyrrhizic acid whether in licorice root or in pure glycyrrhiza extract. These can now be tested in blood, urine and bile. [2]

PHARMACOLOGY: As a result of licorice's extensive folk history for gastric irritation, it has undergone extensive research for use as an anti-ulcerogenic agent. These investigations have centered on a semi-synthetic succinic acid ester of 18B glycyrrhetic acid, carbenoxolone. While the specific mechanism of action is unknown, carbenoxolone does not act to enhance mucous secretions, increase the lifespan of gastric epithelial cells, inhibit back diffusion of hydrogen ions induced by bile and possibly inhibit peptic activity.

Controlled trials comparing carbenoxolone with cimetidine indicate it is less effective in treating gastric and duodenal disease. In one study, 78% of patients receiving cimetidine demonstrated ulcer improvement by gastro-scopy compared with 52% receiving carbenoxolone. Additionally, those patients receiving carbenoxolone experienced more side effects including edema, hypertension and hypokalemia. These side effects are more pronounced in elderly patients, as well as those with underlying renal, hepatic or cardiovascular disease. A proposed mechanism of action for these side effects involves the action of carbenoxolone on the renin-aldosterone-angiotensin axis. Spironolactone relieves the side effects but also attenuates the therapeutic effects.

Another licorice product tested as an anti-ulcer agent is deglycyrrhizinated licorice (DGL), which consists of licorice that has had virtually all of its glycyrrhizin removed. Several studies have evaluated the efficacy of DGL but all have been inconclusive. While these agents have not shown consistent results, neither do they show the serious side effects exhibited by carbenoxolone.

Another use for glycyrrhizins is in suppression of scalp sebum secretion. A 10% glycyrrhizin shampoo prevented sebum secretion for 1 week compared with citric acid shampoo, which delayed oil accumulation by 1 day.

Alcohol extracts of *G. glabra* also have in vitro antibacterial activity and weak in vivo antiviral activity.

Glycyrrhetic acid has shown anti-inflammatory and anti-arthritic activity in animal studies. These actions may be caused by PGE_2 inhibitive qualities demonstrated by several glycyrrhizin analogues.

Prepared Chinese licorice, "Zhigancao," was found to have anti-arrhythmic effects, such as prolonging P-R and Q-T intervals. [3] Japanese researchers Matsumoto, et al, tested to see if increased immune complex levels could be lowered by adding licorice to a person's regimen. This was tested on mice and was found to aid in the clearance of excess immune complexes, which are produced in systemic lupus erythematosus. The study was the first of its kind to work on reducing immune complexes in vivo.[4]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: The toxic manifestations of excess licorice ingestion are well documented. One case documented the ingestion of 30 to 40 g of licorice per day for 9 months as a diet food. The subject became increasingly lethargic, having flaccid weakness and dulled reflexes. She also suffered from hypokalemia and myoglobinuria. Treatment with potassium supplements reversed her symptoms. Excessive licorice intake can result in sodium and fluid retention as well as hypertension and inhibition of the renin-angiotensin system. [5]

After consuming large amounts of licorice, human intoxication caused by aldosterone-like effects was found. [6]

A 70-year-old patient with hypertension and hypokalemia caused by chronic licorice intoxication in excess of around 80 candies (2.5 g each having 0.3 glycyrrhizic acid) per day over the past 4 to 5 years, discontinued use one week before hospital admission. After discontinuing the use of licorice and monitoring a treatment plan including licorice, it was found that the activity of 11-ß-hydroxysteroid dehydrogenase was suppressed when the patient had been without licorice, but the 11-ß-hydroxysteroid dehydrogenase increased as the levels of urinary glycyrrhetic acid decreased. [7]

Other documented complications include paraparesis, hypertensive encephalopathy and one case of quadriplegia. Products that contain licorice as a flavoring, such as chewing tobacco, have also been implicated in cases of toxicity. Hypersensitivity reactions to glycyrrhiza-containing products have also been noted.

SUMMARY: Licorice is widely used as a candy and flavoring agent. Consumption of 30 to 40 grams per day for extended periods may lead to severe and potentially dangerous electrolyte imbalances. Patients with pre-existing renal, hepatic or cardiovascular diseases should be warned of potential toxicities associated with excessive consumption. Also, the retention of sodium and fluids, as well as human intoxications are relevant in terms of toxicities. A recent animal study indicates that licorice may be useful in treating lupus.

PATIENT INFORMATION — Licorice

Uses: Used historically for gastrointestinal complaints, licorice is used today as a flavoring and in shampoos. It is being investigated as an anti-inflammatory and as a treatment for lupus.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Large amounts of licorice taken daily for a long time can cause a range of side effects from lethargy to quadriplegia (body paralysis). Do not over-consume licorice.

Dosing: Licorice root has been used in daily doses from 2 to 15 g for ulcer and gastritis, as well as for coughs; higher doses given for extended periods of time run a risk of hyperkalemia. Deglycyrrhizinated licorice extracts are available. Doses of glycyrrhizin of 200 to 600 mg/day are acceptable. [8,9,10]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LICORICE

LIFE ROOT

DATE OF ISSUE: APR 2000

REPLACES MONOGRAPH DATED: JUL 1992

SCIENTIFIC NAME(S): *Senecio aureus* L. Family: Asteraceae (Compositae)

COMMON NAME(S): Life root, golden groundsel, golden senecio, ragwort, false valerian, coughweed, cocashweed, female regulator, grundy-swallow [1,2,3,4,5]

BOTANY: Life root is a perennial herb with a slender, erect stem that bears bright yellow flower heads. It grows to a height of about ˜1.2 meters in swampy thickets and moist ground in the eastern and central U. S. The lower leaves are heart-shaped. The entire dried plant, not only the roots, is used medicinally. [2,3,5]

HISTORY: Do not confuse life root with a variety of other plants that have been ascribed broad healing powers, including the mandrake root and ginseng root. Life root has played an important role in traditional Native American herbal medicine and was used by the Catawba women as a tea to relieve the pain of childbirth as well as to hasten labor.[6] The plant has been used to treat a variety of illnesses, including hemorrhage and colds. [1] Despite concern about its safety, this plant continues to be found in some herbal preparations designed to control irregular menses and other gynecologic disturbances. [7]

CHEMISTRY: The plant contains a number of pyrrolizidine alkaloids including senecionine (˜ 0.006% in the root), senecifoline, senecine, otosenine, floridanine, florosenine, and other related compounds. An astringent tannin has been reported to be present. [1,2,7] Chemical composition of other various *Senecio* species has been reported.[8,9]

PHARMACOLOGY: Traditional use of the plant includes treatment for amenorrhea, menopause, and leucorrhea. [7] Life root has also been used for its uterine tonic, diuretic, and mild expectorant properties.[7] Although it is widely recognized that this plant can influence the activity of female reproductive organs (hence the name "female regulator"), there is little pharmacologic evidence that this plant has a uterotonic effect or that it can influence hormone levels in women. [2,4,7]

Antimicrobial analyses of related species *S. graveolens* have been performed on the essential oil.[9]

TOXICOLOGY: Pyrrolizidine alkaloids have been associated with the development of hypertensive pulmonary vascular disease. However, of greatest concern appears to be the association of this class of alkaloids with the development of hepatotoxicity and liver cancer. [10] In general, pyrrolizidine alkaloids have been shown to produce toxic necrosis of the liver, particularly in grazing animals that have ingested large amounts of plants containing these compounds. There is strong evidence that such alkaloids are involved in human liver diseases, including primary liver cancer (see monograph on Comfrey).[2,11] The mechanism of pyrrolizidine alkaloids can lead to veno-occlusive disease and liver congestion leading to acute and chronic liver disease. The *Senecio* species are generally most toxic when young, and there is some indication that the combination of alkaloids in *S. aureus* may be at the lower end of the toxicity scale for this genus.[10] However, because of the presence of pyrrolizidine alkaloids, do not recommended this plant for internal use.

Life root is contraindicated during pregnancy and lactation, partially because of its abortifacient and uterine tonic effects. Animal studies confirm transferring of pyrrolizidine alkaloids into the placenta and breast milk. [7]

SUMMARY: Life root has been used in traditional medicine for the management of disorders of the female reproductive tract, but there is little pharmacologic evidence to support these uses. Furthermore, members of the *Senecio* genus contain hepatotoxic alkaloids. Therefore, the ingestion of this plant cannot be recommended for any purpose.

PATIENT INFORMATION — Life Root

Uses: Life root has been used as a traditional medicine to hasten labor and relieve labor pains. It has also been used to treat a wide range of illnesses, from colds to hemorrhage.

Side Effects: Use is not recommended; the plant is toxic and possibly carcinogenic.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LIFE ROOT

LINDEN

DATE OF ISSUE: JUL 1997

REPLACES MONOGRAPH DATED: DEC 1990

SCIENTIFIC NAME(S): Several species of the genus *Tilia* produce flowers that are used in traditional herbal medicine. In large part, flowers derived from *T. cordata* Mill. and *T. platyphyllos* Scop. are selected for the preparation of teas. Family: Tiliaceae

COMMON NAME(S): Linden, European linden, basswood, lime tree, lime flower.

BOTANY: Linden trees can grow to heights approaching 100 feet. They are native throughout Europe but also found in the wild or purposely planted in gardens. Linden tree bark is smooth and gray, and its leaves are heart-shaped. The five petaled, yellow-white flowers are collected after the spring bloom, dried and preserved under low-moisture conditions. These are the parts used for the drug. [1,2]

HISTORY: Since the Middle Ages, the flowers of the linden tree have been used to promote sweating. In addition, the flowers have been used traditionally as a tranquilizer and to treat headaches, indigestion and diarrhea. Infusions of the flowers make a pleasant-tasting tea. Several sources report the lore that linden flowers were once believed to be so effective in treating epilepsy that one could be cured simply by sitting beneath the tree. [3,4] Sugar is obtained from the sap of the tree and the seed oil resembles olive oil. [4] In Greek mythology, "Philyra," a nymph, was transformed into a linden tree after begging the gods not to leave her among mortals. [2]

CHEMISTRY: Quercitin, kaempferol and other related flavonoid compounds are the major components found in linden flowers. These compounds, along with p-coumaric acid, appear to be responsible for the diaphoretic (sweat inducing) effect of the plant. Other constituents include caffeic, chlorogenic and p-coumaric acids and amino acids including alanine, cysteine, cystine and phenylalanine. Also present in the plant are volatile oil components (0.02% to 0.1%) including alkanes and esters, citral, eugenol and limonene. Carbohydrates are also found such as arabinose, galactose, glucose, mannose and xylose. Gum and mucilage polysaccharides (3%) are also seen. Tannins are present as well. [1,2,4,5] The ratio of tannins to mucilage appears to be important in determining the flavor of teas prepared from linden flowers. Those teas with a high (2% or greater) tannin level and low mucilage content produce the more flavorful teas. Flowers from *T. cordata*and *T. platyphyllos* contain relatively more tannin than mucilage. [3]

Traces of benzodiazepine-like compounds have been found in linden. [2]

More than two dozen additional minor compounds have been identified in the wood, flowers and fruits of linden. [1,2,4,5] The fragrant components of the flowers degrade rapidly under conditions of high moisture.

PHARMACOLOGY: The diaphoretic activity of the flowers is caused by quercitin, kaempferol and p-coumaric acid. Where "sweat cures" would be an advantage, linden has been used, mainly for feverish colds and infections. [1] Linden can also reduce nasal congestion and relieve throat irritation and cough. [1,2]

A recent report isolates pharmacologically active benzodiazepine receptor ligands from *Tilia tomentosa*. This may explain the plant's use as an anxiolytic. [6]

Linden is also known to possess sedative effects. These effects were significant upon inhalation of *Tilia* species oil in mice. [7] Other sedative effect therapies include relief of sinus headache and migraines and remedies for insomnia, stress and panic disorders. Linden has been used to treat nervous palpitations and has also lowered high blood pressure brought on by stress and nervous tension. [2,5] Folk medicine has employed linden as an anti-spasmodic. [2] Animal studies in vitro using rat duodenum has supported this claim. [5] The antispasmodic properties are said to be due to p-coumaric acids and flavonoids present in the plant. [5] Homeopaths use linden for enuresis, incontinence, hemorrhage, prolapsed uterus and epilepsy. [4]

An extract of *Tilia* sp. was found to possess in vitro antibacterial activity against organisms associated with stomatologic infections, and these extracts have been found clinically useful. [8] Lime flower has been reported to have antifungal activity as well. [5]

Linden's emollient quality has been used in lotions for itchy skin. [2] It also has been employed for rheumatism. A recent report discusses *Tilia sylvestris'* anti-inflammatory and wound healing properties. [9]

Other effects of linden include diuretic and astringent, [5] and possibly antidiabetic. [10] *Tilia* has also promoted iron absorption in rats, which may be helpful in iron deficiency anemia. [11]

TOXICOLOGY: There is no evidence to support the belief that old linden flowers may induce narcotic intoxication. [3] Frequent use of linden flower teas has been associated with cardiac damage. This rare event suggests that linden teas should not be ingested by those patients with a history of heart disease. [3,4,5]

Many sources list few side effects from linden. However, reports do exist on specific toxicology such as: Contact urticaria, [12] allergy from certain *Tilia* species' fruit oils in rats, [13] organochlorine pesticide residues in linden-containing beverages [14] and soft wood dust exposure from linden, containing volatile and unsteady substances which are micronucleus-inducing matters in peripheral lymphocytes. [15]

SUMMARY: *Tilia* flowers have been used for the preparation of teas and medicinally to induce sweating. Linden has been used to treat colds, infections, throat irritation and cough. It also possesses sedative effects and can treat palpitations, headaches and insomnia. Its antispasmodic qualities make linden useful in incontinence and hemorrhage as well. The use of linden flowers has not generally been associated with toxicity, although several authors have raised concerns about the potential for cardiotoxicity following long-term ingestion of the tea.

PATIENT INFORMATION — Linden

Uses: Linden has been used to induce sweating for feverish colds and infections and can reduce nasal congestion and relieve throat irritation and cough. It possesses sedative effects and can treat nervous palpitations and high blood pressure. It has also been used in lotions for itchy skin.

Side Effects: Rarely, frequent use of linden flower teas has been associated with cardiac damage.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LINDEN

LOBELIA

DATE OF ISSUE: DEC 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Lobelia inflata* L., Campanulaceae, harebell family

COMMON NAME(S): Indian tobacco, Indian weed, pukeweed, asthma weed, gagroot, vomitwort, bladderpod, eyebright

BOTANY: *Lobelia* is a branching, perennial herb that is completely self-fertilizing and reproduces only once in its lifetime (monocarpy). [1] It grows from 0.3 to 0.9 m in height and produces small, violet-pinkish flowers in the alternate leaf axils. The base of the flowers expands to form the seed capsule, which is the source of the name "inflata." It is found in the eastern United States and Canada from Georgia and Arkansas to Labrador. [2]

HISTORY: American Indians smoked the leaves as tobacco and used them medicinally for respiratory ailments. Similar folk uses for asthma, chronic bronchitis, whooping cough, cholera, and many other conditions were recorded. *Lobelia*'s emetic properties were well known in the nineteenth century. [3]

CHEMISTRY: The piperidine alkaloid lobeline was isolated as the main active component of *Lobelia* in 1921. [4] Its absolute stereochemistry was determined in 1965. [5] A number of related alkaloids also have been isolated, including lobelanine and lobelanidine. [2] These alkaloids are present in several other species of *Lobelia*, with lobeline a major constituent in all of them. [2] The triterpene ester beta-amyrin palmitate has been reported from *L. inflata*, [6] while several polyacetylenes have been identified in plant tissue culture. [7]

PHARMACOLOGY: The primary bioactive component of *Lobelia*is the alkaloid lobeline, although the minor alkaloids have been shown to have similar but distinct pharmacology in a number of nicotinic cholinergic systems. The following discussion focuses on the activities of lobeline.

Nicotinic acetylcholine receptor activity: Vast pharmacologic literature exists for lobeline, which has long been classified as a nicotinic receptor ligand. [8] Indeed, lobeline has been found to bind to neuronal nicotinic cholinergic receptor preparations with low nanomolar affinity, and structure-activity studies of analogs have explored the structural requirements for nicotinic receptor-binding activity. [9] However, it has become clear that there is a large diversity of nicotinic receptor subtypes that differ in subunit composition and function and that lobeline's actions are only partly caused by agonism at nicotinic receptors. [10] A panel of subunit combinations was found to vary in affinities for lobeline as well as for other nicotinic ligands. [11] However, the homomeric a_7 nicotinic receptor was insensitive to lobeline as an agonist. [12]

In more complex experimental systems, lobeline behaved differently from nicotine, inhibiting dopamine uptake into synaptosomes and depleting levels of dopamine in rat striatal slices. [13] In nicotine-pretreated rats, lobeline appeared to act as a short-acting antagonist of nicotinic receptors, mediating the effects of nicotine on mesolimbic dopamine activity and locomotor stimulation. [14] In freely moving rats, lobeline did not attenuate dopamine release from striatum as nicotine did, as measured by microdialysis. [15] Similarly, nicotine increased release of acetylcholine in rat hippocampal microdialysis, while lobeline had no effect. [16] The effects of lobeline on *N*-methyl-D-aspartate (NMDA), [17] serotonin, [18] and norepinephrine [19] release have been reported to be complicated phenomena.

Smoking cessation: Lobeline was a component of OTC products for withdrawal from tobacco addiction for many years. Results from clinical studies of the efficacy of lobeline have been mixed, [20,21,22] and a meta-review found that none of the available studies have been controlled adequately or were of sufficient duration to prove its efficacy. [23] The FDA removed lobeline from the market because of lack of demonstrated efficacy as part of its OTC review process in 1993. [23]

Amphetamine abuse: Experimental work has provided evidence that lobeline may be useful in the treatment of amphetamine abuse, based on the blockade of amphetamine-induced dopamine release in rat striatum. Lobeline attenuated the self-administration of amphetamine, but not sucrose, by rats. [24] In several rodent models, lobeline had a selective effect on amphetamine-induced behavior and neurochemistry. [25] The postulated mechanism of activity in this context is inhibition of dopamine uptake and promotion of dopamine release from presynaptic storage vesicles. [26] Limitations of lobeline may include the observation of self-administration in drug-naive mice [27] and the fact that cross-tolerance to nicotine has been observed. [8] The addiction liability of lobeline in humans has not been established.

Respiratory effects: Lobeline's effects on respiratory physiology may be responsible for its initial use in smoking cessation. Stimulation of respiration and bronchoconstriction are observed with lobeline and nicotine. [28] At high doses, lobeline induces sensations of choking or breathlessness. [29,30]

Analgesia: A role for spinal nicotinic receptor subtypes in nonopioid analgesia has been found using the frog alkaloid epibatidine, and lobeline inhibited its analgesic properties, but potentiated epibatidine-induced agitation. [31,32,33]

Memory, learning, and anxiety: Lobeline has been studied for its ability to improve learning and memory. Mice treated with lobeline for 5 days before training showed improved performance in a water maze; however, the effect was limited to younger mice. [34] Lobeline, along with other nicotinic agonists, has been shown to improve performance in memory function in animal experiments. [35] Lobeline also has been found to have activity along with nicotine in anxiolytic models. [36] Identification of the specific nicotinic subtypes involved may lead to better understanding of the mechanism of these effects. One unconfirmed study attributed antidepressant activity to a fatty acid ester of a common triterpene; however, no further work has substantiated this report. [6]

TOXICOLOGY: As might be deduced from the common names for the plant, *Lobelia* and lobeline are capable of inducing nausea, vomiting, and dizziness at high doses (ie, 8 mg lobeline sulfate). [23] Clinical studies of lobeline for smoking withdrawal used doses of 5 mg twice daily, with 0.5 mg lozenges used in addition when there was an urge to smoke. [22] Thus, the therapeutic dose of lobeline is very close to the toxic dose. In use of the whole plant, minor variations in alkaloid content could increase the potential for toxicity.

SUMMARY: *L. inflata* and its major alkaloid, lobeline, have been used in smoking cessation programs and have been proposed for treatment of other drug dependencies; however, there is only modest evidence for efficacy and a definite potential for toxicity. Lobeline has been a useful pharmacological tool for elucidating the function of nicotinic cholinergic receptors.

PATIENT INFORMATION — Lobelia

Uses: *Lobelia inflata* and its major alkaloid, lobeline, have been used in smoking cessation programs and have been proposed for treatment of other drug dependencies; however, there is only modest evidence for efficacy.

Side Effects: *Lobelia* and lobeline are capable of inducing nausea, vomiting, and dizziness at high doses (ie, 8 mg lobeline sulfate). The therapeutic dose of lobeline is very close to the toxic dose.

Dosing: Clinical studies of lobeline for smoking withdrawal used doses of 5 mg twice daily, with 0.5 mg lozenges used in addition when there was an urge to smoke. [22] The useful dose of lobeline is very close to the toxic dose. In use of the whole plant, minor variations in alkaloid content could increase the potential for toxicity.

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Document Bibliographic Information:

- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "L" MONOGRAPHS
  LOBELIA

LORENZO'S OIL

DATE OF ISSUE: SEP 2003

REPLACES MONOGRAPH DATED: NOV 1993

SCIENTIFIC NAME(S): *1,3-Docosenoic acid (erucic acid)*, *cis-9-octadecenoic acid (oleic acid)*

COMMON NAME(S): Lorenzo's oil, glyceryl trierucate with glyceryl trioleate, erucic acid, and oleic acid [1]

HISTORY: A widely publicized movie about the use of Lorenzo's oil to treat a devastating neurological syndrome catapulted this compound into the public spotlight.

CHEMISTRY: Lorenzo's oil is a combination of glyceryl trierucate (a component of erucic acid, a 22-carbon monounsaturated fatty acid) and glyceryl trioleate (a component of oleic acid, an 18-carbon monounsaturated fatty acid). These generally are combined in an approximate ratio of 1:4 (glycerol trierucate:glycerol trioleate) and have been used for the clinical evaluation of Lorenzo's oil.

PHARMACOLOGY: The oil has been touted for the treatment of a rare genetic disease known as adrenoleukodystrophy (ALD) when it appears in children, and adrenomyeloneuropathy (AMN) when it takes a more insidious path in adults. This X-linked recessive disorder is characterized by demyelination of cerebral nerves resulting in a variety of neurological symptoms including peripheral neuropathy, blindness, spastic tetraplegia, and death. [2,3]

The primary metabolic abnormality in this disease is the accumulation of saturated very long fatty acids in body fluids and tissues, which occurs because of a genetically impaired ability to degrade them by normal oxidation. Hexacosanoic acid (C26:0) is the most consistently elevated fatty acid. In the absence of normal cellular oxidation of these fatty acids, the saturated very long chain fatty acids accumulate and are believed to be responsible for the neurological symptoms (ie, from demyelination within the CNS) associated with the disorder and with adrenocortical insufficiency and hypogonadism. [4]

Theoretically, treatment of these diseases involves reducing the level of saturated very long chain fatty acids present in the blood and nerves. In vitro, monounsaturated fatty acids have been shown to inhibit the synthesis of saturated very long chain fatty acids and to reduce their accumulation in cells obtained from patients affected by ALD.[2] Therefore, the saturated very long chain fatty acids that are believed to be toxic even at low concentrations appear to be exchanged for nontoxic monounsaturated fatty acids.

Results of clinical trials of patients with diets enriched with monounsaturated fatty acids, such as oleic acid, have shown a partial reduction in the plasma levels of saturated very long chain fatty acids. Peripheral nerve function has improved in some patients with AMN. [5]

Although the addition of erucic acid to oleic acid (the combination used in Lorenzo's oil) was found to have led to complete normalization of plasma levels of very long chain fatty acids and promised to represent an even more effective therapy, [6] there is little to no evidence that this improves or delays progression of ALD or AMN. [4]

Preliminary investigations of the efficacy of the oil mixture in the childhood form of the disease generally found no consistent effect, presumably because the fulminant childhood form did not permit sufficient time for the lipid-modifying effects of therapy. [2] Additionally, a case report described a 5-year-old boy who responded to 5 months of therapy with the oil mixture[7] as evidenced by an increased ability to swallow and an improvement in cerebral structure. In contrast, another case report described the failure of the oil to prevent clinical deterioration, and the child developed progressive visual loss and spastic tetraparesis despite dietary changes, steroid therapy, and gamma globulin treatment.[8]

Well-designed studies of the oil suggested that treatment with Lorenzo's oil offers little evidence for a cessation or remission of the disease in adults.

In one study, in which 24 patients were treated for up to 48 months, the plasma levels of very long chain fatty acids declined to nearly normal within the first 10 weeks of treatment. However, none of the patients improved and 9 of 14 adult males had functional deterioration (eg, new cerebral lesions on MRI). Because of ethical considerations, this was not a placebo-controlled study. It is not clear if treatment may have slowed disease progression without resulting in a measurable improvement.[1]

In an analogous but larger open trial of 108 patients, [9] treatment with the oil for up to 1 year demonstrated no improvement in nerve transmission as determined by assessment of visual evoked potentials. There was no correlation between the plasma levels of very long chain fatty acids and the rate of deterioration of visual function. Nerve transmission was examined in another study involving 8 patients on Lorenzo's oil dietary therapy for 3 years; Lorenzo's oil had no effect on modifying the natural course of the disease.[3,10] The disappointing results of dietary therapy for ALD may be associated with the failure of erucic acid entering the brain. [11,12] However, therapy with lovastatin reduces plasma concentrations of very long chain fatty acids, particularly hexacosanoic acid (C26:0). [13]

TOXICOLOGY: Long-term hematological side effects must be considered.[14,15] Thrombocytopenia has been reported following treatment with Lorenzo's oil.[14] In one study, it was noted that the platelet count declined in 23 of 24 patients, but this was not correlated with plasma levels of erucic acid or other metabolites. None of these patients had abnormal bleeding or hematoma. Some of the patients had asymptomatic neutropenia. Dietary supplements of safflower and fish oils were given to the patients during this study, and while a 30% decrease in plasma docosahexaenoic acid levels occurred in all patients, none reported symptoms of essential fatty acid deficiency.

Purpura, petechiae, and bleeding have been reported. [16] Lymphocytopenia and depression of natural killer cells have been observed in ALD patients on Lorenzo's oil.[17] One author suggests avoiding therapy with Lorenzo's oil in patients who are already symptomatic, due to the side effect profile of the oil and because of the continued neurological progression of the disease in most patients treated with the oil. [18]

SUMMARY: Lorenzo's oil represents a combination of oleic and erucic acids, which are long-chained monounsaturated fatty acids. The use of this preparation in adrenomyeloneuropathy, a genetically transmitted disease, has resulted in generally poor efficacy. While the use of this combination appears logical based on the pharmacology of the genetic defect, clinical studies have not shown valid clinical effect.

PATIENT INFORMATION— Lorenzo's Oil

Uses: Lorenzo's oil has been used to treat certain rare genetic diseases such as adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN), without verified success.

Side Effects: Thrombocytopenia has been reported following treatment. Purpura, petechiae, bleeding, lymphocytopenia, and depression of natural killer cells have also been reported. Lorenzo's oil should be avoided in patients who already have neurological deficits due to the side effect profile of the oil and likely neurological progression of the disease.

Disease-State Concerns: Lorenzo's oil may enhance thrombocytopenia or neutropenia.

Dosage Concerns: Lorenzo's oil is a combination of erucic acid and oleic acid in a 1:4 ratio. Patients typically are placed on a low-fat diet; one clinical trial used oleic acid or glycerol trioleate at 1.7 g/kg and 0.3 g/kg of erucic acid or glycerol trierucate. Due to lack of clinical trial data, use is best avoided during pregnancy and lactation. Avoid use in patients with known hypersensitivity reactions to any component of the oil.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LORENZO'S OIL

LOVAGE

DATE OF ISSUE: APR 1997

REPLACES MONOGRAPH DATED: JAN 1989

SCIENTIFIC NAME(S): *Levisticum officinale* Koch. syn. *Angelica levisticum* Baillon. Also referred to as *Hipposelinum levisticum* Britt. and Rose in older texts. Family: Umbelliferae

COMMON NAME(S): Lovage, maggi plant, smellage

BOTANY: Lovage is an aromatic umbelliferous perennial that is similar in appearance to angelica. It carries yellow-green flowers arranged in dense clusters, which bloom from July to August on top of the thick, hollow stems. The plants grow up to 2 meters high. Its leaves are divided by sharply toothed leaflets. Its characteristic, strongly aromatic odor resembles celery. It tastes "spicy-sweet" and slightly bitter. [1,2] Lovage is native to Europe, but is found throughout the northeastern US and Canada. This plant should not be confused with *Oenanthe cocata* L. known commonly as water lovage and *O. aquatica* (L.) Lam. (water fennel), toxic members of the family Apiaceae.

HISTORY: Lovage has been used in folk medicine for > 500 years, primarily for its GI effects. It has a reputation for use as a carminative and antiflatulent, but it has also been used as a diuretic and for the management of sore throats and topical boils. It has been used as a breath lozenge, a skin wash and a lotion. The name "lovage" is from the Latin word meaning "from liguria" because, at one time, the herb flourished in this region. Translated to English, it evolved into "love parsley." Misled by its descriptive name, lovage has been included in numerous otc "love tonics." [2] Today it is a common ingredient in commercial herbal teas. Extracts of lovage are used as flavorings for liqueurs, spice extracts and bitter spirits and fragrances for cosmetics. Cooked leaves and roots have been eaten.

CHEMISTRY: Lovage contains approximately 2% of a volatile oil responsible for its characteristic flavor and odor. This oil is composed primarily (70%) of phthalide lactones, (eg, 3-butylphthalide [32%], cis- and trans-butyldenephthalide, cis- and trans-ligustilide [24%], sen-kyunolide and angeolide). In addition, lesser amounts of compounds such as terpenoids, volatile acids and furocoumarins contribute to the flavor of the extract. Other compounds found are camphene, bergapten, psoralen and caffeic, benzoic and other volatile acids. [1] Several of the compounds identified in lovage have also been found in celery (see monograph), another member of Umbelliferae. HPLC analysis has been performed to determine glycoside content in lovage. [3] Other reports discuss isolation and identification of phthalides from the roots of the plant by chromatographic and spectrometric methods. [4,5] Chemial composition of lovage oil has been reported. [6]

PHARMACOLOGY: Although teas of this plant have been used primarily for their GI effects, there is little documentation for these indications. In general, many volatile oils, including lovage, induce GI hyperemia resulting in a carminative effect; other oils have also been shown to reduce gas within the GI tract. Lovage extracts probably exert their GI effects through common mechanisms, increasing saliva and gastric juice production by their aroma and mildly bitter taste. Lovage is also used to dissolve phlegm in the respiratory tract. Two constituents of lovage, butylphthalide and ligustilide, have been shown to have spasmolytic action. [1] The phthalides have been reported to be sedative in mice, and the furocoumarins have been associated with a phototoxic reaction following ingestion or contact. Following parenteral administration, extracts of lovage were shown to exert a diuretic effect in rabbits. [7] This effect is presumed to be caused by a mild irritation of the renal tubules by the volatile oil. [7] Lovage has been indicated for pedal edema in humans. [1]

TOXICOLOGY: Furocoumarins in plants of the Umbelliferae family may cause photosensitivity resulting in dermatitis.

SUMMARY: Lovage is a fragrant plant that has been used in herbal medicine for centuries. Although there is only limited evidence to support many of its traditional claims, the plant contains a volatile oil that most likely contributes to its carminative and diuretic effects. Photosensitivity has been reported with the harvesting of the plant, but not with its therapeutic use.

PATIENT INFORMATION — Lovage

Uses: Lovage has been used historically as an antiflatulent and diuretic. Its extracts are used in flavorings and fragrances.

Side Effects: Lovage can cause photosensitivity with resultant dermatitis at harvest, but not as a therapeutic agent.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LOVAGE

LYCOPENE

DATE OF ISSUE: APR 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): ?, ?-carotene

COMMON NAME(S): Lycopene

BOTANY: Lycopene is a carotenoid, occurring in ripe fruit, especially tomatoes. [1] Other sources include watermelon, grapefruit, and guava. [2]

HISTORY: The tomato (*Lycopersicon esculentum*) continues to be a popular and highly consumed fruit in the US, second in production to potatoes. [3] Epidemiological evidence finds the constituent lycopene to be associated with a reduced risk of certain diseases and cancers. [4]

CHEMISTRY: Lycopene is the most prominent carotenoid in tomatoes, followed by beta-carotene, gamma-carotene, phytoene, and other minor carotenoids. [3] Lycopene is also responsible for the red color of the fruit. [5] The carotenes exert antioxidant activity. Lycopene exhibits "the highest overall single oxygen-quenching carotenoid, double than that of beta-carotene." [2] The isolation and structure of lycopene have been determined. [1]

Lycopene is relatively resistant to heat-induced geometrical isomerization in the processing of tomatoes. [4] Processed tomato products are a better source of lycopene than fresh tomatoes [6] and are more bioavailable as well. [7] In addition, human uptake of lycopene is greater from heat processed tomato juice vs unprocessed. [8] Raw tomatoes contain 3.1 mg lycopene (per 100 g of fruit) compared with tomato paste or sauce, which contains an average of 6.4 mg. [2]

PHARMACOLOGY: Factors affecting uptake and absorption of carotenoids have been reported. [9] Pharmacokinetic parameters of lycopene have been evaluated in mice, [10] rats, [11,12] monkeys, [11] and humans. [13,14,15,16,17,18,19,20,21]

Cooking releases desirable antioxidants from tomatoes. Absorption of lycopene, which is lipid soluble, is improved in the presence of oil or fat. [22] Lycopene's protective mechanisms include antioxidant activity, induction of cell-cell communication, and growth control. [18,23]

Lycopene's antioxidant actions are well documented. Its presence as a supplement in liquid form reduces lipid peroxidation in one report. It is also suggested that it may ameliorate the oxidative stress of cigarette smoke. [24] Another study reports that certain concentrations of lycopene (and other antioxidants) may protect against cognitive impairment. [25] In 19 subjects, lycopene supplementation decreased serum lipid peroxidation and low-density lipoprotein (LDL) oxidation, suggesting a decreased risk for coronary heart disease (CHD). [26] Lycopene demonstrated a protective effect against MI in the EURAMIC study, confirming its beneficial effects on the heart. [27] Carotenoid mixtures display synergistic activity against oxidative damage, most pronounced with the presence of both lycopene and lutein. [28] This combination was also found to have potent anticarcinogenic activity. [29]

Oxidative stress is recognized as a major contributor to increased cancer risk. Lycopene's ideal absorption from tomato products act as antioxidants and may also play important roles in cancer prevention. [30] It achieves high concentrations in testes, adrenal glands, and prostate. The intake of lycopene and decreased cancer risk association have been observed in prostate, pancreas, and stomach cancers. [31,32,33,34] Tocopherol exhibited synergistic inhibitory effects against 2 human prostate carcinoma cell proliferation lines. [35] Lycopene may also play a protective role in the early stages of cervical carcinogenesis as seen in a study. [36] Plasma levels of lycopene and other carotenoids were lower in women with cervical intraepithelial neoplasia and cervical cancer, suggesting protection with higher lycopene concentrations. [13]

Reports are available on the international symposium on lycopene and tomato products in disease prevention. [37,38] Reviews describing lycopene and disease prevention can also be referenced. [39,40,41,42]

Literature addressing beta-carotene's positive outcomes in skin problems (including cancer, pigment balance, and photodermatoses) is available [43,44,45,46] but lycopene may not share these effects because of its structural configuration. One report finds beta-carotene to be active in wound healing, where lycopene was inactive. [47]

TOXICOLOGY: No literature on lycopene toxicity was found.

SUMMARY: Lycopene is a carotenoid present mainly in tomatoes. It is an antioxidant and is being studied for its role in cancer prevention including prostate, pancreatic, and stomach cancers. Lycopene has synergistic effects in some cases when used in conjunction with other antioxidants. Processed tomato products are a better source of lycopene than the raw fruit.

PATIENT INFORMATION — Lycopene

Uses: Lycopene has antioxidant activity and may be used in cancer prevention.

Side Effects: No literature on toxicity was found.

Dosing: Lycopene administered as a pure compound has been studied in clinical trials at doses of 13 to 75 mg/day. [48,49,50,51,52]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LYCOPENE

LYSINE

DATE OF ISSUE: SEP 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): 2,6-diaminohexanoic acid, alpha-epsilon-diaminocaproic acid

COMMON NAME(S): Lysine

HISTORY: Lysine is an essential amino acid, "essential" in human nutrition, meaning the body cannot produce it, and therefore it must be taken in either by diet or by supplementation.[1] Lysine was first isolated from casein (a milk phosphoprotein) by Drechsel in 1889. [2]

CHEMISTRY: Lysine is a hydrolytic cleavage product of protein, cleaved either by digestion or by boiling with hydrochloric acid. [2] Many forms of lysine exist, including L-lysine dihydrochloride, L-lysine monohydrochloride, calcium lysinate, lysortine (L-lysine monoorotate), L-lysine succinate, and the lysine salt of aspirin, "lysine acetylsalicylate."[1,3,4,5,6] The chemical structure of all amino acids contain an amino group (-NH_2) and a carboxyl group (-COOH).[1]

PHARMACOLOGY: Amino acids are fundamental constituents of all proteins. They promote protein production, reduce catabolism, promote wound healing and act as buffers in extra- and intracellular fluids. [7]

Lysine improves calcium assimilation. However, most clinical data are available on its use in the treatment of herpes infection.

One report describes a relationship between lysine and herpes simplex virus (HSV). The amino acid arginine's composition is high in the HSV viral coding, thus, replication of the virus requires high consumption of arginine. Lysine appears to be an "antimetabolite," acting as an analog of arginine, competing for absorption and entrance into tissue cells. Lysine inhibits HSV replication by limiting arginine (by competing with it) during viral replication. Lysine prophylaxis was 100% effective in preventing herpetic labialis in patients suffering from frequent lesion occurrence. Treatment for recurrent aphthous ulcers (RAU; acute painful oral ulcers, "canker sores") was also evaluated in this study. Only 1 of 28 patients did not benefit from lysine therapy. Dosing was 500 mg lysine/day for prevention and 1000 mg every 6 hours upon development of prodrome in both treatments.[8]

Another report in the form of an epidemiological survey (subjective response questionnaire) was mailed out, and 1543 were completed and returned. Data showed 92% of patients with cold sores, 87% of those with canker sores and 81% with genital herpes stated lysine supplementation was effective. Twelve percent reported no effect of lysine against herpes attacks. Others reported shortened healing time and less severe symptoms with supplementation. [9] An earlier report in 45 patients taking 312 to 1200 mg lysine/day demonstrated beneficial effects from treatment in the form of accelerating herpes simplex infection recovery and suppressing recurrence. Tissue culture studies indicate that viral replication is suppressed as the lysine-to-arginine ratio increases. [10]

In contrast, at least 2 other studies report some failure of lysine in herpes treatment. Lysine 500 mg twice daily had no effect on 251 treated episodes of recurrent herpes simplex labialis in 119 patients.[11] Lysine HCl 750 mg/day, administered to 31 herpes simplex labialis or genitalis patients showed no reduction in number of episodes; however, the 1 g dose showed a 47% reduction.[12]

A case report exists concerning lysine supplementation for hyperargininemia in an 11-year-old girl. Lysine 250 mg/kg/day along with ornithine, produced a marked reduction of plasma ammonia and urinary orotic acid during a 6-month therapy period. [13]

Lysine acetylsalicylate has been used to treat rheumatoid arthritis and to detoxify heroin. [3,6]

TOXICOLOGY: In rats, effects of dietary lysine on toxicity of barbiturates and ethanol have been evaluated. An increase in onset of loss of righting reflex was observed.[14]

Because the average American consumes 6 to 10 g of lysine daily, prophylaxis of 500 to 1000 mg and treatment dose of 4000 mg/day are insignificant amounts comparatively speaking. Dosages such as these have proven to be safe and free of side effects. [8]

SUMMARY: Lysine is an essential amino acid, important as a building block for protein synthesis. Controversial reports exist as to whether lysine can be helpful or not in treating herpes infections including cold sores. Patients with kidney or liver disease should not take the supplement; otherwise lysine has been shown to be safe in dosages up to 4000 mg/day.

PATIENT INFORMATION — Lysine

Uses: Lysine has been studied for the prophylaxis and treatment of herpes infections and cold sores. It also improves calcium assimilation and may be helpful in the treatment of Bell's palsy. Lysine acetylsalicylate has been used to treat rheumatoid arthritis and to detoxify heroin.

Side Effects: Dosages up to 4000 mg/day have been proven to be safe and free of side effects. Lysine supplementation is contraindicated in patients with kidney or liver disease.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "L" MONOGRAPHS
    LYSINE

"M" MONOGRAPHS

MA HUANG

DATE OF ISSUE: MAR 2003

REPLACES MONOGRAPH DATED: NOV 1995

SCIENTIFIC NAME(S): *Ephedra sinica* Stapf., *E. intermedia* Schrenk et C.A. Meyer, or *E. equisetina* Bge. Family: Ephedraceae (ephedra)

COMMON NAME(S): Ephedra, ma huang, yellow horse, yellow astringent. Ephedra is the major component of supplements such as *Herbal Ecstasy*, *DietMax*, *Metabolife 356*, *Solaray*, *Xenadrine*, *Metabolean*, *Energel*, *Stacker 2*, *Black Beauty*, and *Yellow Jacket*. Note that many manufacturers have recently reformulated their products to remove Ephedra because of legal liability questions.

BOTANY: Ephedra species are low shrubby plants with small leaves on jointed, ribbed, green stems. They are dioecious (male and female flowers are usually found on separate plants). The 3 species that are sources of the drug are native to China, where the aboveground parts are collected in the fall and dried for drug use. The ephedras are gymnosperms and are most closely related to the conifers, although many aspects of their botany are different. [1,2] The root of *E. sinica* or *E. intermedia* is known as ma huang gen and is considered to be a distinct drug, used for its antisudorific properties. A chapter on ephedra has been published in the *Flora of China* project.[3]

HISTORY: Ma huang is one of the earliest and best known drugs of Chinese traditional medicine, mentioned in the *Shen Nong Ben Cao Jing*, one of the foundation books of Chinese medicine, about 100 AD. It was and still is used to induce perspiration and to treat the symptoms of bronchial asthma, colds, and influenza.

CHEMISTRY: Chemical investigations of ephedra in the early 20th century resulted in the isolation of the alkaloids ephedrine and pseudoephedrine, which were identified as the major pharmacologically active compounds in the aboveground portions of the plant. The ephedra alkaloids possess 2 adjacent chiral atoms, which can form 4 possible isomers for every planar structure;[4] however, the plant produces only 2 of the possible isomers. Synthetic ephedrine and pseudoephedrine are usually produced as a racemate. A total of 6 major alkaloids of this type are found in the 3 species known as ma huang; the major alkaloid of all species is ephedrine, with pseudoephedrine the next most abundant, and norephedrine, norpseudoephedrine, methylephedrine, and methylpseudoephedrine making up the balance. [5] The proportion of single alkaloids and total alkaloid content of the aboveground portions can vary widely, from 0.5% to 2.5%; the highest concentration of alkaloids is found in the fall. Biosynthesis of the ephedra alkaloids has been studied; ephedrine is formed from pyruvate and benzoic acid. [6,7] The supercritical fluid extraction of ephedrine from *E. sinica* has been studied using a mixture of carbon dioxide, diethylamine, and methanol. [8]

Because of the importance of ephedrine, a large number of analytical methods for ephedra alkaloids have been devised. Gas chromatography has been used [9] as well as chiral gas chromatography[10] and gas chromatography-mass spectrometry of both plant material[11] and urine specimens.[12] Numerous high performance liquid chromatography (HPLC) methods have been developed,[5,13,14,15,16] including analysis of urine samples[17] and a liquid chromatography-mass spectrometry method for dietary supplements.[18] Capillary electrophoresis and isotachophoresis also have been applied, with some methods using cyclodextrin as a matrix to confer resolution of optically isomeric alkaloids. [19,20,21,22,23] Carbon-13 nuclear magnetic resonance (NMR) also has been used to qualitatively and quantitatively analyze ephedra alkaloids.[24]

Several systematic studies of alkaloid content in commercial ephedra samples have been made. One study used capillary electrophoresis to analyze 22 samples from Taiwan herbal markets and found that *E. sinica* samples were generally higher in alkaloid content than *E. intermedia* (1.6% vs 1.2%) and that the relative amounts of specific alkaloids correlated well with the species studied. Root samples had no detectable alkaloids. [25] Because ephedrine can be used as a starting material for the synthesis of amphetamines, the profile of impurities was used to determine the origin of illicit amphetamine in Japan. [26] Another study examined 20 different supplements from the US market by HPLC and found that some products had no ephedra alkaloids, others had only ephedrine, suggesting use of synthetic material, while others were properly labeled and contained the specified amount of alkaloid. [27] American species of ephedra have been found to be devoid of, or to have very low amounts of, alkaloids. Thus, such species as *Ephedra nevadensis* (Mormon tea) should not be regarded as appropriate substitutes for ma huang. [28]

Other types of compounds also have been isolated from ma huang. Tetramethylpyrazine has been identified as a pharmacologically active constituent of stems, and analytical methods have been developed.[11,29] In the roots, which do not contain appreciable amounts of the ephedrine class of alkaloid, feruloylhistamine [30] and ephedradines A-D[31,32] were isolated. The flavonoid derivative ephedrannin A was also isolated from the root. [33] The polysaccharides ephedrans A-E have been isolated from ephedra stems.[34]

PHARMACOLOGY: Ephedrine is the main active principle of ephedra and has sympathomimetic activity, which accounts for its clinical use for bronchial asthma and low blood pressure. It is active when given orally, parenterally, or ophthalmically. It also is regarded as a CNS stimulant but is much weaker than amphetamine.

Experiments in animals have examined various activities of ephedrine and ephedra herb. Antitussive effects were found against sulfur dioxide-induced cough in mice, especially in combination with amygdalin.[35] Rats were trained to discriminate ephedrine stimulation from saline; this stimulus was generalized to amphetamine, cocaine, and caffeine, but the stimulant properties were not entirely identical. In this system, ephedrine was about one tenth as potent as amphetamine. [36] Ephedrine, its congeners, and crude ephedra herb have been shown to have activity in anti-inflammatory models in mice. [37,38] Passive cutaneous anaphylaxis in rats was blocked by oral administration of ephedrine; this effect was not caused by a direct effect on histamine release from mast cells. [39] A component of ephedra herb thought to be an anionic carbohydrate blocked the activation of classical and alternative complement pathways. [40] The growth of influenza virus was inhibited in tissue culture by an extract of ephedra herb, and tannins were identified as the likely active constituents. [41]

The 3 subtypes of beta-adrenergic receptor have different pharmacology; ephedrine and congeners are known to activate all 3 subtypes. The activation of the beta-3 subtype has been shown to be responsible for at least part of the thermogenesis observed on administration of ephedrine; blockade of the type 1 and 2 receptors with selective inhibitors still allows about half of the increase in energy expenditure in human subjects while entirely blocking the increase in heart rate and plasma glucose caused by ephedrine.[42] The pharmacokinetics of ephedra in humans have been studied, with ephedrine in crude herb requiring twice as long to reach the peak plasma concentration as pure ephedrine dosage forms.[43] Similarly, the combination of a single dose of ephedra and caffeine has been studied; ephedrine and pseudoephedrine had similar peak concentrations at 140 to 150 minutes, while caffeine blood levels peaked at 90 minutes. Heart rate was increased a maximum of 15 bpm over baseline. Overall results were similar to the individual compounds in pure form. [44]

While asthma treatment is one of the classical clinical uses for pure ephedrine, dietary supplement use and promotion of ephedra herb is concentrated on weight loss and increasing athletic performance.

Weight loss: For weight loss, a combination of ma huang with a caffeine-containing supplement such as guarana or cola nut is most frequently used. The origin of this combination can be traced to the empirical observation of a Danish physician that obese asthma patients treated with a combination of ephedrine, caffeine, and phenobarbital lost weight.[45] This so-called "Elsinore pill" became popular in Denmark for weight loss. Because of skin rashes attributed to phenobarbital, this component of the combination was removed without affecting weight loss.

Subsequent clinical trials have documented weight loss over various time periods using combinations of ephedrine and caffeine or ephedrine alone but found no statistically significant effect. A double-blind study for 3 months with ephedrine and limited diet, but no caffeine, found no effect for 75 and 150 mg/day ephedrine. [46] In a different trial, treatment with ephedrine for 3 months was shown to lead to higher oxygen consumption and thermogenesis and to reduced body weight. [47] An

increase of 3.6% in energy expenditure was observed in patients given 50 mg ephedrine 3 times/day for 1 day, but no increase in mechanical work was observed. [48]

The effect of an ephedrine- and caffeine-containing supplement on peak oxygen consumption was studied in 10 obese females. The combination increased oxygen consumption significantly.[49] Thirty-two obese adolescents given ephedrine and caffeine lost weight and body fat in a double-blind, placebo-controlled pilot study. [50] Another study of ma huang and guarana in 67 adults resulted in fat and weight loss over an 8-week period, although side effects in the treatment arm caused a substantial number of dropouts.[51] The same group conducted a larger 6-month trial in which herbal ephedra and caffeine promoted body weight and body fat reduction and improved blood lipids without adverse effects. [52]

Reviews have concluded that ephedrine and caffeine combinations, whether in pure form or in herbal supplements, can stimulate weight loss through enhanced thermogenesis.[45,53] A survey estimated the use of such products in 5 US states in 1998; ephedra was used by 1% of the total population. [54] Estimates of ephedra sales range as high as 2 to 3 billion doses per year, primarily for weight loss. [55]

Athletic performance: Supplements containing ephedra also have been promoted for increasing athletic performance. [56] While insignificant effects on performance have been noted for ephedra alone, combinations of ephedra and caffeine have been found to increase endurance in running and cycling experiments. [57,58] Ephedrine alkaloids are banned in amateur sports; thus, use of ephedra or other supplements containing ephedra alkaloids are grounds for disqualification.

Other: Polysaccharides named ephedrans A-E have been identified from *Ephedra distachya* herb and have hypoglycemic activity in mice.[34] The roots of Ephedra have yielded a variety of hypotensive compounds, including the flavonoid ephedrannin A, [33] feruloylhistamine,[30] and the spermine alkaloids ephedradines A-D.[31] These latter compounds have not been found in the aboveground parts of ephedra.

INTERACTIONS: The potential for drug-ephedra interactions has been profiled, noting that monoamine oxidase (MAO) inhibitors are contraindicated with ephedra.[59]

TOXICOLOGY: There is wide agreement that ephedrine and related ephedra alkaloids have a relatively narrow therapeutic index. The major area of concern is their effect on the cardiovascular system because ephedrine increases heart rate and elevates blood pressure. The pharmacokinetics and cardiovascular effects of ma huang were examined in normotensive adults. While ephedrine was well-absorbed after oral ephedra dosage, only 6 of 12 subjects experienced an increase in heart rate, while effects on blood pressure were inconsistent.[43] In another experiment with 8 normotensive subjects, the combination of 200 mg caffeine and 20 mg ephedrine found in ephedra increased systolic blood pressure a maximum of 14 mm Hg 90 minutes after a single dose, while heart rate peaked 6 hours after dosage at 15 bpm over baseline.[44] In obese women, a combination of ephedrine with caffeine had insignificant cardiovascular adverse effects at rest and during exercise. [60] A larger placebo-controlled trial found no significant adverse cardiovascular effects over 14 days in obese adults. [61]

While these clinical studies have found modest effects under controlled conditions, case reports and spontaneous adverse effect reports (AERs) to the FDA have been interpreted as harbingers of a more serious problem. One hundred forty AERs related to ephedra reported between 1997 and 1999. One third of the AERs were considered definitely or probably related to ephedra and another third possibly related. Of these 87 AERs, half reported cardiovascular symptoms, primarily hypertension, while tachycardia, stroke, and seizures were less frequent. Ten deaths and 13 events resulting in permanent disability were recorded. [62] Responses to this study pointed out that such AERs did not prove causation.[63,64] A review of AERs on ephedra from 1995 through 1997 found 37 serious cases including 16 strokes, 10 MIs, and 11 sudden deaths.[65] Again, these findings were controversial.[66,67] A detailed case report of stroke associated with ephedra use has been published.[68]

Other toxicological data on ephedra are less extensive. While ephedra extracts are cytotoxic to cultivated cells, the cytotoxicity is not primarily due to ephedrine. [69] N-nitrosamines of ephedrine and pseudoephedrine have been formed under physiological conditions. N-nitrosoephedrine has been shown to be a carcinogen. [70,71] Acute hepatotoxicity has been associated with use of ma huang; however, the authors of the case report admitted that contamination with other hepatotoxic herbs was the most likely explanation.[72] Numerous reports of toxicity in dogs accidentally ingesting ephedra/caffeine supplements have been collated. [73] The psychoactive aspects of ephedrine alkaloids in the context of drug abuse have been reviewed. [74]

Due in part to the fact that ephedra AERs constituted the largest single category of adverse events and that a number of them were fatal or severe, the FDA proposed rules limiting dosage and establishing warning labels for ephedra products in June 1997. [55] However, in July 1999, the US General Accounting Office issued a report challenging the FDA's basis for the proposed rules, and the FDA subsequently withdrew part of the proposal. [55] In 2000, the dietary supplement industry provided a comprehensive analysis of safety and appropriate dosing issues concluding that a daily dosage corresponding to 90 mg ephedrine was safe. [75] A government-commissioned study of ephedra by the RAND Corporation was begun in June 2002. [76] A chronology of the ephedra controversy from the FDA viewpoint is contained in Senate testimony.[77] A jury awarded more than $4 million to families of stroke and heart attack patients who had used *Metabolife 356*.[78] An industry group, the Ephedra Education Council, maintains an archive of many relevant documents. [79] Consumers and health professionals should exercise appropriate caution until definitive legislative or regulatory action resolves the status of ephedra.

SUMMARY: Ephedra herb is official in the *Pharmacopoeia of the People's Republic of China*, *JAPTA List: Japanese Drug Directory*, and the German pharmacopeia. It was monographed by the World Health Organization (vol.1) and by the German Commission E for treatment of bronchospasm and other respiratory diseases. Ephedrine and its salts were official in the *U.S. Pharmacopeia* from 1936 to 1955, and in the *National Formulary* from 1955 to date. Ma huang might be effective for bronchodilation in asthma and in combination with caffeine for weight loss. Current guidelines suggest limiting dosage of ephedrine to less than 90 mg/day. Medical supervision may be the most appropriate mode for safe administration of ma huang. Patients with hyperthyroidism, benign prostatic hyperplasia, glaucoma, diabetes mellitus, and seizures and women who are pregnant should exercise particular caution. Ma huang is contraindicated with MAO inhibitors.

PATIENT INFORMATION — Ma Huang

Uses: Ma huang may be effective for bronchodilation in asthma and is used in combination with caffeine for weight loss and to increase athletic performance. Its use is not recommended.

Interactions: Ma huang is contraindicated with MAO inhibitors.

Side Effects: Ephedra use has been linked to cardiovascular adverse effects, including hypertension, stroke, and MI. Patients with hyperthyroidism, benign prostatic hyperplasia, glaucoma, diabetes mellitus, and seizures and women who are pregnant should exercise particular caution.

Dosing: Current guidelines suggest limiting dosage of ephedrine to less than 90 mg/day. Medical supervision may be the most appropriate mode for safe administration of ma huang.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MA HUANG

MACA

DATE OF ISSUE: AUG 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Lepidium meyenii* Walp. Family: Brassicaceae (Mustards)

COMMON NAME(S): Peruvian ginseng, Maino, Ayuk willku, Ayak chichira

BOTANY: Maca is cultivated in a narrow, high-altitude zone of the Andes Mountains in Peru. The plant's frost tolerance allows it to grow at altitudes of 3500 to 4450 meters above sea level in the puna and suni ecosystems, where only alpine grasses and bitter potatoes can survive. [1] It and several related wild species are also found in the Bolivian Andes.[2] The plant grows from a stout, pear-shaped taproot and has a matlike, creeping system of stems. While traditionally cultivated as a vegetable crop, use for its medicinal properties has become more prominent in Peru. Maca is related to the common garden cress, *Lepidium sativum L*.

HISTORY: Maca was domesticated at least 2000 years ago and has been used commonly as a food by Peruvian peasants who live in high altitudes. It was considered to be a "famine food," but recent analyses have shown that the root is high in nutritional value, containing essential amino acids and important fatty acids. [3] The root can be dried and powdered, after which it is stored for several years without serious deterioration. Dried roots are cooked in water to make a sweet, aromatic porridge known as "mazamorra." According to Peruvian folk belief, maca enhances female fertility in both humans and livestock, countering the reduction in fertility seen in high altitudes.[4] However, maca is believed to have an antiaphrodisiac effect on males.[5]

CHEMISTRY: *Lepidium meyenii* has not been subjected to close chemical scrutiny. Johns reported the isolation of p-methoxybenzyl isothiocyanate from the plant, [6] although a positive alkaloid test has not been confirmed.

Other species of *Lepidium* have been analyzed more thoroughly; *L. sativum* has been found to contain many glucosinolates that have bactericidal, antiviral, and fungicidal activity in in vitro assays, as well as inhibiting tumorigenesis. [7,8] An alkaloid, lepidine, has been isolated from the seeds of *L. sativum*.[9] Evomonoside, a cardiac glycoside, has been isolated in substantial yield from the seeds of *L. apetalum*, a Korean species.[10] Several flavones and flavonoid glycosides have also been isolated from the genus *Lepidium*.[11]

PHARMACOLOGY: Aphrodisiac and antistress properties have also been claimed. The pharmacology of other *Lepidium* species is documented as the following: *L. capitatum* had anti-implantation activity in rats.[12,13] The ethanolic extract of the seeds of *L. sativum* was found to increase collagen deposition in a rat model of fracture healing.[14] *L. latifolium* was found to have diuretic action in rats.[15]

TOXICOLOGY: The presence of substantial amounts of a cardiac glycoside in the related species, *L. apetalum*,[10] is cause for concern. Cardioactive substances have also been detected in *L. sativum*.[16] However, the fact that dried maca roots have been consumed for many years would argue against a risk for cardiotoxicity. *L. virginicum* was inactive in a screen for genotoxicity.[17]

SUMMARY: Maca is promoted for a variety of fertility and adaptogenic uses. However, there is very little scientific information to support its medicinal use. Its long history as a food in the Andes suggests low potential for toxicity.

PATIENT INFORMATION— Maca

Uses: Maca has been used as an aphrodisiac, fertility aid, and to relieve stress.

Side Effects: There is little information on maca's long-term effects. Its long-time use as a food product suggests low potential for toxicity.

Dosing: Maca root is used at 3 to 5 g/day or as 900 mg of root extract; however, there are no published clinical trials to justify these doses.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MACA

MACE

DATE OF ISSUE: SEP 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): The dried aril of *Myristica fragrans*Houtt. Family: Myristicaceae

COMMON NAME(S): Mace, muscade(French), seed cover of nutmeg

BOTANY: Mace and nutmeg are two slightly different flavored spices both originating from the fruit of the nutmeg tree, *Myristica fragrans*. The fruit is a drupe which splits open when mature, exposing the nutmeg (stony endocarp or seed) surrounded by a red, slightly fleshy network (aril). Once the aril is peeled off and dried, it is referred to as mace.[1] Botanical mace should not be confused with the same word which also can describe a weapon of offense (iron or steel) capable of breaking through armor or a relatively modern riot control synthetic compound used as an irritating and debilitating spray or gas. [1,2]

The nutmeg tree is a densely foliazed evergreen tea commonly grown in Grenada (West Indies), Indonesia, Ceylon and the Moluccas in the East Indian Archipelago. [2] The trees first produce fruit in about 7 years and then yield approximately 10 pounds of dried shelled nutmeg and 1 $^{1}/_{2}$ pounds of dried mace per tree.[2] At low concentrations, both nutmeg and mace possess a sweet, warm and highly spicy flavor with mace being slightly "stronger." Ground nutmeg is tan in color, while mace has an orange hue.

HISTORY: Both nutmeg and mace have been used in Indian and Indonesian cooking and in folk medicine. Historical medicinal uses of mace range from the treatment of diarrhea to mouth sores, insomnia and rheumatism.

CHEMISTRY: Numegs, depending on origin and condition, yield, on steam distillation, 5-15% of essential oil. [2] The essential oils of nutmeg and mace are very similar in chemical composition and aroma, with wide color difference (brilliant orange to pale yellow). Both nutmeg and mace contain about 4% of a highly toxic substance called myristicin (methoxysafrole).[2] Other compounds isolated include safrole, elemicin, methoxyeugenol, (±) camphene, ß-terpineol, a- and ß-pinene, myrcene, (±)-limonene and sabinene.[3] Recently, two resorcinols, malabaricone B and malabaricone C have been isolated from mace by Orabi et al. [4] New lignans have been isolated by Kuo[5] and Zacchino et al.[6]

PHARMACOLOGY: A number of interesting articles have appeared on potential anti-cancer properties (chemo-preventor effects of chemically induced carcinogenesis) of mace, including: transmammary modulation of xenobiotic metabolizing enzymes in the liver of mouse pups by mace; [7] effect of nutmeg essential oils on activation and detoxification of xenobiotic compounds (chemical carcinogens and mutagens); [8] potential anticarcinogenic role of *Myristica* volatile oils;[9] modulatory effects of mace on hepatic detoxification;[10] reduction of induced skin papilloma incidence via diet containing 1% mace; [11] reduction of induced carcinogenesis in uterine cervix in mice by mace;[12] and increased level of acid-soluble sulfhydryl (SH) groups in the liver of young mice (chemoprotective) by mace. [13]

A number of miscellaneous pharmacological studies show strong antifungal and antibacterial properties of two antimicrobial resorcinols (malabaricone B and C from mace;[4] anti-inflammatory properties of myristicin from mace;[14] antimicrobial action of mace against oral bacteria; [15] and a larvicidal principle in mace.[16]

TOXICOLOGY: The majority of the literature of the last decade continues to verify the possibility of acute intoxication possible with overdoses of nutmeg itself [17] and of contact or systemic contact-type dermatitis to nutmeg as a spice.[18] Very few, if any, articles appear in the recent literature specifically dealing with mace intoxication.

SUMMARY: Mace continues to be used safely in small amounts as a spice flavoring for pound cakes, doughnuts, fish sauces and meat stews. [2] Mace has been shown to possess potential anti-cancer or chemoprotective effects in several animal models. These have been stimulated, no doubt, by recent ethnobotanical and ethnopharmacological studies aimed at verifying human historical medical uses which range from the use of both nutmeg and mace for the treatment of diarrhea, mouth sores, insomnia and rheumatism.[19] Some of these uses seem to have been verified in the studies mentioned above. However, recent human clinical supporting data are much needed. Attention should be paid to high doses of mace, since it may well produce similar effects known as nutmeg during acute poisoning (eg, hallucinations, palpitations, feelings of impending doom) [17] and potential allergy.[18]

PATIENT INFORMATION — Mace

Uses: Mace has been used as a flavoring and folk medicine for a range of ills, such as diarrhea, insomnia, and rheumatism. Studies show anticancer, antifungal, antibacterial, anti-inflammatory, and larvicidal properties.

Side Effects: Large doses may produce acute intoxication. It may cause dermatitis in sensitive individuals.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MACE

MAGGOTS

DATE OF ISSUE: AUG 1997

REPLACES MONOGRAPH DATED: JUN 1993

SCIENTIFIC NAME(S): *Phaenicia sericata*; *Lucilia caesar*, *Pharmia regina*

COMMON NAME(S): Maggot, fly larva, grub, botfly maggot, "viable antiseptic," "living antiseptic," "surgical maggot"

BIOLOGY: Maggots are the larvae of various flies. The species *Phaenicia sericata* (green blow fly) has been used successfully in maggot therapy for many decades.[1] The life cycle of those used in medicine begins with the laying of eggs by the adult female on meat or other substrate suitable for the larvae to feed on. The eggs hatch within one day, and the larvae then proceed to feed and grow. After 5 to 7 days, they become sessile, non-feeding pupae. After about 2 weeks of pupation, the adults emerge and the females begin laying eggs about five days later. [2]

Larvae-rearing in the clinical setting can be a simple, low-cost procedure if done correctly. [3] A report on species *Lucilia sericata* (Meigen) evaluates a sterile mixture of pureed liver and agar as growth medium. This method was not only inexpensive but provided longer storage capacity and no progressive decomposition or odor problems.[4]

HISTORY: The effects of maggots on wounds have been known since the 1500s when Ambroise Pare described their beneficial actions. It was observed that maggots cleaned untreated wounds, removing necrotic tissue without apparent harm to living tissues. Many military surgeons noticed that soldiers' wounds that became maggot-infested did better than non-infested wounds.[1] The first scientific paper on the surgical use of maggots appeared in 1931, and there was significant interest in the technique during the 1930s and early 1940s. Maggot debridement therapy (MDT) was routinely performed in over 300 hospitals during this time. [1] The first civilian use, based on observations during World War I, was in treating four children with osteomyelitis who did not respond to other available treatments. Subsequent occurrence of tetanus in other cases led to the development of bacteriologically sterile maggots. Early uses for maggot therapy included abscesses, burns, cellulitis, gangrene and ulcers.[2]

Around the mid-'40s, use of maggots declined rapidly with the development of antibiotic drugs. Maggot therapy was occasionally employed when all other therapies failed. For example, a 1976 report described use of maggots to treat subacute mastoiditis. [5] In addition, maggots were used to treat women undergoing low-voltage X-ray therapy for cervical carcinoma. The organisms were used to prevent radiation-induced sloughing of the tissues over the sacrum, buttocks and lower abdomen. [6] Actual clinical use of maggots preceded the literature; there was a thriving industry for commercial preparations of maggots at least 10 years before the 1931 report. [2]

PHARMACOLOGY: The mechanisms by which maggots promote wound healing have not been proven conclusively. However, a variety of mechanisms have been suggested. The exudate produced in response to the maggots physically washes bacteria out of the wound. The crawling larvae mechanically stimulate viable tissues to rapidly produce granulation tissue. They also enzymatically liquefy necrotic tissue. Bacteria are destroyed within the alimentary tracts of the larvae, which also use necrotic tissue as food. Maggots may produce antibacterial agents released in their secretions. They also increase the alkalinity of the wound, promoting healthy granulation. Substances proposed as beneficial secretions of maggots include allantoin, ammonium ions and calcium carbonate. [5]

The most common use of maggots in surgery has been to prevent bone destruction, deformities and other effects of recalcitrant osteomyelitis in which topical wounds heal poorly. Treatment begins with debridement of the affected area. The wound is then left unsutured for about 2 days, after which, 200 to 1000 maggots are applied to the wound. The maggots are contained by a dressing or cage. They are removed in 3 to 5 days to prevent pupation in the wound, and fresh maggots are applied as needed. Application of maggots is followed by rapid formation of a serosanguineous exudate. Healing occurs within 6 to 7 weeks in children and may take somewhat longer in adults.[2]

A 1986 report described the use of maggots to treat two patients with severe skin infections. One patient had a large, necrotic, foul-smelling decubitus ulcer of the perianal and presacral areas. The second was an insulin-dependent diabetic with ketoacidosis and a right scrotal ulcer. Excellent wound healing was achieved in both patients although the second patient subsequently died of general debility. [5] Maggot therapy has also been performed effectively for venous stasis ulcers, [7] pressure ulcers in spinal cord injury patients[8] and wound debridement.[9,10,11] A plantar foot ulcer in one patient existed for several years yet resolved after about 13 weeks of MDT.[10] Some patients with severe tissue destruction may also be receiving antibiotics along with MDT. A report evaluates this combination. Larvae survival was decreased when very high doses of gentamicin and cefazolin were administered. Antibiotics showing no change in survival rate included ampicillin, ceftizoxime, clindamycin, mezlocillin and vancomycin.[12]

Analysis of maggots found in decomposing bodies can provide information on the time of death, as well as on the presence of specific drugs in the bodies. [13] Maggots can also provide clues about crime location and circumstances. The study of maggots (and other insects) used in this way is termed "forensic entomology." [1]

TOXICOLOGY: Surgical maggots in themselves do not appear harmful to living tissues although it should be noted that maggots of screwworms can cause serious tissue damage. The surgical organisms, however, produce intense pruritus. Most patients adapt to this, but some require mild sedation. [5]

Non-surgical maggots are commonly used as fishing lures. At least one report has described delayed-onset asthma in an angler who used *Calliphora* (blue bottle) larvae for bait. The patient was found to have circulating IgG antibody to a larval extract, and symptoms suggestive of immune complex disease subsequently developed.[14] It has been suggested that dyes used to enhance the effectiveness of maggots as fishing lures can induce bladder cancer. [15] A case-control study of more than 1800 subjects found no evidence of an association between the dyes and bladder cancer; however, the number of subjects who used dyed maggots in fishing was small so that an actual association may have escaped detection.[16]

Maggots can transmit parasitic diseases resulting in severe destruction of tissues of the ears, nose and throat. This problem is common in India, where it occurs most frequently from September to November.[17] This larval invasion has also been reported in the eye. One case report details the invasion of the ocular orbit of a man by maggots. This infestation was treated successfully by classical wound-cleaning therapy. [18] Another case reports *cuterebra larva* in the conjunctiva of a boy suffering from decreased vision and subretinal hemorrhages. Successful removal was performed after positive identification of this offending agent by light microscopy. [19] A third case of ophthalmic invasion by larva is reported, this time with successful removal by photocoagulation with an argon green laser resulting in good visual recovery.[20]

SUMMARY: Maggots have long been known to promote the healing of wounds without generally causing harm to living tissues. The use of surgical maggots experienced a certain popularity among surgeons during the 1930s and 1940s, but this waned with the development of antibiotic drugs. Nevertheless, maggots have been used successfully in recent years when other methods of treatment failed. Examples of maggot therapy include its use in bone destruction/infection and poorly healing wound debridement, including bedsores and other ulcers. Their medical use requires close supervision to ensure that secondary infections or other invasive complications do not arise. Other uses of maggots include "forensic entomology." Surgical maggots may not be harmful to living tissues but may cause itching. Unwanted larval invasion has occurred in the eyes, ears, nose and throat.

PATIENT INFORMATION — Maggots

Uses: Maggots have been used to promote wound healing and also to treat abscesses, burns, cellulitis, gangrene and ulcers. The most common use of maggots in surgery has been to prevent bone destruction, deformities and other effects of recalcitrant osteomyelitis.

Side Effects: Surgical maggots do not appear harmful to living tissues but produce intense pruritus. Maggots can transmit parasitic disease, and larval ocular

invasion has occurred.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MAGGOTS

MAITAKE

DATE OF ISSUE: JUNE 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Grifola frondosa* (polyporaceae)

COMMON NAME(S): Maitake, "king of mushrooms," " dancing mushroom," "monkey's bench," "shelf fungi"

BOTANY: The maitake mushroom is from northeastern Japan. It grows in clusters at the foot of oak trees and can reach 20 inches in base diameter. One bunch can weigh up to 100 lbs. Maitake has no cap but has a rippling, flowery appearance, resembling "dancing butterflies" (hence, one of its common names "dancing mushroom").[1]

HISTORY: In China and Japan, maitake mushrooms have been consumed for 3000 years. The maitake is the most valued because of its "near-miraculous" properties. Maitake's scientific name, *Grifola frondosa*, is derived from an Italian mushroom name, referring to a mythological beast, half lion and half eagle. Years ago in Japan, the maitake had monetary value and was worth its weight in silver. This mushroom was offered to Shogun, the national leader, by local lords. In the late 1980s, Japanese scientists identified the maitake to be more potent than lentinan, shiitake, suehirotake and kawaratake mushrooms, all used in traditional oriental medicine for immune function enhancement. It was found that maitake also possesses this quality.

CHEMISTRY: The polysaccharide beta-glucan is present in most of the mushrooms in the polyporaceae family (eg, reishi mushroom) and has been shown to possess anti-tumor activity.[1] The "D fraction" of beta-glucan appears to be the most active and potent form of the polysaccharide, which is the protein-bound extract developed in Japan.[2] Both structure-functional relationship[3] and fractionation by anion exchange chromatography of beta-glucan[4] have been reported. Neutral and acidic polysaccharides have been extracted from maitake[5] and their structure determined.[6] Two different glycan conformations have been obtained from the plant.[7] The beta-1,3-glycan, grifolan's conformation, has been elucidated using magnetic resonance spectroscopy.[8] Ascorbic acid analogs and glycoside studies have been reported.[9] In addition, a lectin from maitake has been isolated and characterized.[10]

Structural characterization of maitake extract constituents[11] and carbon-13 nuclear magnetic resonance spectral analysis of the fruit body's constituents[12] also have been evaluated.

PHARMACOLOGY: Immunostimulant activity is characteristic of many of the medicinal mushrooms, including shiitake, enokitake or kawaratake. Maitake's polysaccharide may be slightly different from beta-glucans found in these. Maitake exerts its effects by activation of natural killer cells, cytotoxic T-cells, interleukin-1 and superoxide anions, all of which aid in anti-cancer activity.[13] It has also been determined that the large molecular weight of the polysaccharide molecule and certain branch structure configurations of this molecule are necessary for its anti-tumor effect or immunological enhancement.[14,15,16]

The following list is a representative summary of information available on maitake's anti-cancer effects. Maitake extract has been studied in *Escherichia coli*;[17] it has activated macrophages, enhancing cytokine production in vivo;[18] maitake has potentiated anti-tumor activity in mice.[13] Also in mice, maitake has enhanced nitric oxide synthesis of peritoneal macrophages,[19] enhanced antigen-specific antibody response[20] and has exhibited marked inhibitory activity against induced sarcoma when administered intraperitoneally but not orally.[21] At least one report is available on anti-tumor actions of orally administered maitake extract in mice.[22] Another report finds dose-dependent anti-tumor activity in mice also dependent on injection routes and timing.[23] Biological response modification affected anti-tumor action in another report.[24] Some pharmacokinetic parameters of beta-D-glucan have been evaluated in mice.[25]

Animal studies indicate that maitake has a role in treatment of metastatic cancer. Metastasis was prevented in 91.3% of mice injected with cancer cells, then given D-fraction injections (1 mg/kg), compared with control mice experiencing no inhibition.[26]

There is a small number of clinical trials investigating maitake's effects in cancer therapy. Some were unpublished, while others were not blinded or placebo controlled. Additional controlled studies are needed. Some of the available studies are summarized here. In a 165-patient study, results suggested that quality of life indicators had improved, including cancer symptoms (eg, nausea, hair loss) and pain reduction.[27] Previous cancers not identified that were improved by maitake in clinical cases include liver, lung, breast, brain and prostate.[1]

A few animal reports on maitake's effects on diabetes, hypertension and cholesterol are available. Upon oral adminstration of maitake powdered fruit body to genetically diabetic mice, blood glucose reduction was observed compared with control groups.[28] Maitake may control blood glucose levels by possible reduction of insulin resistance and enhancement of insulin sensitivity.[1]

Hypertensive rats given 5% maitake mushroom powder had a reduction in blood pressure.[29,30] Similar pressure-lowering activity was seen in another study performed in rats, where maitake extract lowered blood pressure from 200 to 115 mmHg in 4 hours.[31] In an unpublished human trial, 11 patients with documented essential hypertension took 500 mg of maitake mushroom caplets twice daily. A mean decrease in diastolic blood pressure of approximately 8 mmHg and a mean decrease in systolic blood pressure of about 14 mmHg were reported.[32]

Maitake had the ability to alter lipid metabolism by inhibiting both the accumulation of liver lipids and elevation of serum lipids in hyperlipidemic rats.[33] Similar results were seen in rats fed a high cholesterol diet.[34] Total cholesterol and VLDL-cholesterol decreased in rats given powdered mushroom preparation in another report.[29]

At least two studies are available concerning maitake's anti-obesity activity. After 18 weeks, overweight rats fed unheated maitake powder lost weight compared with controls.[35] In an observatory trial, 30 patients lost between 7 and 26 pounds from administration of 20 to 500 mg tablets of maitake powder per day for 2 months.[36]

TOXICOLOGY: Little or no information regarding maitake toxicity is available. Most studies report no side effects.[1] Because potential toxicity exists from mistaken mushroom identity, use caution when obtaining this particular natural product. (For more information, see the Mushroom Poisoning Decision Chart monograph).

SUMMARY: Mushrooms have been consumed in Asian countries for thousands of years. Maitake has recently been found to possess anti-cancer qualities because of the polysaccharide beta-glucan. The mushroom not only demonstrates immunostimulant properties but has also been tested in diabetes, hypertension, cholesterol and HIV therapies. Little is known about the plant's toxicity. More research is needed to fully explore and understand the potential of this "king of mushrooms."

PATIENT INFORMATION — Maitake

Uses: Maitake has been used for cancer, diabetes, high blood pressure, cholesterol and obesity.

Side Effects: Most studies report no side effects.

Dosing: Maitake usually is taken in doses of 3 to 7 g/day; however, there are no clinical studies to substantiate the efficacy or safety of this dose.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MAITAKE

MANUKA OIL

DATE OF ISSUE: MAR 2004

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Leptospermum scoparium* J.R. Forst. et G. Forst.[1] Family: Myrtaceae[1]

COMMON NAME(S): Red manuka, tea tree, manuka oil [1,2]

BOTANY: *L. scoparium* is the only *Leptospermum* species native to New Zealand. Its size ranges from a creeping plant to a small tree (of 8 m in height) and it is widely distributed in various climatic and altitudinal zones in New Zealand. The physical characteristics, such as flower and leaf color, leaf size and shape, branching habit, and foliage density vary considerably among populations. [1,3,4]

HISTORY: Early New Zealand records indicate that the plant's bark, leaves, sap, and seed capsules were used in beverages and medicinal preparations. [4] The plant was valued for its medicinal properties and wood by the indigenous Maori people; the wood was utilized for gardening tools, fishing, housing structures, and weapons.[1,2]

Captain James Cook used the leaves of the plant as a tea to combat scurvy during long explorations of the southern hemisphere; early European settlers of New Zealand adopted Captain Cook's use of the plant as a tea.[1]

Commercial development of the essential oils has led to a range of OTC products marketed in New Zealand and exported to European and Asian markets. These products are used for topical treatment of various conditions including the following: Fungal and bacterial skin infections; inflammation from sunburn, insect bites, or joint pain; eczema or psoriasis. The oils also are used in perfumes and soaps. [1]

CHEMISTRY: The *L. scoparium* populations of New Zealand are highly variable in oil chemical composition and activity. [5,6] Standardized steam distillation and gas chromatography-mass spectrometry of the essential oils of 15 New Zealand *L. scoparium* populations identified the following in various quantities per species: a-pinene, ß-pinene, myrcene, ?-cymene, 1,8-cineole, linalol, methylcinnamate, a-farnesine, isoleptospermone, leptospermone, sesquiterpenes such as cadina-3,5-diene and d-amorphene, and triketones. [3,4,5]

Triterpenoids and flavonoids (including methylated and methoxylated flavonoids such as 5,7-dimethoxyflavone, 5-hydroxy-7-methoxy-6-methylflavone, and 5-hydroxy-7-methoxy-6,8-dimethylflavan-3-one) have been identified in a dichloromethane extract of *L. scoparium*.[7,8] Oligosaccharide components include maltose (the major component), isomaltose (or maltulose), kojibiose, turanose (or gentiobiose), and nigerose. [9]

The average content of total flavonoids in New Zealand manuka (*L. scoparium*) honey was 3.06 mg/100 g honey; the main flavonoids consisted of quercetin, isorhamnetin, chrysin, and luteolin.[10]

PHARMACOLOGY: The antimicrobial activity of manuka oil against 10 microorganisms was determined by both 2-fold dilution method and agar plate 2-fold dilution method. Manuka oil has selective antibacterial activity against gram positive organisms, [11] such as *Staphylococcus aureus* and *Micrococcus luteus*. Enhanced antibacterial activity against the *Staphylococcus* was higher when manuka oil ointment was used in combination with other drugs (ie, gentamicin sulfate, clotrimazol and hydrocortisone acetate, diphenhydramine HCl, hydrocortisone acetate). [12] Manuka oil has little to no activity against gram negative organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus vulgaris*.[11,12,13] A ketonic fraction of *L. scoparium* showed a synergistic effect with bacitracin, cefadroxil, cephradin, and meropenem but an antagonist effect with ofloxacin, enoxacin, and sparfloxacin. [13]

Some studies document the activity of *L. scoparium* against fungi and yeast;[11,13] however, there are limited data to support these claims for *L. scoparium* as compared with other species of Myrtaceae (eg, kanuka or *Kunzea ericoides*).[14]

The pharmacological action of manuka oil for treating diarrhea, colds, and inflammation was studied on a field-stimulated guinea pig ileum. Manuka oil induced a spasmolytic effect;[14,15] the mechanism of action is likely to be the result of a postsynaptic mechanism and associated with cAMP. [15]

L. scoparium contains a lipophilic flavonoid that specifically interacts with benzodiazepine receptors in the GABA-A receptor-chloride channel complex. A sedating and potentially anxiolytic effect was recorded in a locomotion study with rats. [16,17]

TOXICOLOGY: There are limited clinical toxicological data on manuka oil in the scientific literature. Anecdotal information from OTC use of topical manuka oil products suggests good potential for its future use as an antimicrobial agent. [1] Avoid use during pregnancy because of spasmolytic activity.[14,15]

SUMMARY: Historically, the plant's bark, leaves, sap, and seed capsules were used in beverages and medicinal preparations. [4] The wood was utilized for gardening tools, fishing, housing structures, and weapons. [1,2] Manuka oil has selective antibacterial activity against Gram-positive organisms, [12] particularly *S. aureus*.

PATIENT INFORMATION — Manuka Oil

Uses: Manuka oil has selective antibacterial activity against Gram-positive organisms, [12] particularly *S. aureus*.

Side Effects: Avoid use during pregnancy because of spasmolytic activity. [14,15]

Drug Interactions: There is potential synergistic effect with bacitracin, cefadroxil, cephradin, and meropenem but an antagonist effect with ofloxacin, enoxacin, and sparfloxacin.[13]

Disease-State Concerns: *L. scoparium* contains a lipophilic flavonoid that specifically interacts with benzodiazepine receptors (GABA-A receptor-chloride channel complex).[16,17]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MANUKA OIL

MARIJUANA

DATE OF ISSUE: JUN 1997

REPLACES MONOGRAPH DATED: AUG 1990

SCIENTIFIC NAME(S): *Cannabis sativa* More than a dozen other species names have been used to describe marijuana. Family: Cannabaceae

COMMON NAME(S): A variety of common names have been attributed to the plant. There are, however, specific terms for the various plant parts and extracts. These include: anascha and kif(resinous material and flowering tops mixed with the leaves); banji, hemp, cannabis, shesha, dimba, dagga, suma, vingory and machona (entire plant); bhang and sawi (dried mature leaves); charas (resinous material); ganga(flowering tops); hashish and esrar (resinous material with flowering tops); and marijuana or marihuana (leaves and flowering tops). Names vary with local customs. [1]

BOTANY: More than 100 species of cannabis grow wild throughout most temperate climates, although several species have adapted to harsher climactic conditions. Cannabis is a leafy annual, some species of which attain heights of more than 10 feet.

The stalk may grow 3 to 4 inches thick, is square and hollow and has ridges running along its length. Each leaf has 5 to 11 leaflets radiating from the top of the stalk. These are soft-textured, 7 to 10 inches long, narrow and lance-shaped with regular dentation like the sawblade. The plant is dioecious showing male or female flowers. The female plants have a heavy foliage, while the male plants are sparse. The resin mixture is found in the glandular hairs of the leaflets and floral bracts and is called hashish. Hashish is made up of numerous tetrahydrocannabinol compounds. Cannabis is cultivated worldwide for fiber, seed oil and hashish. The controversy over legitimate and illegal use of cannabis persists. [2,3]

HISTORY: The use of cannabis dates back more than 4,000 years. It has been used for the treatment of catarrh, leprosy, fever, dandruff, hemorrhoids, obesity, asthma, urinary tract infections, loss of appetite, inflammatory conditions and cough. It has been used as a source of fiber for ropes and clothing. The plant's sedative effects were recognized by the ancient Chinese, but the widespread use of the plant for its psychoactive effects most likely began only in the past century. [2,4]

The history and details of the health hazards of cannabis have been reviewed. [4]

CHEMISTRY: More than 420 different compounds have been isolated from cannabis and reported in the chemical literature. [5] The most commonly described compounds are the cannabinoids [delta-9-tetrahydrocannabinol (THC), cannabidiol, and numerous related compounds]. In addition, marijuana contains alkaloids, steroidal compounds and mixtures of volatile components. [5]

Feruloyltyramine, a new amide compound, and p-coumaroyltyramine have recently been identified in cannabis seeds. [6] From the fruits, three new acyclic bis-phenylpropane lignan amides have additionally been isolated. [7]

The concentration of THC varies in different parts of the plant, being higher in the bracts, flowers and leaves and lower in the stems, seeds and roots. THC concentration varies from 0.1% in Kansas hemp to 4% or more in Jamaican or Vietnamese specimens. [8]

Analysis of dried cannabis samples from 1896 to 1905, reported the presence of cannabinol. [9] Additional reports on illicit cannabis samples from Great Britain, Northern Ireland and Denmark exist, evaluating THC content, cannabinoid content and locational differences between regions. [10,11] Cannabinoids in hemp (cultivated for fiber production) have also been reported. [12] Analysis of cannabis includes methods such as gas chromatography (GC), high-performance liquid chromatography (HPLC), random amplification of polymorphic DNA (RAPD) and thin layer chromatography (TLC). These methods are of use in sample differentiation, forensic analysis and other applications. [13,14,15,16] Radioimmunoassay of hair for marijuana presence in body systems has also been performed. [17]

PHARMACOLOGY: The pharmacology of whole marijuana and many of its individual compounds has been investigated in detail over the past decade. THC appears to contribute most significantly to the pharmacologic effects observed. Cannabinol may potentially contribute to the psychoactivity of the plant. This compound is a degradation product of THC and is not found in the fresh plant. Marijuana exerts its activity following inhalation of the smoke or oral ingestion. When inhaled, THC is absorbed rapidly. The systemic bioavailability of THC following smoking is approximately 18% but higher in heavy users and lower in light users.

THC is distributed rapidly throughout the body, in particular to tissues with high lipid contents. Approximately 80% to 90% of an IV dose of THC is excreted in urine and the remainder excreted in the feces via the bile. [5]

Cannabinoid metabolites remain detectable in urine for more than 10 days after a single use and for more than 20 days after chronic use. A French report on detection, evaluating newborn infants of addicted mothers, suggests not only urine testing of the infant to detect drug exposure, but to also test meconium and hair as well. Testing all three parameters increases sensitivity of analysis for parenteral drug exposure detection. [18]

Marijuana's effects can be categorized as follows:

Cardiovascular effects: Ingestion or inhalation of marijuana often results in tachycardia (especially supraventricular). ECG changes are not observed regularly in healthy young adults. [19] The drug may reduce exercise tolerance in anginal patients. Although marijuana may raise blood pressure, there is no evidence that the drug may cause permanent deleterious effects on the normal cardiovascular system. [20]

Pulmonary effects: Bronchial and pulmonary irritation are well-documented following smoking of marijuana. Although short-term inhalation has been found to increase bronchodilation and to reduce bronchospasm in asthmatics, long-term administration impairs lung function. Chronic use may result in constrictive lung disease such as interstitial fibrosis. In one study comparing the adverse effects of marijuana and tobacco, smoking less than one marijuana cigarette a day diminished vital capacity as much as smoking 16 tobacco cigarettes. [21] A later report also evaluating marijuana and tobacco smoke, finds that the gas-phase cytotoxins that are present may have no cytotoxic potential when inhaled by humans. [22]

Various types of marijuana may contain up to 50% more polyaromatic hydrocarbons in its smoke than tobacco does, high levels of which are associated with susceptibility to bronchial carcinoma. Marijuana appears to be frequently contaminated with aspergillus mold. In one study, 11 of 12 samples tested were contaminated. Spores of aspergillus pass readily through marijuana cigarettes into smoke, [23] and can result in fungal sensitization. [24] This is important in light of the use of marijuana by immunocompromised patients. Paraquat (a herbicide sprayed to control marijuana growth) toxicity was identified several years ago, but does not appear to be a clinically important problem. [25]

Neoplastic effects: Mouse skin painted with marijuana smoke particles produced metaplasia of the sebaceous glands. In another study, tobacco tar applied to the skin of mice was more carcinogenic than marijuana tar. Bronchial biopsies from humans have identified atypical cells, basal cell hyperplasia and squamous cell metaplasia to the greatest degree in subjects who used both marijuana and tobacco. [19]

Psychomotor/CNS effects: Marijuana intoxication impairs reaction time, motor coordination and visual perception. Marijuana can produce panic reactions, "flashbacks" and other emotional disturbances for which children and adolescents appear to be at highest risk. Distortion of time and distance and visual and auditory hallucinations have been reported. [1] Marijuana's high potential for abuse explains its classification as a schedule ? drug under the jurisdiction of the Controlled Substances Act. [26] Humans and other species prefer higher doses (over lower doses) with many drugs of abuse. Subjects choose high-potency marijuana (1.95% THC) more than low-potency (0.63% THC), linking the drug's abuse liability to the content. [27] "Drug liking" and higher THC dose choice in marijuana cigarettes over placebo has similarly been reported. [28]

A structural relationship has been identified between cannabidiol and phenytoin, suggesting that cannabidiol meets the steriochemical requirements suggested for anticonvulsant drug action.[29] At least one report suggests that marijuana smoking can assist in the control of epileptic seizures; [30] however, marijuana use has also been shown to exacerbate grand mal convulsions.[31] THC has induced catalepsy (abnormal maintenance of posture associated with mental state) in mice, but cannabis oil and related cannabinoids have not. [32]

Endocrine effects: Long-term use of marijuana in females may cause abnormal menstruation, including anovulatory cycles. Fetal damage has been reported in animals and appears to occur in humans. THC mediates the secretion of pituitary gonadotropins. In ovariectomized rats, injected THC in relatively low doses suppressed the release of leuteinizing hormone by up to 68%. [33] In males, conflicting data have been reported regarding the lowering of testosterone levels. Although reduced sperm counts have been reported in controlled trials, these are probably less important than the development of sperm structural abnormalities and motility changes induced by marijuana.

Ocular effects: Increased conjunctival vascular congestion is a common feature of marijuana use. Marijuana and THC have been investigated for the reduction of intraocular pressure in glaucoma. Although some studies indicate that the drug is effective, it is not clear whether treatment preserves visual function. [32]

Antiemetic effects: Considerable attention has been given to the evaluation of THC as an antiemetic agent. THC administered as oral capsules appears to be at least as effective as prochlorperazine but may have more CNS side effects. THC is effective in patients refractory to other agents and the drug appears to be particularly useful against the effects of high-dose methotrexate, BCNU (carmustine) or radiotherapy. Only nine cases of serious adverse effects caused by THC therapy were reported in 1565 patients who received THC treatment. These have ranged from agitation and panic to seizure and tachycardia. One analog, nabilone (*Cesamet*) has been found to be effective but may be difficult to use clinically because of the potential for accumulation. [8] Several publications in the popular press have shown that there is a continued conflict between marijuana's schedule ? status vs the rights of physicians to prescribe it for medical purposes.

Miscellaneous effects: Marijuana has been associated with xerostomia, nausea and vomiting. The cannabinoids are highly allergenic when evaluated in the guinea pig.[35] Some fractions of marijuana may have trypanocidal effects,[36] and immune system effects.[37]

SUMMARY: Marijuana has been used in traditional medicine for more than 4,000 years. Today it is most widely known as a psychoactive drug. Marijuana's many effects include cardiovascular, pulmonary, neoplastic, CNS, endocrine, ocular and antiemetic. Although more than 400 compounds have been identified in the plant, none of these have been found to have sufficient therapeutic efficacy to warrant a major role in modern therapy. Continued controversy on this point may change its status in the future.

PATIENT INFORMATION— Marijuana

Uses: Marijuana appears to be medicinally useful as an antiemetic, but its potential for abuse has so far outweighed proposals for its use as a therapeutic agent.

Side Effects: Marijuana can be harmful to the heart, lungs, brain, endocrine system and eyes. It also has a strong potential for abuse and is classified as a schedule ? drug.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MARIJUANA

MASTIC

DATE OF ISSUE: SEP 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Pistacia lentiscus* L. Family. Anacardiaceae

COMMON NAME(S): Mastic, mastick(tree), mastix, mastich, lentisk

BOTANY: Mastic is collected from an evergreen, dioecious shrub, which can grow to ˜ 3 m in height. It is native to the Mediterranean region, primarily in the Greek Island of Chios. Its leaves are green, leather-like, and oval. The small flowers grow in clusters and are reddish to green. The fruit is an orange-red drupe that ripens to black.

Mastic is "tapped" from the tree from June to August by making numerous, longitudinal gouges in the bark. An oleoresin exudes and hardens into an oval tear shape, about the size of a pea (3 mm). The transparent, yellow-green resin is collected every 15 days. If chewed, it becomes "plastic," with a balsamic/turpentine-like odor and taste. A related species is *P. vera*, the pistachio nut.[1,2,3,4,5,6]

Mastic resembles the resin "sanderach" (obtained from *Tetraclinis articulata*), without the chewable "plastic" qualities of mastic.[4,5]

HISTORY: Mastic resin was used in ancient Egypt as incense and to embalm the dead.[3,7] It has also been used as a preservative and a breath sweetener.[7] Mastic oil was mentioned by Dioskourides in ancient Grecian times and by Christopher Columbus in 1493.[8] Mastic resin is still used as a flavoring in some Greek alcoholic beverages (eg, "retsina" wine) and in chewing gum from the island of Chios.

CHEMISTRY: Mastic is an oleoresin containing ˜ 2% volatile oil.[2,4] The resin contains alpha and beta masticoresins, masticin, mastic acid, masticoresene, and tannins.[3] It is a complex mixture of tri-, tetra-, and pentacyclic triterpene acids and alcohols.[9] Reports of certain fractions from the plant include polymer fraction isolation/characterization,[10,11] and acidic triterpenic fractions of mastic gum.[12]

The essential oil component in mastic contains > 70 compounds, some of the primary constituents being alpha-pinene, myrcene, caryophyllene, beta-pinene, linalool, and germacrene D.[13,14,15,16,17] A later report lists certain percentages of essential oils from galls and aerial parts of the plant, such as sequiterpene hydrocarbons (47%), beta-caryophyllene (13%), and cadinene (8%).[18] Essential oil composition in this species *P. lentiscus* differs from region to region. Reports on this topic from the areas of Chios,[19] Egypt,[20] and Corsica[21] are available. Changes in essential oil chemical composition in mastic also differ with solidification and storage[22] and with the time of year samples are taken.[23] Chemical composition of various parts of the plant are discussed, including leaves, fruits, and aerial parts.[24,25,26,27] Lipids in the bark of *P. lentiscus* are also addressed.[28]

PHARMACOLOGY: The pharmacology and use of mastic is diverse. Mastic's role in improving benign gastric ulcers is discussed.[29] A double-blind clinical trial in 38 patients with duodenal ulcers given 1 g mastic daily (vs placebo) proved to exhibit ulcer healing effects.[30] A report in rats proposed antisecretory and cytoprotective effects of mastic.[31] A letter in the *New England Journal of Medicine* discusses these studies, as well as others, concluding that 1 g of mastic daily for 2 weeks can cure peptic ulcer rapidly. Its antibacterial actions against *Helicobacter pylori* may explain, in part, these beneficial effects.[32]

Mastic's antibacterial effects have been shown in other reports as well. It has actions against gram-positive and gram-negative strains;[33] some organisms include *Sarcina lutea*, *Staphylococcus aureus*, and *Escherichia coli*.[34] Mastic also possesses significant antifungal actions. The growth of the fungi *Candida albicans*, *C. parapsilosis*, *Torulopsis glabrata*, and *Trichophyton* sp. have all been inhibited by mastic.[34,35]

Various reports are available discussing miscellaneous uses and effects of mastic, including use as a drug-release vehicle,[36] improvement of adhesive strength in surgical tapes,[37,38,39] and aromatherapy.[7] Mastic has also been reported to be useful in the area of dentistry as a tooth cement and in reducing plaque.[2,8] It can also be used as a flavoring agent, perfume additive,[5] chewed as a gum, or used to retouch photographic negatives.[2] Mastic is also reported to possess some hypotensive effects,[10,40] as well as antioxidant actions because of tocopherol content.[41,42,43] Effects on blood lipids by mastic have been reported.[44] An herbal mixture including mastic was effective in treating diabetic rats.[45] Mastic as an insecticide has proven to be effective.[46] Other uses include the following: To improve circulation, for muscle aches, bronchial problems,[3,5] as skin care for cuts, and as an insect repellant.[5]

TOXICOLOGY: Most toxicity regarding mastic or source *P. lentiscus* involves allergic reactions. The plant pollen is a major source for allergic reactions.[47,48,49] The first report of immunological reactions to pollen extracts of *Pistacia* genus occurred in 1987.[47] A monographic review on mastic discussing chemistry, pharmacology, and toxicity is available.[50] Children ingesting mastic may develop diarrhea.[51]

SUMMARY: Mastic has been used as far back as ancient Egyptian times to embalm the dead. It is an oleoresin with "plastic" characteristics. Although few studies have been conducted, the use of mastic is widely varied and includes treatment of ulcer disease, antibacterial and antifungal effects, and use in dentistry. Allergic reactions are the most frequently reported toxicity of the plant. Mastic chewing gum is available in some Greek grocery stores usually imported from the island of Chios.

PATIENT INFORMATION — Mastic

Uses: Mastic has been used as a flavoring and a breath sweetener. It has also been studied for the treatment of ulcers. Mastic may also have antibacterial, antihypertensive, antioxidant, and cytoprotective effects.

Side Effects: Allergic reactions have occurred.

Dosing: Mastic resin has been studied as a treatment for ulcers at a daily dose of 1 g.[51]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MASTIC

MATE

DATE OF ISSUE: FEB 1997

REPLACES MONOGRAPH DATED: APR 1988

SCIENTIFIC NAME(S): *Ilex paraguariensis* (St. Hill.) Family: Aquifoliaceae

COMMON NAME(S): Mate, yerba mate, Paraguay tea, St. Bartholomew's tea, Jesuit's tea

BOTANY: Mate itself is a beverage, rather than a plant. It is prepared from the leathery leaves of *Ilex paraguariensis*, a species of holly. The genus *Ilex* includes over 400 species of trees and shrubs, many of which are used as ornamentals. They have alternate, simple leaves and single or clustered small berries that may be red, black or yellow. *Ilex* species require a relatively wet, moderate climate and are found worldwide except in polar regions. *I. paraguariensis* is found in Central and South America. The leaves (harvested from May to September) are dried, then powdered to produce the tea. Mate has a faintly aromatic smell and the flavor is astringent and smoky.[1]

HISTORY: Yerba mate was used as a beverage by ancient Indians in Brazil and Paraguay; however, *I. paraguariensis*was first cultivated by Jesuit missionaries. Consumption of mate is common in Brazil south of the Amazon and in Paraguay and Argentina. In those areas, the beverage largely replaces coffee and tea. Preparations are also available in the United States, where they are sold in health food stores. Traditionally, yerba mate is served in a small gourd called a mate. It is drunk through a drinking tube, or bombilla, also with a filter attached to the lower end to prevent consumption of the leaf fragments. Leaves are prepared for use by plunging them briefly into hot water, drying them in a brick oven and fragmenting them. The beverage is prepared by putting a little hot water and some sugar in the gourd. The leaves are then placed in a gourd, then the gourd is filled with boiling water. Burnt sugar, lemon juice or milk may be used to flavor the infusion. [2]

CHEMISTRY: Yerba mate contains phenylpropanoids, including caffetannin, that yield caffeic acid when hydrolyzed, chlorogenic acid, neochlorogenic acid and isochlorogenic acid. The fruits of *I. paraguariensis* contain the anthocyanins cyanidin-3-xylosylglucoside and cyanidin-3-glucoside. The leaves contain rutin. Other components of the leaves include alpha-amyrin, trigonelline, choline and ursolic acid. Mate has been shown to contain sterols resembling cholesterol and ergosterol. [3] In one report, xanthines present in the dried leaf portion using HPLC analysis include 0.56% caffeine, 0.03% theobromine and 0.02% theopylline. A typical amount of caffeine in an average "mate-round" is approximately 100 mg.[4] More than 15 amino acids are present in the leaves. Oil from the seeds contains lauric, palmitic, arachidic, stearic, palmitoleic, oleic and linoleic acids. [3] A small amount of essential oil and a resin fraction are also present in the plant. [1] Carbohydrates include sucrose, raffinose, glucose and levulose. [3] In 1989, a new saponin, "matesaponin" from *Ilex Paraguayensis* (St. Hill) leaves was isolated.[5] Vitamins and carotenoids present in mate include vitamins C, B_1 and B_5, nicotinic acid and carotene.[3] Analysis of elements present in mate show high content of K, Mg and Mn. Other elements present include Na, Ca, Cu, Fe and Zn.[6] Another report compares yerba mate with *mangifera indica* (mango) and discusses evidence of it being an adulterant.[7]

Chemistry-related research is also being performed on related Ilex species including: studies on the chemical constituents of *I. cornuta*,[8] saponin isolation and identification of *I. pseudobuxus*,[9] *I. taubertiana*[10] and *I. pubescens*,[11] isolation and identification of new p=coumaroyl triterpenes from *I. asprella*,[12] isolation and identification of *I. chinensis* sims[13,14] and *I. rotunda* thunb.[15] Further chemical studies include: xanthine alkaloid constituents of *I. dumosal*, *I. diuretica*and *I. glazoviana*,[16] high caffeine concentration and ritualistic use of *I. guayusa*,[17] proof by thin-layer chromatography and other methods of theobromine presence in *I. perado*AIT.,[18] comparison of flavonoids on six "Australsouthamerican" species of Ilex,[19] and natural constituents and uses of Ilex species.[3]

PHARMACOLOGY: Yerba mate has traditionally been used as a depurative (to promote cleansing and excretion of waste), a stimulant and diuretic. [3] Because of its caffeine content, mate is used as a centrally acting stimulant. A German monograph lists its uses for mental and physical fatigue, having "analeptic, diuretic, positively inotropic, positively chronotropic, glycogenolytic and lipolytic" effects. [1] In patients given mate infusion for 7 days, theophylline was found as a metabolic product of caffeine. After a week, theophylline levels in blood averaged 1.1 mcg/mL. [20] It is reported that in colonial times, some South Americans consumed a diet consisting almost exclusively of meat. The absence of vitamin deficiencies has been attributed to the vitamins present in the widely consumed yerba mate. [3]

Other Ilex species being evaluated include *I. asprella* as an antitumor agent[12] and *I. kudingcha* as a hypotensive agent in animals.[21]

TOXICOLOGY: A Uruguayan case-control study of 226 patients with esophageal cancer and 469 controls showed that heavy use of yerba mate was associated with a significant increase in the risk of esophageal cancer. Among heavy users, the relative risk was 6.5 for men and 34.6 for women. The risk for men was increased synergistically by alcohol consumption and tobacco smoking, but this increase was not evident among women. The increase in cancer risk was dose-dependent for men and women. It has been speculated that carcinogenesis may be cause by tannins (mate contains 7% to 14% tannin) or the high temperature of the beverage. Another factor may be the presence of phenanthrene derivatives such as 1,2-benzpyrene. [22] Because of the caffeine content, teas made from this plant should be used with caution by persons with high blood pressure, diabetes or ulcer disease.

Pyrrolizidine alkaloids were recovered from a contaminant in a mate tea sample of a woman who drank the tea for years. The consumption of such large amounts over time was associated with her hepatic disease.[23]

Seven cases of anticholinergic poisoning (some later reversed by physostigmine) occurred within 2 hours of ingestion of a tea labeled commercially as "Paraguay tea." It was found that not *Ilex paraguariensis* itself, but a contaminant containing belladonna alkaloids caused the ill effects. This plant was evidently misidentified as *I. paraguariensis* at harvest and was an isolated incident in these reported cases. [24]

For further toxicology information on other related Ilex species, refer to the "holly" monograph.

SUMMARY: Yerba mate is a beverage made from an infusion of the dried leaves of *Ilex paraguariensis*. It contains many types of compounds with nutritional value and has been used as a depurative, stimulant and diuretic. Among many people in Central and South America, it replaces coffee and tea as a common beverage. Mate has been associated with esophageal cancer and liver disease. Its related species, the "holly" *Ilex aquifolium*, *I. opaca*and *I. vomitoria* are poisonous.

PATIENT INFORMATION— Mate

Uses: Yerba mate has been traditionally used as a stimulant, diuretic and depurative. It is a caffeine- and vitamin-containing beverage that also acts as a centrally-acting stimulant.

Side Effects: Heavy use can increase risk of esophageal cancer, especially in women.

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Document Bibliographic Information:
- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
      MATE

MEADOWSWEET

DATE OF ISSUE: MAY 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Filipendula ulmaria* L. Maxim., *Spiraea ulmaria* L. Family: Rosaceae

COMMON NAME(S): Meadowsweet, queen of the meadow, dropwort, bridewort, lady of the meadow

BOTANY: Meadowsweet is a herbaceous perennial shrub growing up to 2 m tall. The plant is native to Europe but also grows in North America, preferring damp, moist soil. The erect stem is red-marbled and hollow. The toothed leaves are dark green in color. Meadowsweet's aromatic, ornamental wildflowers are creamy, yellow-white, and contain 5 petals. The flowers are 5 mm in length and have an aroma reminiscent of oil of wintergreen. The dried herb consists of flower petals and some unopened buds, which are the parts used as the drug.[1,2,3,4,5,6,7,8]

HISTORY: In 1597, Gerard mentioned how the smell of meadowsweet "delighteth the senses." In 1652, Culpeper wrote about the plant's therapeutic effects on the stomach.[5] In 1682, meadowsweet was mentioned in a Dutch herbal. Holland called the plant "*Filipendula*," while in the rest of Europe, it was known as "*Spiraea*." Queen Elizabeth ? adorned her apartments with meadowsweet. The flowers were used to flavor alcoholic beverages in England and Scandinavian countries. [8] In the Middle Ages, meadowsweet was known as "meadwort" because it was used to flavor "mead," an alcoholic drink made by fermenting honey and fruit juices.[5]

In 1838, salicylic acid was isolated from the plant. In the 1890s, salicylic acid was first synthesized to make aspirin. [5] "Aspirin" is derived from "spirin," based on meadowsweet's scientific name, "*Spiraea*."[8]

The plant was used in folk medicine for cancer, tumors, rheumatism, and as a diuretic.[4,7] Today, it is used as a digestive remedy, as supportive therapy for colds, for analgesia, and other indications.

CHEMISTRY: Flavonoids in meadowsweet include the flavonol glycosides rutin, hyperin, and spiraeoside. [1] Spiraeoside has been evaluated in the plant's flowers.[9] Glycoside spiraein (salicylaldehyde primveroside) is present, as are phenol glycosides including gaultherin. [2,8] A phenolic glycoside from meadowsweet flowers has been reported.[10] Quercetin and kaempferol derivatives have also been found in the plant, and hyperoside is present as well, primarily in the leaves and stalks. [1] A report is available on 7 flavonoids isolated from meadowsweet flowers, fruits, leaves, and stalks. [11]

Constituents in meadowsweet also include hexahydroxydiphenic acid esters of glucose and tannins, 10% to 20%. [1,5,7,8] One report finds tannin content to be high compared with other rosaceae species.[12]

The essential oil contains primarily salicylaldehyde (75%), as well as phenylethyl alcohol, benzyl alcohol, anisaldehyde, methyl salicylate, salicin, gaultherin, spiraein, spiraeoside, heliotropin, phenyl acetate, and vanillin. [1,3,4]

Salicylates in the plant include salicylic aldehyde, salicylic acid, salicin, methyl salicylate, and others. [1,3,4,7] HPLC and TLC screening for meadowsweet salicylates has been performed.[13]

Meadowsweet flowers contain heparin, which binds to the plant's proteins, forming a complex.[14] Heparin isolated from meadowsweet shows some similarity to heparin of animal origin.[15]

Other constituents in meadowsweet include mucilage, carbohydrates, ascorbic acid, sugars, and minerals. [3,8]

Phytochemical study of meadowsweet is available.[16]

PHARMACOLOGY: Meadowsweet is used for supportive therapy in colds, probably because of its analgesic, anti-inflammatory, and antipyretic actions. [1,2,6,8] The roots have been used to treat respiratory problems such as hoarseness, cough, and wheezing. [4]

The plant is also useful as a digestive remedy for acid indigestion or peptic ulcers. It protects the inner lining of the stomach while providing the anti-inflammatory benefits of salicylates.[5] A reduction in ulcerogenic action has been documented in rats, promoting the healing of (induced) chronic ulcers and preventing ASA-induced lesions in the stomach.[17] However, meadowsweet also has been reported to potentiate ulcerogenic properties in animals. [3]

Because joint problems may be related to increased acid, the ability of meadowsweet to reduce acidity is also beneficial in treating joint problems. [5] It has also been mentioned that meadowsweet improves the condition of connective tissue of joints.[8] In folk medicine, meadowsweet was used for rheumatism of muscles and joints, and for arthritis.[1]

A heparin-plant protein complex was found to have anticoagulant and fibrinolytic properties. [15] Meadowsweet flowers and seeds demonstrated an increased level of anticoagulant activity in vitro and in vivo in another report. [18] In vitro complement inhibition from the plant's flowers has been studied.[19]

Bacteriostatic activity from meadowsweet flower extracts include actions against *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*.[3] The salicylic acid in the plant is a known disinfectant used to treat ailments such as skin diseases. [4] Meadowsweet is also a urinary antiseptic, the mechanism of action being its close relation to phenol. [8]

The tannins in the plant possess astringent properties. Root preparations have been used in the treatment of diarrhea. [3,4]

Local administration of a meadowsweet decoction resulted in a 39% decrease in the frequency of induced squamous-cell carcinoma of the cervix and vagina in mice; 67% of patients had a positive response.[20]

Meadowsweet has been used as a sedative and to soothe nerves.[4] Reduction of motor activity and potentiation of narcotic action has also been observed in animals given the herb.[3]

Meadowsweet had no effect on glycemic control when studied in mice for treatment of diabetes.[21]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: The German Commission E Monographs lists no known side effects, contraindications (except those with salicylate sensitivity), or drug interactions with use of meadowsweet.[2] The FDA has classified the plant as an "herb of undefined safety." [4]

Use caution because of the toxicity profile of salicylates. Methyl salicylate can be absorbed through the skin, resulting in fatalities, especially in children. [3,4]

Bronchospasm has also been documented from use of the plant; therefore, use caution in asthmatics. Uteroactivity has also been observed from meadowsweet, warranting avoidance during pregnancy and lactation. [3]

SUMMARY: Meadowsweet is an herb that has been used for centuries and has been granted "approved" status by the German Commission E. It contains salicylate derivatives, which make it useful for analgesia. The plant has been used for cold therapy, GI disturbances, and joint problems. It also possesses bacteriostatic actions and antitumor activity. Few toxic events have been reported.

PATIENT INFORMATION— Meadowsweet

Uses: Meadowsweet has been used for colds and respiratory problems, acid indigestion or peptic ulcers, joint problems, skin diseases, and diarrhea.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Few toxic events have been reported. Do not use in patients with salicylate or sulfite sensitivity, and use caution in asthmatics.

Dosing: Doses of 2.5 to 3.5 g/day of flower and 4 to 5 g of herb are considered conventional; however, no clinical trials support the safety or efficacy of these dosages.[22]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MEADOWSWEET

MELATONIN

DATE OF ISSUE: JAN 2002

REPLACES MONOGRAPH DATED: JAN 1996

SCIENTIFIC NAME(S): *Melatonin*, *MEL*

COMMON NAME(S): Melatonin, MEL

HISTORY: Melatonin (MEL) is one of the hormones of the pineal gland that also is produced by extrapineal tissues. Early animal studies (mid-1960s) revealed its ability to affect sexual function, skin color, and other mammalian functions. It is the mediator of photo-induced antigonadotrophic activity in photoperiodic mammals and affects thermoregulation and locomotor activity rhythms in birds. It also has been implicated in time-keeping mechanisms in the pineal gland. Early studies showed that diurnal variations in estrogen secretion in rats could be regulated by changes in melatonin synthesis and release, both induced by the daily cycle of light and dark via the efferent limb of the reflex in the sympathetic innervation of the pineal gland. Continual darkness depresses the estrous cycle. [1,2]

Melatonin secretion is inhibited by environmental light and stimulated by darkness, with secretion starting at 9 p.m. and peaking between 2 and 4 a.m. Nocturnal secretion of melatonin is highest in children and decreases with age. [3,4] Studies in the 1990s have widely expanded the use of melatonin, in an extemporaneous manner, for easing insomnia, combating jet lag, preventing pregnancy (in large doses), protecting cells from free-radical damage, boosting the immune system, preventing cancer, and extending life. [5]

Although melatonin is not approved for marketing as a drug product, it has been classified as an orphan drug since November 1993 [4] for the treatment of circadian rhythm sleep disorders in blind people with no light perception. It is commercially available as a nutritional supplement either as a synthetic product or derived from animal pineal tissue. Use of the tissue-derived product should be discouraged because of a possible increased risk of contamination or viral transmission. Most commercial brands are available as 300 mcg or 1.5 or 3 mg tablets under various names. Patients should seek medical advice before undertaking therapy.

CHEMISTRY: Chemically, it is defined as melatonin N-[2-(5-Methoxy-IH-indol-3-l)ethyl]acetamide or N-acetyl-5-methoxytryptamine. It can be isolated from the pineal glands of beef cattle or synthesized from 5-methoxyindole as a starting material via 2 different routes. It is a relatively low molecular weight hormone (M.W. 232.27) and is a pale yellow crystalline material. [1]

PHARMACOLOGY: Pharmacological disruption of melatonin production can occur via beta-1 and alpha-1 receptors because of sympathetic innervation in the pineal gland. Tryptophan is converted to serotonin, the immediate precursor of melatonin. [3,4,6] Its synthesis is inhibited by light and stimulated by periods of darkness independent of sleep. To date, 2 types of G-protein-coupled melatonin receptors have been cloned. They are present in the periphery and CNS. [7] Once in circulation, melatonin is metabolized in the liver with > 85% excreted as 6-sulphatoxyMEL, a reliable marker for melatonin production. Plasma half-life is short, 20 to 50 minutes, [3,4,8] and plasma levels return to baseline within 24 hours after discontinuation of chronic dosing (< 10 mg/day). [4,9] Melatonin doses of 5 mg produce estimated peak blood levels 25 times above physiological levels but do not alter endogenous melatonin production. [4,9] In the 1990s, dozens of articles appeared in the medical literature on the various purported activities of melatonin. A selected overview of studies includes those regarding melatonin's role as an antioxidant and free radical scavenger, [10,11,12] use in general health and disease, [3] hypothermic properties, [13] control of seasonality and winter depression, [14,15] oncostatic actions on estrogen-responsive MCF-7 human breast cancer cells, [16] treatment of neoplastic cachexia, [17] effect on primary headaches [18] and prophylaxis of cluster headache, [19] direct effect on the immune system [20,21] including activation of human monocytes, [22] role in GI physiology, [23] function in thermoregulatory processes, [24] involvement in the cardiopulmonary system, [25] potentially beneficial cardiovascular effects [26,27] including reduction in hypercholesterolemia, [28] use in treatment of myoclonus in children, [29] effects on puberty, [30] improvement in tinnitus, [31] its place in human and animal reproduction, [32] studies on human sleep, [33] use as a premedication for gynecological procedures, [34] modulation of sympathetic neurotransmission, [35] possible role in infant colic, [36] as a proconvulsive hormone, [37] and purported chronobiotic and anti-aging properties. [38,39]

It would be impossible to cover all of these properties in detail in this monograph. Not only are there too many supposed effects, but almost all of the studies are preliminary and await future verification. In addition, many studies are flawed in design and rely on subjective measures.

A number of trials have attempted to resolve some unanswered questions and have shown a lack of effect on tardive dyskinesia, [40] rapid-cycling bipolar disorder, [41] and rate of improvement of major depressive disorder. [42]

Among the most common medical claims for positive effects are entraining the blind, overcoming jet lag, having immunotherapeutic potential, hastening the onset of sleep, and dampening the release of estrogen. Melatonin may diminish breast cancer rates and be useful at higher doses (ie, 75 mg) for oral contraception.

The FDA has not yet controlled melatonin and warns users that they are taking it "without any assurance that it is safe or that it will have any beneficial effect." In the meantime, many health food manufacturers and some pharmacies and clinics have begun to make this inexpensive hormone available for various medical and related purposes.

Blind entrainment: The sleep-wake cycle in humans without light-dark cues approximates 25 hours, causing the sleep cycle to shift by 1 hour each day, so that such individuals are eventually awake at night and asleep during the day. Blind people with little or no perception of light often develop free-running circadian rhythms > 24 hours and subsequently develop sleep disturbances characterized by chronic fatigue and involuntary napping during the day. In case reports and small controlled studies, oral melatonin (daily dosage range, 0.5 to 10 mg) has been used to entrain free-running activity rhythms in blind people by advancing and stabilizing the phase of endogenous melatonin secretion. [4,9,43] Although success has varied in these reports, the importance of melatonin administration time has been recognized. For example, the administration of melatonin (5 or 10 mg for 2 to 4 weeks at bedtime) to an 18-year-old blind man with chronic sleep disturbances produced slightly improved sleep onset but did not reduce daytime fatigue or hypersomnolence. [4,43]

However, the administration of melatonin (5 mg for 3 weeks) at 2 to 3 hours prior to habitual bedtime decreased sleep onset (˜ 1.4 hours), slightly increased sleep duration (34 minutes), and improved sleep quality and daytime alertness. The authors suggest that there is a Phase Response Curve (PRC) for the exogenous administration of melatonin; the maximum phase advancing effects occur when melatonin is administered ˜ 6 hours prior to onset of endogenous melatonin secretion. [4,44] The average cumulative phase advancement (CPA) of melatonin rhythms after 3 weeks of treatment with 5 and 0.5 mg daily was 8.41 and 7 hours, respectively. [4,9]

Jet lag: Melatonin's ability to modulate circadian rhythms has prompted several studies investigating the use of this agent in the prevention of jet lag. [4,45,46,47] Although the effects have been variable, most patients have reported general improvement in daytime fatigue, disturbed sleep cycles, mood, and recovery times. These studies are limited by the small number of participants and a focus on subjective ratings of effects with little or no evidence of actual changes in circadian shift (ie, changes in oral temperature or cortisol levels).

Several melatonin regimens have been examined (5 to 10 mg daily) for various durations. In one study, 52 aircraft personnel were randomized to placebo, early, or late melatonin groups. The early group started melatonin (5 mg daily) 3 days before departure until 5 days after arrival. [4,46] The late group received melatonin upon arrival and for 4 additional days. When compared with placebo, the late melatonin group self-reported less jet lag, fewer overall sleep disturbances, and a faster recovery of energy and alertness. However, the early group (receiving melatonin for 8 days) reported jet lag symptoms similar to the placebo group and a worsened

overall recovery.

Additional data suggest that benefits were also experienced by international travelers. However, there is little information on the optimal dose or formulation. As a guide, the most appropriate timing for melatonin administration appears to be preflight early evening treatment followed by treatment at bedtime for 4 days after arrival when traveling eastbound, whereas on a westbound flight it is better to take melatonin for 4 days at bedtime when in the new time zone. [48] (Note to travelers: Drowsiness may be experienced within 30 minutes after taking melatonin and may persist for ˜ 1 hour, and thus it may affect driving skills.)

Insomnia: Although the administration of melatonin has been shown to shift melatonin secretion and circadian rhythm patterns, its direct hypnotic effect, if any, has not been clearly established. Decreased circulating melatonin serum levels have been demonstrated in people of all ages with insomnia and in the healthy elderly. [3,4]

In small studies of healthy volunteers or people with chronic insomnia, very large doses of melatonin (75 to 100 mg) administered at night (9 to 10 p.m.) have produced serum melatonin levels exceeding normal nocturnal ranges and hypnotic effects. These include decreases in sleep onset, fewer nighttime awakenings, and increases in stage 2 sleep and sleep efficiency (percentage of time asleep/time in bed). [4,49,50] Midday administration of large doses also has increased serum melatonin levels beyond normal nocturnal ranges, increased subjective fatigue, and decreased cognitive function and vigor. [4,51]

The administration of smaller doses (0.3 to 6 mg) has produced inconsistent hypnotic results, but this may be because of the inclusion of patients with a variety of sleep disorders, different drug formulations, and different administration times (midday to 15 minutes before bedtime). [4,52,53,54,55,56,57] The time to reach peak hypnotic effect was longer when melatonin (5 mg) was administered at 12 p.m. vs 9 p.m. (3.66 hours vs 1 hour). [4,53] Delayed latency with daytime administration may be related to the already low circulating melatonin levels during the day. Low doses (0.3 or 1 mg) administered to healthy volunteers at 6 p.m., 8 p.m., or 9 p.m. decreased onset latency and latency to stage 2 sleep, but did not suppress REM sleep nor induce hangover effects.

In patients with difficulty falling asleep, low doses of melatonin should be sufficient in promoting sleep onset. Administration of 5 mg of melatonin 3 to 4 hours before an imposed sleep period (over a 4-week period) decreased the time to sleep onset without affecting other sleep parameters, such as total duration or sleep architecture. [58] However, in patients with difficulty maintaining sleep, low doses of melatonin may not produce sufficient blood concentrations to maintain slumber. A 2 mg oral melatonin dose produced peak levels ˜ 10 times higher than physiological levels, but it remained elevated for only 3 to 4 hours. [4,8] To maintain effective serum concentrations of melatonin throughout the night, a high dose, repeated low doses, or a controlled-release formulation may be needed. When compared with placebo in a trial of 12 elderly people with chronic insomnia, melatonin increased sleep efficiency (75% vs 83%) and decreased wake time after sleep onset (73 vs 49 minutes). [4,56] However, there were no differences between the groups for total sleep time (365 vs 360 minutes) or sleep onset (33 vs 19 minutes).

Sleep onset and sleep maintenance were improved in elderly people with insomnia after 1 week of immediate (1 mg) and sustained release (2 mg) melatonin preparations. Sleep onset improved further when the sustained-release form was continued for 2 months. [4,57] Physically ill patients with insomnia in a hospital setting who were given a low dose (averaging 6 mg) also fell asleep faster and slept longer than their placebo-matched counterparts. [59] Melatonin may be particularly useful when traditional hypnotics are contraindicated.

Children with sleep disorders: Several case reports have described the use of melatonin (2 to 5 mg) in children (6 months to 14 years of age). [4,60] Outcomes of studies in children suggest findings similar to those in adults. Melatonin given to either healthy or developmentally impaired children was most effective in treating delayed sleep onset. [61,62] A controlled-release formulation was required for sleep maintenance. It has been proposed that children with multiple complex neurodevelopmental problems may require higher doses (2 to 12 mg) than initially thought. [62]

Immunotherapeutic potential: Activation of melatonin receptors has been shown to enhance the release of a number of cytokines, including gamma-interferon, IL-1, IL-2, IL-6, and IL-12 in human monocytes. It has been suggested that melatonin may be used to stimulate the immune system during viral and bacterial infections. A potential role has been postulated in the treatment of viral encephalitis, septic shock, and secondary immunodeficiencies (eg, acute stress). However, through this proinflammatory action, melatonin may play an adverse role in autoimmune diseases. [21]

Cancer protection: Several studies suggest that partial responses and stabilization of disease occur, to varying degrees, with the use of melatonin as adjunctive therapy in patients with malignant solid tumors. However, the majority of these studies are open-labeled trials in patients in poor clinical condition with advanced disease who had not responded to conventional therapy. Melatonin has demonstrated some inhibitory effects on tumor growth in animal models [63] and in vitro cancerous breast cell lines. [3] Proposed oncoprotective mechanisms of melatonin include stimulatory effects on circulating natural killer cells and potent antioxidant activity. Preliminary studies have examined the use of melatonin in patients with solid tumors, for example, melanoma and pineal tumors, [64] and as adjunctive amplifier therapy with interleukin in various metastatic tumors (eg, endocrine, colorectal). [4,65,66,67,68,69] European studies on *B-Oval* (containing melatonin) appear to show that it can slow the growth rate of human tumor cells. A nightly supplement (10 mg of melatonin) has been shown to improve 1-year survival rates in patients with metastatic lung cancer. [3]

Well-controlled trials are needed before the role of melatonin as an oncostatic agent can be confirmed.

Oral contraceptive: Because melatonin plays a role in the endocrine-reproductive system and reduces circulating LH, the use of melatonin as a contraceptive agent has been studied. [4,70] Melatonin administered in various dosage combinations with a synthetic progestin in 32 women for 4 months produced anovulatory effects.

Anovulatory properties might not translate to contraceptive efficacy but might reduce fertility. One should not count on efficacy similar to accepted methods.

Skin protection from ultraviolet light: Topical melatonin was tested in combination with vitamins C and E in a randomized, double-blind study. The agents were applied topically either alone or in combination 30 minutes before ultraviolet irradiation of the skin. The best protection was obtained using all 3 agents in combination. The role of reactive oxygen species and oxygen-derived free radicals, as well as potential sunscreening properties, may explain the photoprotective effect. [71]

INTERACTIONS: In a double-blind, randomized, placebo-controlled study, the effect of evening ingestion of melatonin on the antihypertensive action of nifedipine Gastrointestinal Therapeutic System (GITS) was evaluated in 47 patients with mild to moderate hypertension. [72] Compared with placebo, concurrent ingestion of nifedipine and melatonin resulted in an increase in blood pressure throughout the day (ie, 24-hour period: 6.5 mmHg increase in systolic blood pressure; 4.9 mmHg increase in diastolic blood pressure). The increase in systolic blood pressure was highest during the afternoon and first part of the night, while the increase in diastolic blood pressure was greatest in the morning. In addition, there was a 3.9 bpm increase in the heart rate throughout the 24-hour period, being highest in the morning.

TOXICOLOGY: There are very few short-term and no long-term safety data. Toxicological studies have shown that an LD_{50} could not be obtained even at extremely high doses. Researchers gave human volunteers 6 g of melatonin each night for 1 month and found no major problems, except for stomach discomfort or residual sleepiness. [5]

Most clinical studies note the absence of adverse events associated with melatonin administration. A randomized, double-blind trial (n = 40), in which melatonin or placebo was administered for 28 days, found no statistical difference between the adverse effects reported by patients nor in their lab results (including CBC, urinalysis, electrolytes, cholesterol, LFTs). [73] Minor side effects with doses < 8 mg have included "heavy head," headache, and transient depression. [4,46,47] In psychiatric patients, melatonin has aggravated depressive symptoms. [3,4,6] Single case reports in the literature have related use to a fixed drug eruption, [74] a psychotic episode, [75] painful gynecomastia, [76] and autoimmune hepatitis. [77] However, melatonin was not the drug definitively identified as the causal agent in any of these reports.

Morning ingestion of melatonin could be more problematic. A small study of 9 patients has shown impaired psychomotor vigilance. [78] Prolonged studies are needed to verify its safety.

Drowsiness may be experienced within 30 minutes after taking melatonin and may persist for ˜ 1 hour and thus may affect driving skills.

SUMMARY: There are numerous studies exploiting the role that melatonin plays as a hormone in the body. Possible uses include treatment of insomnia, overcoming jet lag, as an antioxidant, improving the effectiveness of the immune system, and possibly preventing cancer. Many of the more recent studies show some promise in these areas; however, large-scale, double-blind studies are needed because of concern for potentially adverse long-term effects. Major promise is currently seen in short-term treatment of insomnia at low-dose schedules (a few milligrams) nightly.

PATIENT INFORMATION — Melatonin

Uses: Melatonin is used for numerous conditions but is showing the most promise in short-term regulation of sleep patterns, including jet lag.

Interactions: Melatonin may interfere with the antihypertensive effect of nifedipine.

Side Effects: Possible adverse effects include headache and depression. Melatonin should not be used by patients who have autoimmune diseases. Drowsiness may be experienced within 30 minutes after taking melatonin and may persist for ˜ 1 hour and thus may affect driving skills.

Dosing:
Jet lag: Eastbound travel: Take a preflight early evening treatment of melatonin followed by treatment at bedtime for 4 days after arrival. Westbound travel: Take melatonin for 4 days at bedtime when in the new time zone.

Difficulty falling asleep: Take 5 mg of melatonin 3 to 4 hours before an imposed sleep period (over a 4-week period).

Difficulty maintaining sleep: Take a high dose, repeated low doses, or a controlled-release formulation.

Children (6 months to 14 years of age with sleep disorders): 2 to 5 mg melatonin has been used.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MELATONIN

METHYLSULFONYLMETHANE (MSM)

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Methylsulfonylmethane*, *DMSO2*

COMMON NAME(S): MSM

SOURCE: MSM is a natural chemical in green plants such as *Equisetum arvense*, certain algae, fruits, vegetables, and grains. It is also seen in animals (eg, the adrenal cortex of cattle, human and bovine milk, and urine). MSM is naturally occurring in fresh foods; however, it is destroyed with even moderate food processing, such as heat or dehydration.[1]

HISTORY: Literature searches on MSM provide mostly animal studies. MSM has been suggested for use as a food supplement.

CHEMISTRY: MSM is the normal oxidation product of DMSO (dimethyl sulfoxide). Unlike DMSO, MSM is odor-free and is a dietary factor. MSM has been referred to as "crystalline DMSO."[2] MSM provides a source of sulfur for methionine.[1]

PHARMACOLOGY: MSM has been said to alleviate GI upset, musculoskeletal pain, arthritis, allergies, and to boost the immune system. It is also said to possess antimicrobial effects against such organisms as *Giardia lamblia*, *Trichomonas vaginalis*, and certain fungal infections. The suggested mechanism is that MSM may bind to surface receptor sites, preventing interface between parasite and host.

Tumor onset in colon cancer-induced rats was markedly delayed in animals receiving MSM supplementation vs controls, suggesting a chemopreventative effect. [3] Four percent MSM had a similar delaying effect on rat mammary breast cancer.[4]

MSM showed no effect in preventing diabetes when tested in spontaneously diabetic mice compared with DMSO or dimethylsulfide (DMS). [5]

A 10-day course of MSM also has been evaluated in 13 horses with COPD, and no changes occurred in parameters such as lung sounds, respiratory rate, heart rate, temperature, nasal discharge, or arterial blood gas. [6]

TOXICOLOGY: No important toxicities were noted in animal reports.[3,4]

SUMMARY: MSM is a natural chemical, which may be of some use for skin problems, GI upset, and certain cancers. No toxicities have been reported. Human trials are needed to fully assess MSM's therapeutic benefits.

PATIENT INFORMATION — Methylsulfonylmethane (MSM)

Uses: MSM is said to alleviate GI upset, musculoskeletal pain, arthritis, and allergies; to boost the immune system; and to possess antimicrobial effects.

Side Effects: No important toxicities were noted in animal reports.

Dosing: MSM commonly is given first at a loading dose of 2 to 5 g/day, then as a maintenance dose of 50 to 200 mg/day for arthritis and other joint conditions.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    METHYLSULFONYLMETHANE (MSM)

MILK THISTLE

DATE OF ISSUE: JAN 1997

REPLACES MONOGRAPH DATED: MAR 1988

SCIENTIFIC NAME(S): *Silybum marianum* (L.) Gaertn. Family: Compositae referred to in older texts as *Carduus marianus*. Recently changed to *Carduus marianum*.

COMMON NAME(S): Holy thistle, lady's thistle, marian thistle, Mary thistle, Milk thistle, St. Mary thistle, silybum

BOTANY: This plant is indigenous to Kashmir, but is found in North America from Canada to Mexico. *Silybum* grows from 5 to 10 feet and has large prickly leaves. When broken, the leaves and stems exude a milky sap. The reddish-purple flowers are ridged with sharp spines. The drug consists fo the shiny mottled black or grey-toned seeds (fruit). These make up the "thistle" portion, along with its silvery pappus, which readily falls off. [1]

HISTORY: Milk thistle was once grown in Europe as a vegetable. The de-spined leaves were used in salads and for spinach substitution; the stalks and root parts were also consumed, even the flower portion was eaten "artichoke-style." The roasted seeds were used as a coffee substitute. Various preparations of milk thistle, especially the seeds, have been used medicinally for over 2000 years. Its use as a liver protectant can be traced back to Greek references. Pliny the Elder, a first century Roman writer, (A.C. 23 to 79) noted that the plant's juice was excellent for "carrying off bile." [2] Culpepper (England's premier herbalist) noted milk thistle to be of use in removing obstructions of liver and spleen, and to be good against jaundice. The Eclectics (19th-20th century) used milk thistle for varicose veins, menstrual difficulty and congestion in liver, spleen and kidneys. [3]

In homeopathy, a tincture of the seeds has been used to treat liver disorders, jaundice, gall stones, peritonitis, hemorrhage, bronchitis and varicose veins. [4]

CHEMISTRY: Silymarin, a mixture of three isomeric flavonolignans, was first isolated from milk thistle seeds in 1968. Silymarin (molecular formula: $C_{25}H_{22}O_{10}$, MW 482.45, 4% to 6% in ripe fruits) consists primarily of three flavonolignans: Silybin (silibinin), silychristin (silichristin) and silidianin. [5] A review of isolation and structure of these flavonolignan components is available. [6] Silybin is the most biologically active component with regard to milk thistle's antioxidant and hepatoprotective properties. A standardized milk thistle extract composed of silymarin and silybin was developed in Europe and is known commercially as *Legalon*®.[7] Other flavonolignans include dehydrosilybin, 3-desoxysilichristin, deoxysilydianin (silymonin), siliandrin, silybinome, silyhermin and neosilyhermin. [5] The compound 5,7-dihydroxychromone has also been isolated from *Silybum marianum*.[8] Other seed components include apigenin; silybonol, a fixed oil (16% to 18%) consisting largely of linoleic and oleic acids, plus myristic, palmitic and stearic acids; betaine hydrochloride; triamine; histamine and others. [5] From the roots of *Silybum marianum* Gaertn., twelve polyacetylenes and one polyene have been detected. [9]

Silymarin is poorly soluble in water, so aqueous preparations such as teas are ineffective, except for use as supportive treatment in gallbladder disorders because of cholagogic and spasmolytic effects.[10] The drug is best administered parenterally because of poor absorption of silymarin from the gastrointestinal tract (23% to 47%). The drug must be concentrated for oral use.[11]

Many analyses of milk thistle using different isolation techniques have been reported. The following serves as a brief listing of available information that may be helpful in this specific area of interest.

Gel absorption and column chromatography methods have been employed to investigate flavones in milk thistle; [12] constituents from aerial parts and fruits also have been analyzed;[13] betaine hydrochloride was isolated form milk thistle seeds and was analyzed by chemical and spectroscopic methods; [14] spectrophotometric assay to determine flavone lignans from milk thistle and its preparations is described; [15] a NIR reflectance spectroscopic method was capable of identifying silybum samples from different geographical locations;[16] silymarin has been analyzed by extraction in small amounts using liquid carbon dioxide (supercritical conditions) in HPLC-packed columns. The separation by this method may be useful for flavonolignan analysis; [17] solubility and bioequivalence of silymarin products has also be performed.[18]

PHARMACOLOGY: Milk thistle's therapeutic efficacy involves a variety of molecular mechanisms, although the mechanism of action is not clearly understood. Its primary activities are of use as a hepatoprotectant and antioxidant. The properties of silymarin (the extract from milk thistle seeds containing the three flavonolignans) are due mainly to its flavonolignans content.[19] Medicinal value may also be attributed in part to the presence of trace metals in the plant. [20]

Mechanisms: 1. Actions of silymarin are almost entirely on liver and kidneys. It undergoes pronounced enterohepatic circulation, which allows for a continuous loop between intestine and liver. Silymarin moves from plasma to bile and concentrates in liver cells. [3]

2. In vivo tests proving increased protein synthesis in liver cells due to increased activity of ribosomal RNA were reported in 1980 by Sonnenbichler. Silybin contains a steroid structure that stimulates DNA and RNA synthesis, resulting in activation of the regenerative capacity of the liver through cell development. [21]

3. Silymarin's hepatoprotective effects may be explained by its altering of the outer liver cell membrane structure, as to disallow entrance of toxins into the cell. [2,22] This alteration involves silymarin's ability to block the toxin's binding sites, thus, hindering uptake by the cell. [3] The poisonous Amanita mushroom studies are remarkable examples of this mechanism of action and are discussed later.

4. Hepatoprotection by silymarin can also be attributed to its antioxidant properties by scavenging prooxidant free radicals and increasing intracellular concentration of glutathione, a substance required for detoxicating reactions in liver cells. [23] Silybin also inhibits peroxidizing enzymes like lipoxygenase, thus blocking peroxidation of fatty acids and damage to membrane lipids.[24,25]

The numerous clinical studies performed on silymarin involve: Hepatoprotection from toxins and other drugs, cirrhosis and hepatitis therapies, blood and immunomodulation, lipid and biliary effects and various other effects.

Earlier clinical studies (1969 to 1989) of silymarin use may be accessed through reference 3. More recent and other selected reports are categorically presented below.

Hepatoprotection: Silymarin protects liver cells against many hepatotoxins in humans and animals. Some Amanitas (eg, *A. phalloides*, the death cup fungus) contain two toxins: Phalloidine, which destroys the hepatocyte cell membrane and alpha-amanatine, which reaches the cell nucleus and inhibits polymerase-b activity, thereby blocking protein synthesis. Silymarin is capable of negating both of these effects by blocking the toxin's binding sites, increasing the regenerative capacity of liver cells and blocking enterohepatic circulation of the toxin. [3] In one study, 60 patients with severe Amanita poisoning were treated with infusions of 20 mg/kg of silybin with good results. Although the death rate following this type of mushroom poisoning can exceed 50%, none of the patients treated in this series died. [26] In a clinical trial of 205 patients with Amanita toxicity, 46 patients died; however, all 16 patients who received silybin survived. [27] Administration of silybin within 48 hours of ingestion at a dose of 20 to 50 mg/kg/day was an effective prophylactic measure against severe liver damage. [28] A multicenter trial performed in European hospitals between 1979 and 1982 was conducted using silybin in supportive treatment of 220 Amanita poisoning cases. A 12.8% mortality rate was reported. [29] The death rate using other modern supportive measures such as activated charcoal can be 40%.[3] Silymarin alone or in combination with penicillin reduced death rates from ingestion of death cup fungus to 10%.[30]

In addition to mushroom toxin protection, silymarin also offers liver protection against tetracycline-induced lesions in rats, [31] d-galactosamine-induced toxicity,[32] thallium-induced liver damage[33] and erythromycin estolate, amitriptyline, nortriptyline and tert-butylhydroperoxide hepatotoxin exposure of neonatal hepatocyte cell cultures.[34] In a later Italian double-blind, placebo controlled report, silymarin was elevated in 60 women on long-term phenothiazine or butyrophenone therapy. Results suggested that silymarin treatment can reduce lipoperoxidative hepatic damage caused by chronic use of these psychotropic drugs. [35]

Studies on silymarin's liver-protective effects continue to show it protects against carbon tetrachloride (CCl_4)-induced liver cirrhosis in animals and prevents increases in lipid peroxidation by this toxin, among other beneficial alterations. [36,37,38] When injected intravenously in rats and dogs, silymarin has been shown to protect liver destruction following injection with frog virus-3 (a lethal hepatotoxic virus). Although Kupffer cells were injured, the compound protected endothelial cells form destruction, primarily by inhibiting the release or synthesis of hepatotoxic enzymes. [39] Biologically equivalent activities of silybinin at doses of 30 mg/kg are discussed in another report.[40] Cisplatin, (an anti-cancer drug) toxic to nephrons, was injected in rats to induce renal damage for evaluation of silybin's protective effects in the kidney. Using tubular morphology, observation, proteinuria presence, etc, it was found that silybin could be beneficial in this area as well. [41] Specific evaluations of silymarin's mechanism of plasma membrane stability have been reported.[35,42] There is no evidence yet reported on liver enzyme P450 2E1 involvement in the hepatoprotective mechanism of silymarin.[43]

Cirrhosis: Silymarin's mechanisms offer many types of therapeutic benefit in cirrhosis with the main benefit being hepatoprotection. Use of milk thistle, however, is inadvisable in decompensated cirrhosis. [44]

In two one-month, double-blind studies performed on an average of 50 patients with alcoholic cirrhosis treated with silymarin, elevated liver enzyme levels (AST, ALT) and serum bilirubin levels were normalized. It also reduced high levels of gamma-glutamyl transferase, increased lectin-induced lymphoblast transformation and produced other changes not seen in the placebo group.[45,46,47] A report on free-radical scavenger activity of silymarin suggested that hepatoprotection could be due to antioxidant activity.[48] Similar results were obtained in another double-blind study evaluating a six-month treatment at 420 mg/day of silymarin (*Legalon*®).[49] A 41-month double-blind study performed in 170 patients with alcoholic cirrhosis indicated silymarin to be effective in treatment as well. [50] Silymarin ameliorated indices of cytolysis in a study also using ursodeoxycholic acid in active cirrhosis patients. [51] One study, providing contrasting evidence, suggested no change in evolution or mortality of alcoholic liver disease as compared with placebo in a controlled trial of 72 patients using 280 mg/day of silymarin. [52]

Hepatitis: In patients with acute viral hepatitis, silymarin shortened treatment time and showed improvement in serum levels of bilirubin, AST and ALT. [53,54] Biochemical values returned to normal sooner in silymarin-treated patients. [55] Histological improvement was seen in patients with chronic hepatitis vs placebo in another controlled trial.[56]

In a 116-patient double-blind study of silymarin vs placebo, silymarin 420 mg/day given to histologically-proven alcoholic hepatitis patients was shown not to be clinically useful in treating this disease. [57] A later report suggests stable remission in a 6- to 12-month Russian study evaluating treatment of chronic persistent hepatitis.[44] In 20 chronic active hepatitis patients given 240 mg of silybin twice daily vs placebo, improved liver function tests related to hepatocellular necrosis was reported.[58] A Bulgarian report evaluated two silymarin preparations, *Carsil*® and *Legalon*®, in treatment of various hepatitis types. The preparations did not differ much from each other.[59]

Blood and Immunomodulation: Silymarin's immunomodulatory activity in liver disease patients may also be involved in its hepatoprotective action. [60] Silybin can increase activity of superoxide dismutase and glutathione peroxidase, which may also explain its protective effects against free radicals. [61] Silymarin had an anti-inflammatory effect on human blood platelets.[62] Silybin may have anti-allergic activity. Its effect on histamine release from human basophils was reversed and may be due to membrane stabilizing activity.[63] Silybin inhibition of human T-lymphocyte activation is also reported. [64] In vitro effects of silybin on human polymorpho-nuclear leukocyte (PMN) have been reported. Inhibition of hydrogen peroxide may be a mechanism by which silybin inhibitis luminol-enhanced chemiluminescence (a biochemical technique) generated by stimulated PMNs.[65] Another report on PMN activity showed silybin to be effective in enhancing spontaneous motility of leukocytes.[66] Prolonged application of silymarin preparations improved immunity by increasing T-lymphoctyes and reducing all classes of immunoglobulins.[44]

Lipid and Biliary Effects: Administration of silymarin 420 mg/day for 3 months to 14 type **II** hyperlipidemic patients resulted in slightly decreased total cholesterol and HDL-cholesterol levels.[67] Biliary cholesterol and phospho-lipid concentrations in rats were also slightly reduced. Silybin-induced reduction of biliary cholesterol both in rats and humans may be due in part to decreased liver cholesterol synthesis. [68] An anti-aggregant effect of silymarin in cholesterol atherosclerosis in rabbits was also reported.[69]

Biliary excretion of silybin was evaluated by HPLC. Bioavailability of silybin is greater after silipide (a lipophilic silybin-phosphatidylcholine complex) administration than after silymarin administration; therefore, increased delivery of silipide to the liver results. [70] Pharmacokinetics of silybin have also been evaluated in patients with cholestasis.[71] Use of silymarin prevents disturbance of bile secretion, thereby increasing bile secretion, cholate excretion and bilirubin excretion. [44]

Various Other Effects: Silybin and silymarin have also been evaluated (including case reports) in diabetes patients for possible value in prophylaxis of diabetic complications,[72] in combination therapy to treat aged skin[13] and in oral treatment for prevention of ulceration in rats, both by reduction of neutrophils in gastric mucosa and inhibition of mechanisms of enzymatic peroxidation, thus, avoiding leukotriene synthesis. [74,75] Traditional uses of milk thistle include stimulation of milk production in nursing mothers and antidepressant therapy.[19] Other uses include steroide secretory modulation[76] and as therapy of acute promyelocytic leukemia.[77]

Indications for milk thistle are for any liver-based problems such as cirrhosis, jaundice, alcohol abuse, etc. At risk for liver toxins are those exposed to such pollutants as pesticides or heavy metals. Certain occupations such as those of painters, farmers, chemical workers and those in polluted urban environments are all associated with high risk.[3,78]

Extracts, tablets or capsules (35 to 70 mg) standardized to 70% silymarin are available as commercial preparations in average daily doses of 200 to 400 mg. [5]

TOXICOLOGY: Human studies performed with silymarin have shown little need for concern with adverse effects.[19] Tolerability of silymarin is good; only brief disturbances of GI function and mild allergic reactions have been observed, but rarely enough to discontinue treatment. [44] Mild laxative effects in isolated cases have been reported.[7] A case of urticaria with a foreign commercial milk thistle preparation has been noted in a Russian report. [79]

Silymarin has proved nontoxic in rats and mice after oral doses of 2500 or 5000 mg/kg were given without producing symptoms. In a 12-month study, rats received silymarin 50, 500 and 2500 mg/kg. Investigations including urine analysis and post-mortem studies showed no evidence of toxicity. A similar report in dogs was also performed. No evidence of ante- or postnatal toxicity in animals was reported, nor did silymarin affect fertility in rats. [25]

SUMMARY: Milk thistle extract and its major components have been found to be effective in treating toxin-poisoning, cirrhosis and hepatitis. Although data regarding usefulness in the treatment or prevention of alcoholic cirrhosis and hepatitis are equivocal. It also plays a role in blood and immunomodulation, lipid and biliary effects among others. Silymarin's mechanisms are due mainly to its flavonolignan content and involve hepatoprotection, increased regenerative capacity of liver cell turnover, the alteration of cell membranes preventing toxin uptake and scavenging free radicals, thus, limiting liver damage. Human studies with silymarin have shown few adverse effects. Milk thistle shows great promise and has been used medicinally for over 2000 years. It is widely used in Europe for Amanita mushroom poisoning treatment.

PATIENT INFORMATION— Milk Thistle

Uses: Treatment and protection against Amanita mushroom poisoning, reduced liver damage due to long-term treatment with phenothiazine or butyrophenone

therapy. Data regarding protection against alcoholic cirrhosis and hepatitis are equivocal. It shortened treatment time in patients with acute viral hepatitis, had an anti-inflammatory effect on human platelets, and slightly decreased total and HDL-cholesterol levels.

Side Effects: Few adverse effects have been seen other than brief GI disturbances and mild allergic reactions; possible urticaria in one patient.

Dosing: Crude milk thistle seed has been administered at 12 to 15 g/day in clinical trials for hepatitis and other liver conditions. Milk thistle also is widely available in several extracts, standardized to 70% to 80% silymarin. These include IdB1016 (*Silipide*, Indena), which is a silybin phosphatidylcholine complex, *Legalon*(Madaus), and *Silimarol*. Doses of these extracts range from 200 to 800 mg/day.[35,58,80]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MILK THISTLE

MISTLETOE

DATE OF ISSUE: DEC 2001

REPLACES MONOGRAPH DATED: DEC 1992

SCIENTIFIC NAME(S): *Viscum album* L. (European mistletoe) and *Phoradendron flavescens* (Pursh.) Nuttal, *P. serotinum* (Raf.) M.C. Johnston or *P. tomentosum* (DC) Engler (American mistletoes), Family Loranthaceae/Viscaceae

COMMON NAME(S): Mistletoe, bird lime, all heal, devil's fuge, golden bough, mistel (German)

BOTANY: Mistletoe is a hemiparasitic plant that grows on a wide variety of host trees such as pine, oak, birch, and apple. The term hemiparasitic is used to indicate that the mistletoe plant carries out photosynthesis independently but obtains its water and minerals from the host. European mistletoe is dioecious, with male and female flowers on separate plants, which are pollinated by insects and bear small white berries on evergreen foliage. There are several subspecies and varieties of European mistletoe, which are defined by the host that they parasitize.[1]

HISTORY: Mistletoe preparations have been used medicinally in Europe for centuries for such varied indications as epilepsy, infertility, hypertension, and arthritis. The Celtic priests, known as Druids, revered the oak tree and the mistletoe that grew upon it, according to Pliny the Elder. At the winter celebration of Samhain, the sacred oaks were bare except for the green boughs of mistletoe, and this was taken as a sign of eternal fertility. The Celts placed a sprig of mistletoe above the door of their houses, and its sacred nature prohibited fighting beneath it. This evolved over centuries into the custom of kissing underneath mistletoe at Christmas. [2] In 1921, the anthroposophical spiritual leader Rudolf Steiner suggested that mistletoe might be used to treat cancer. Swiss and German clinics were founded to implement this idea and are still actively using a mistletoe preparation fermented with a strain of *Lactobacillus plantarum* for 3 days.[3]

CHEMISTRY: The most distinctive constituents of *Viscum album* are its proteins, which are of the following 2 sorts: The viscotoxins, which are small (5 kDa) cystine-rich basic proteins also known as thionins, and the larger mistletoe lectins.

Four viscotoxins (A1, A2, A3, and B) have been isolated and sequenced.[4] They are highly homologous 46 amino acid proteins differing from one another at only a few positions. The 3-dimensional structure of viscotoxin A3 has been elucidated by NMR methods.[5] The viscotoxin profile of the 3 European subspecies of *V. album* has been determined.[6] Two novel viscotoxins, termed 1-PS and U-PS, were found in subspecies *austriacum* (pine) and subspecies *abietis* (fir). The viscotoxin profile of subspecies *album* did not vary appreciably with 7 different hosts. The American species *Phoradendron tomentosum* yielded a homolog known as phoratoxin.[7] The preparation *Iscador* has been shown to contain similar amounts of viscotoxins compared with the unfermented *V. album* extract.[8]

Lectins: A toxic lectin known as viscumin was isolated from *V. album* and shown to be a type ?? ribosome-inactivating protein.[9] Three distinct lectins (ML1[= viscumin], ML2, and ML3) were isolated by another group and shown to have different carbohydrate-binding specificities. [10] The complete amino acid sequence of ML1 B-chain has been obtained, showing homology to other galactose-specific lectins such as ricin and abrin. [11] The X-ray diffraction 3-dimensional structure of ML1 has been obtained in the free state[12] and bound to beta-galactose.[13] ML1 binds to several sialylglycoproteins in addition to the galactose-binding specificity initially identified.[14,15] The structural features important for carbohydrate recognition has been elucidated in detail. [16,17] A minor chitin-binding lectin completely distinct from ML1-3 was isolated.[18] Examination of the commercial preparation *Iscador* has shown that ML1 is apparently modified or degraded, while ML2 and ML3 are still present.[3,8,19]

Carbohydrates: The water-soluble polysaccharides of *V. album* and *Iscador* have been purified and characterized. A highly esterified galactouronan and a complex arabinogalactan were identified, with the corresponding polysaccharides from *Iscador* having lower molecular weights compared with those of the native, unfermented extract.[20]

Small molecular weight compounds: The phenylpropanoids syringin, syringenin-apiosylglucoside, and eleutheroside E have been found in *V. album*, and have been used to identify and standardize mistletoe preparations. [8,21] The syringin content of mistletoe growing on different host plants has been measured. [22] A number of known and novel chalcone and flavanone glycosides have been reported from European *V. album*.[23,24] Inositol derivatives are widespread in the Viscaceae and occur at relatively high concentrations in all species of mistletoe. They are thought to play a role in osmotic balance. [25] Other miscellaneous compounds have been reported;[26,27] a report of alkaloids in the plant has not been substantiated by their isolation in pure form and structure elucidation. [28]

PHARMACOLOGY

Cardiovascular: A primary use of mistletoe in European folk medicine is for its cardiovascular properties. The viscotoxins have produced reflex bradycardia and possessed negative inotropic effects on the isolated cardiac muscle of cats. In higher doses, vasoconstriction also was observed. [29] Phoratoxin was less potent in the same model. In rabbit heart preparations, viscotoxins at 1 to 10 mg/mL reduced the isometric twitch and produced contracture and progressive depolarization of the muscle. These changes were reversed by addition of calcium to the tissue bath, suggesting that displacement of membrane-bound calcium might play a role in the cardiovascular mechanism.[30] Further studies with phoratoxin in frog skeletal muscle fibers attributed its activity to detergency; however, this may not be the primary cardiovascular mechanism.[31] Other investigators have proposed that phenylpropanoids might play a role in mistletoe's cardiovascular effects through a postulated inhibition of cAMP phosphodiesterase; however, it is unlikely that they are as pharmacologically important as the viscotoxins. [32,33]

Cancer: Despite the nonscientific, relatively recent origin of the use of mistletoe in cancer treatment, extensive scientific literature exists on the topic. Viscumin was initially isolated from mistletoe based on its cytotoxicity to mouse 3T3 cells and its lethality to mice. [9] Viscumin is a potent inhibitor of protein synthesis in cell-free and cellular systems.[34] The cytotoxic effect of mistletoe lectins was substantially reduced for cells grown in the presence of fetal calf serum, presumably caused by glycoproteins in serum that bind the lectin.[35] The viscotoxins also are cytotoxic to cultured cells, although generally less potently than the lectins. [36] It is likely that the galactose- or oligosaccharide-specific binding of the lectins targets only cells bearing the appropriate carbohydrates on the cell surface. The mechanism that renders cells (such as the Yoshida cell line) sensitive to the viscotoxins remains unknown. [37] Fermented mistletoe extracts such as *Iscador* have been found to be cytotoxic to tumor cells[3,38] despite the observations that ML1 content is greatly reduced. [8,39] A 5 kDa protein (likely to be a viscotoxin) was isolated from *Iscador* that reduced solid lymphoma tumor cell growth in mice.[40]

Mechanistic investigations of mistletoe lectins and viscotoxins have shown induction of apoptosis in lymphocytes most effectively by ML3, but also by ML2 and ML1, while the viscotoxins and carbohydrates had no apoptotic effects.[41] ML1 was further found to induce apoptosis in leukemic T- and B-cell lines through caspase-8 independently of death receptor signaling.[42] The galNAc-specific ML3 and ML2, on the other hand, appeared to operate through the death receptor. [43] ML2 was found to activate the c-Jun N-terminal kinase 1 in apoptotic death of U937 cells. [44] It remains to be seen whether induction of apoptosis is a primary event or a secondary result of ribosomal protein synthesis inhibition.

The possibility that mistletoe preparations act through immunomodulatory mechanisms rather than by direct cytotoxicity has been proposed. In mice, *Iscador* was found to double the weight of the thymus and to accelerate the recovery of bone marrow and spleen from X-rays. [45] An ethanol precipitate of fresh mistletoe juice showed adjuvant activity in mice injected with sheep erythrocytes;[46] however, purified polysaccharides isolated from fresh and fermented plant material had no effects on 3 immunological tests.[20] An in vitro experiment with a rhamnogalacturonan isolated from mistletoe showed enhancement of natural killer cell cytotoxicity to K562 cancer cells.[47] Other in vitro experiments showed a slight protection of peripheral blood mononuclear cells from the effects of cyclophosphamide by mistletoe extracts.[48] Subtoxic concentrations of the different mistletoe lectins increased production of several interleukins and TNF-alpha in cultured human monocytes,

although the concentrations at which this happened were different for each donor. [49] Ex vivo studies showed activation of peripheral blood mononuclear cells from healthy human donors by fresh and fermented mistletoe preparations, but the purified lectins did not share this effect. [50] Stimulation of granulocyte phagocytosis by thionins including viscotoxins has been shown, so these proteins may play an immunoactivating role. [51] Lastly, it is possible that components of the *Lactobacilli* used to ferment mistletoe products may contribute to adjuvant activity.

Experimental cancer therapeutic studies in animals have shown mixed results. Recombinant mistletoe lectin (ML1) was active against human ovarian cancer cells xenografted into SCID mice; however, a clear dose-response was not demonstrated.[52] N-methyl-N-nitrosourea-induced bladder carcinogenesis in rats was reduced by ML1, and the effect was shown to not be dependent on interferon-gamma or interleukin-10.[53] Later studies by another group using the same carcinogen,[54] as well as N-butyl-N-(4-hydroxybutyl)-nitrosamine,[55] found ML1 to have no effect. *Iscador* was studied in a mouse model and found to prevent 20-methylcholanthrene-induced sarcoma when given twice weekly for 15 weeks at 1 mg/dose intraperitoneally.[56] Another mistletoe preparation, *Isorel*, was found to slow sarcoma growth when combined with irradiation of the implanted tumor.[57]

Several human clinical studies have attempted to measure changes in immunological status of cancer patients administered mistletoe preparations. Breast cancer patients given a single IV infusion of *Iscador* demonstrated a pronounced febrile reaction and increased natural killer cell activity and granulocyte phagocytosis. The presence of endotoxin in the preparation was ruled out as a cause of the response. [58,59] In the treatment of pleura carcinosis, intrapleural injection of *Iscador* had cytotoxic and immunostimulant activities.[60] The administration of lectin-depleted mistletoe extracts to breast cancer patients was compared with undepleted extracts, with the depleted extracts producing reduced immunological changes, thereby implicating the lectins in such effects. [61] Changes in cytokine levels (TNF-alpha, IL-1, and IL-6) after mistletoe extract injection were detected in 8 cancer patients in a further study by the same investigators. [62] Similar experiments measuring changes in DNA repair in lymphocytes of breast cancer patients found improved DNA repair after *Iscador*.[63] The difficulties of applying the observed changes in immunological status to practical cancer therapy have been reviewed.[64]

A retrospective study of 292 pancreatic cancer patients treated with *Iscador* showed a modest increase in survival time when compared with survival as reported in the literature; however, the absence of matched controls makes this result statistically weak. [65] A randomized clinical trial examined *Eurixor*, a preparation that is standardized for ML1 content, in head and neck cancer patients after treatment with surgery or radiotherapy. No treatment effect was detected for the mistletoe arm of the study, indicating that adjuvant use of mistletoe in this form was not effective. [66] A study on the use of mistletoe extract in melanoma was negative, although full details have not been published.[67] Earlier clinical studies of mistletoe have been reviewed, and it was determined that all of these studies were weak and inconclusive.[68] Further studies are required to assess the appropriate use, if any, of mistletoe preparations in cancer therapy. [69]

TOXICOLOGY: Mistletoe has a reputation as a toxic plant, and its content of toxic lectins lends support to this opinion. [70] Nevertheless, poison center data from the US indicates that symptomatic poisoning by American mistletoe is infrequent.[71] Side effects from clinical use of mistletoe have been reported[69] although the use of preparations standardized to small doses of ML1 (1 ng/injection) or depleted of lectins by fermentation [8] may reduce toxicity.

SUMMARY: Mistletoe preparations have been used in the treatment of cancer, but clinical trials have not been sufficient to prove efficacy. Mistletoe is a toxic plant, and side effects have been reported.

PATIENT INFORMATION— Mistletoe

Uses: Mistletoe has been used to treat cancer and in folk medicine for its cardiovascular properties. Clinical efficacy has not been established.

Side Effects: Mistletoe is a toxic plant, and side effects have been reported in clinical use. The use of preparations standardized to small doses of ML1 or depleted of lectins may reduce toxicity.

Dosing: Crude mistletoe fruit or herb is used to make a tea for hypertension at a dose of 10 g/day. There are a number of extracts of mistletoe used as adjuvant cancer therapies, including *Iscador*, a fermented product with different properties than unfermented mistletoe extracts, specifically, its low levels of mistletoe lectin-?. These extracts usually are given by IV or SC injection at doses of 0.1 to 30 mg several times/week. [59,61,63,65]

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- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
      MISTLETOE

MONASCUS

DATE OF ISSUE: SEP 1997

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Monascus purpureus* Went

COMMON NAME(S): Monascus, ZhiTai, XueZhiKang (China)

HISTORY: Red yeast dates back to 800 AD, where it was described in the ancient Chinese pharmacopeia (published during the Ming Dynasty, 1368-1644). It is a mild, non-poisonous yeast useful for gastric problems such as indigestion, as well as circulation. *Monascus purpureus* yeast is made by a fermentation process using cooked, non-glutinous rice.

CHEMISTRY: The commercial product contains 0.4% naturally occurring HMG-CoA reductase inhibitors, of which lovastatin and biologically active hydroxy-acids are most abundant.[1]

Monascidin A, another constituent of monascus, has been characterized as citrinin by qualitative methods, mass spectra and NMR. [2]

PHARMACOLOGY: The particular inhibitor found in the yeast, competitively inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is the enzyme that catalyzes HMG-CoA to mevalonate and then to cholesterol. The result of this is decreased LDL- and VLDL-cholesterol and plasma triglycerides. HDL-cholesterol ("good cholesterol") is increased, which is beneficial to release free cholesterol from extrahepatic tissues. [3,4]

In the late 1970s, it was discovered that monascus metabolites inhibited HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. [5] ZhiTai (0.25% HMG-CoA reductase inhibitors) and XueZhiKang (the ethanolic extract containing 1.1% HMG-CoA reductase inhibitors) have both been extensively studied in China. Monascus contains both of these.[1] XueZhiKang, in three separate animal studies, was effective in reducing serum cholesterol levels, similar to lovastatin (an HMG-CoA reductase inhibitor available commercially as the prescription drug, *Mevacor* by Merck). XueZhiKang was also found to suppress aortic atherosclerotic plaque formation and lipid accumulation in the animal livers. The dose of 0.4 and 0.8 g/kg in one report reduced serum cholesterol levels by 44% and 59%, respectively.[6]

Seventeen Chinese studies (some unpublished) are available evaluating monascus. One major randomized multicenter trial involved 446 hyperlipidemic patients with cholesterol levels greater than 230 mg/dl. At the end of an 8 week treatment, total serum cholesterol was reduced 23% (average), triglycerides were reduced by 36.5%, LDL-cholesterol was reduced by 28.5% and HDL-cholesterol levels were increased by 19.6%. [7] *Cholestin* product literature recommends its use as a dietary supplement, combined with diet and exercise in healthy men and women, under a physician's care, who are concerned with maintaining desirable cholesterol levels. Although results of the studies appear promising, they have not been evaluated by the Food and Drug Administration and therefore are not intended to "diagnose, treat, cure or prevent any disease."[1]

TOXICOLOGY: Citrinin, produced by *Monascus purpureus* and *Monascus ruber*, is nephrotoxic.[2]

Toxicity studies on monascus show no adverse reactions at doses much greater than typical dosing in both long- and short-term studies. In rats fed monascus 50 times the human dose, results showed no abnormalities in areas such as behavior, blood and urine testing. In human trials, some reported slight digestive tract discomfort.[1,8] The product is not recommended for patients with liver disease. One to two percent of HMG-CoA reductase users in general experience hepatotoxicity and myopathy.[1,8]

SUMMARY: *Monascus purpureus* Went is a yeast developed by a fermentation process. It has recently been evaluated for its cholesterol-lowering effects and has been found to inhibit HMG-CoA reductase, a step in the synthesis of cholesterol. Chinese studies are available, but monascus has not been adequately investigated in the US. The FDA has not evaluated any claims for the product but is investigating whether it should be considered a drug or a dietary supplement. Results from about 20 studies offer promising therapy for hyperlipidemic patients. More research is needed to further evaluate the yeast's effects. Toxicity studies are also needed.

PATIENT INFORMATION — Monascus

Uses: Monascus, marketed as *Cholestin*, has been recommended as a dietary supplement combined with diet and exercise in healthy men and women, under physician care, concerned with maintaining desirable cholesterol levels.

Side Effects: Some patients have reported slight digestive tract discomfort. Not recommended for use in patients with liver disease.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MONASCUS

MORINDA

DATE OF ISSUE: OCT 1997

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Morinda citrifolia*

COMMON NAME(S): Morinda, noni, hog apple, Indian mulberry, mengkoedoe, mora de la India, pain killer, ruibarbo caribe, wild pine

BOTANY: The morinda plant, native to Asia, Australia and Polynesia (eg, Tahiti), is a 3 to 8 m high tree or shrub. Its evergreen leaves are oblong and 10 to 45 cm in length. The plant's white flowers are tubular, with conelike heads. The fruit is yellow-white in color, oval in shape, about the size of a potato and has a "bumpy" surface. The ripened fruit has a characteristic cheese-like, offensive odor. Each fruit contains 4 seeds, 3 mm in length. [1]

HISTORY: It is believed that Polynesian healers have used morinda fruits for thousands of years to help treat a variety of health problems such as diabetes, high blood pressure, arthritis and aging. Ancient healing manuscripts cite the fruit as a primary ingredient in natural healing formulations. Today, fruit preparations are sold as juice, in dried "fruit-leather" form and as a dry extract in capsules. US patents can also be found, including such patents as processing morinda fruit into powder, [2] and for xeronine, an alkaloid isolated for medical, food and industrial use. [3]

CHEMISTRY: *Morinda citrifolia* fruits contain essential oils with hexoic and octoic acids, paraffin and esters of ethyl and methyl alcohols. [1] Ripe fruit contains n-caproic acid, presumably responsible for its distinctive odor, known to attract insects such as drosophilia sechellia. [4] Fresh plants contain anthraquinones, morindone and alizarin.[1] A new anthraquinone glycoside from morinda heartwood has recently been described.[5] Hawaiian researcher Ralph Heinicke discovered a small plant alkaloid he termed "xeronine."[3] Damnacanthal, morindone and alizarin are present in cell suspension cultures. [1]

PHARMACOLOGY: *Morinda citrifolia* has been used medicinally for heart remedies, arthritis (by wrapping the leaves around affected joints), headache (local application of leaves on forehead), GI and liver ailments.[1]

It has been theorized that xeronine works at a molecular level to repair damaged cells, regulating their function. It is claimed that all body cells and systems, including digestive, respiratory, bone and skin can benefit. [2]

An overview of traditional applications of the plant in Samoan culture is available. [6]

Morinda has been evaluated for its anticancer activity on Lewis lung carcinoma in mice. It increased lifespan repeatedly in different batches of mice, all yielding similar results. The proposed mechanism is enhancement of the immune system, with macrophage and lymphocyte involvement.[7]

Damnacanthal from *M. citrifolia*root induced normal morphology and cytoskeletal structure in Kirsten-ras Normal Rat Kidney transformed cells (precursors to certain cancer types). This extract was found to be most effective in inhibiting reticular activating system (RAS) function among the 500 extracts tested. [8]

Alcoholic extracts of *M. citrifolia* leaves displayed good anthelmintic activity in vitro against human *ascaris lumbricoides*.[9] Lyophilized aqueous root extracts of the plant showed central analgesic activity, among other effects, suggesting sedative properties of the plant as well. [10]

The fruit of the plant is used as a food, layered in sugar. Leaves are also consumed raw or cooked. The roots yield a red dye, the bark, a yellow dye. [1]

TOXICOLOGY: No information is available about the toxicity of *M. citrifolia* or its constituents. The fruit has long been reported as edible.

SUMMARY: *Morinda citrifolia* has been used as a general healing agent for thousands of years in Polynesia. Current literature claims it is beneficial for immune system function, anticancer activity and for its anthelmintic effects. Little is known about toxicity of the plant. *M. citrifolia* is commercially available as juice or in dried form and is widely promoted in health food markets.

PATIENT INFORMATION— Morinda

Uses: Morinda has been used for heart remedies, arthritis, headache, digestive and liver ailments.

Side Effects: No information is available on the side effects of morinda.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MORINDA

MUIRA PUAMA

DATE OF ISSUE: JUN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Ptychopetalum olacoides* Benth. Olacaceae (Olax family). Less commonly *P. uncinatum* Anselm. and *Liriosma ovata* Miers

COMMON NAME(S): Muira puama, marapuama, potency wood, raiz del macho, potenzholz

BOTANY: *P. olacoides* is a small tree native to the Brazilian Amazon where the stems and roots are used as a tonic for neuromuscular problems. A root decoction is used externally in massages and baths for paralysis and beriberi. Oral use of tea made from the roots for sexual impotence, rheumatism, and GI problems has been noted.[1]

HISTORY: Muira puama is currently promoted as a male aphrodisiac or as a treatment for impotence. This use can be traced back to the 1930s in Europe but has increased with the success of sildenafil (*Viagra*) and the concurrent promotion of "herbal *Viagra*" preparations. It is also a constituent of a popular Brazilian herbal tonic "catuama" consisting of guarana, ginger, *Trichilia catigua*, and *P. olacoides*. Muira puama was official in the Brazilian Pharmacopeia of 1956.

CHEMISTRY: *P. olacoides* root bark produces a volatile oil containing a-pinene, a-humulene, ß-pinene, ß-caryophyllene, camphene, and camphor as major constituents.[2] Alkaloids have been detected but not fully characterized. TLC of an alkaloid fraction demonstrated the absence of yohimbine. Coumarin was detected. [3] Fatty acid esters of sterols, free fatty acids (C_{21}-C_{25}), and free sterols such as lupeol have been isolated and identified. [3,4,5] Similar compounds were isolated from *L. ovata*.[6]

PHARMACOLOGY: An extract of *P. olacoides* reduced locomotor activity in an open field test in mice when orally given 1 hour before testing; however, the same extract reduced immobility time in a forced swimming test. An a_2-adrenergic mechanism was postulated because clonidine gave similar results and yohimbine antagonized the effects of both clonidine and the extract.[7] A hot water extract of *P. olacoides* did not induce colony stimulating factor or mitogenesis in an ex vivo immunomodulation study of 21 Brazilian plants.[8]

Japanese patents have been issued that claim muira puama preparations are useful against stress-induced gastric ulceration [9] and stress-induced blood calcium elevation.[10]

Pharmacologic investigation of catuama and its constituents found that *P. olacoides* had modest analgesic effects in chemical and thermal mouse models of pain. The combined preparation had an effect on the opioid system, demonstrating morphine cross-tolerance and blockade by naloxone. [11] *P. olacoides* had no vasorelaxant effects in a related study in which the other constituents of catuama were active. [12]

Clinical studies to support the use of muira puama are sparse. Several promotional Web sites cite the work of a French clinician, Jacques Waynberg, [13] to support their claims; however, peer-reviewed publications are currently lacking. Muira puama has been contrasted favorably with yohimbine. [14] A German language review was published many years ago.[15]

TOXICOLOGY: Muira puama does not appear to contain yohimbine, nor to have the serious side effect potential of yohimbine.

SUMMARY: Muira puama is a popular yet poorly studied herbal product promoted for erectile dysfunction.

PATIENT INFORMATION — Muira Puama

Uses: *P. olacoides* is used as a tonic for neuromuscular problems. A root decoction is used externally in massages and baths for paralysis and beriberi. Oral use of tea made from the roots for sexual impotence, rheumatism, and GI problems has been noted. Muira puama is currently promoted as a male aphrodisiac or as a treatment for impotence.

Side Effects: Muira puama does not appear to have the serious side effect potential of yohimbine.

Dosing: Muira puama leaves, stem, and roots typically are used at a dose of 0.5 to 1.5 g/day, although there are no clinical studies supporting this dose. [16]

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MUIRA PUAMA

MULLEIN

DATE OF ISSUE: APR 1998

REPLACES MONOGRAPH DATED: SEP 1989

SCIENTIFIC NAME(S): *Verbascum thapsus* L., *V. phlomoides* L., *V. thapsiforme* Schrad. Family: Scrophulariaceae

COMMON NAME(S): American mullein, European or orange mullein, candleflower, candlewick, higtaper and longwort [1]

BOTANY: The common mullein, usually found throughout the United States, is a woolly-leafed biennial plant. During the first year of its growth, the large leaves form a low-lying basal rosette. In the spring of the second year, the plant develops a tall stem that can grow to 4 or more feet in height. The top portion of the stem develops yellow flowers consisting of a five-part corolla. This, along with the stamens, is what constitutes the active ingredient. The flowers bloom from June to September and have a faint, honey-like odor.[2] Electron microscopy performed on *V. thapsus* reveals distinctive pollen grains and trichomes, which may be helpful for identification purposes.[3]

HISTORY: Mullein boasts an illustrious history as a favored herbal remedy and, consequently, has found use in all manner of disorders. Its traditional uses have generally focused on the management of respiratory disorders where it was used to treat asthma, coughs, tuberculosis and related respiratory problems. However, in its various forms, the plant has been used to treat hemorrhoids, burns, bruises and gout. Preparations of the plant have been ingested, applied topically and smoked. The yellow flowers had once been used as a source of yellow hair dye. In Appalachia, the plant has been used to treat colds and the boiled root administered for croup. Leaves were applied topically to soften and protect the skin. An oil derived from the flowers has been used to soothe earaches. [4]

CHEMISTRY: Few compounds with known therapeutic effects have been identified in the plant. These contain saponins, mucilage and tannins.

In a report on the species *V. thapsus*, luteolin glycoside was identified for the first time.[5] Using spectroscopic methods and chemical evidence, five phenylethanoid glycosides and one lignan glycoside were found (in addition to three known phenylethanoid glycosides and four lignan glycosides). [6]

Saponins from *V. songaricum* were identified in European studies, reporting triterpene saponins from the aerial parts, [7] songarosaponin D based on spectral evidence[8] and songarosaponin E and F, the newest triterpenoid saponins. [9] Saponins from *V. nigrum*, a related species, are also reported.[10]

Also from European reports, iridoids from *V. sinuatum* and *V. olympicum* have been identified. New iridoid diglycosides have been isolated and described. [11,12,13,14]

A Czechoslovakian report on *V. pseudonobile* stoj. et stef., first identified (E)-cinnamamide.[15] A German study characterizes water-soluble polysaccharides from *V. phlomoides* L.[16] The content of verbacoside is reported in six *Verbascum* species growing in Poland.[17] Fatty acids from *V. phlomoides* and *V. thapsiforme* are reported in another Polish study,[18] along with sterols from the essential oils of these species.[19] Another related plant, *V. lasianthum*, yields hydrocarbons, ketone alcohols, beta-sitosterol and a triterpenic alcohol. [20]

PHARMACOLOGY: The flowers and leaves are used medicinally. The saponins, mucilage and tannins contained in the flowers and leaves likely contribute to the soothing topical effects of the plant. Similarly, some of these compounds have demulcent properties that may make them useful for the symptomatic treatment of sore throats.[21] The mild expectorant action of the saponins also supports use of mullein for the relief of coughs. It is included in many mixed teas for use as an antitussive.[2]

The ganglionic-blocking effect of *V. nobile*Vel. has been described.[22]

Antiviral activity of mullein has been reported in two studies. In the lyophilized infusion obtained from *Verbascum thapsiforme* Schrad. flowers, activity against herpes simplex type I virus was evaluated in vitro. A decrease in virus titer and inhibition of viral replication by mullein were demonstrated. [23] Another study confirms and evaluates antiviral activity in vitro against Fowl plague virus and influenza A and B strains. [24]

TOXICOLOGY: Plants from the genera *Verbascum* and *Senecio* have been given the common Spanish name senecio, and may cause some confusion. No adverse effects have been reported from the use of *Verbascum*or its extracts.[25]

SUMMARY: Mullein is a common plant with a long history of use in herbal medicine. There is little evidence to indicate that the plant can offer more than mild astringent and topical soothing effects. It may have mild demulcent properties when ingested. Antiviral activity of mullein has been reported against herpes and influenza. The plant has not been associated with toxicity.

PATIENT INFORMATION— Mullein

Uses: Mullein has expectorant and cough suppressant properties that make it useful for symptomatic treatment of sore throat and cough. Antiviral activity of mullein has been reported against herpes simplex type I virus and influenza A and B strains.

Side Effects: No adverse effects have been reported.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MULLEIN

MUSK

DATE OF ISSUE: JAN 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Moschus moschiferus* L. Family: Moschidae

COMMON NAME(S): Musk, Tonquin musk, deer musk

SOURCE: The musk deer (*M. moschiferus*) is a small, solitary animal that attains a stature of only 0.5 m. It is native to mountainous regions of Asia, including Tibet and northeastern China. Both the male and female lack antlers.[1]

Musk is an odiferous secretion derived from the musk gland under the abdomen near the pubis of the male musk deer. The glands weigh up to 30 g and contain about half their weight in musk.[2] According to Leung, there are two methods of obtaining musk.[1] In the first method, the trapped deer is killed in late winter or early spring and the gland is removed. The dried whole gland (known as the pod) or the dried glandular secretions inside (musk grains) are employed in commerce.

Alternately, musk is collected from deer raised in captivity. The musk is removed from the gland of immobilized animals by use of a special spoon. The musk is collected once or twice a year.

This material should not be confused with musk root (*Ferula sumbul* Hook, Family: Apiaceae), which is sometimes used as a substitute for musk in the perfume industry.[3]

HISTORY: The use of musk dates back more than 1300 years when it was used by rulers of early Chinese dynasties. Consequently, it has a broad historical tradition in Chinese herbal medicine. Today, it is used as a component of fragrances and as a fixative in perfumes.[1]

CHEMISTRY: The fresh musk secretion is a dark-brown viscous semi-solid that turns to brownish-yellow or purple-red granules when dried.[1] The term musk is used to describe other materials with a similar odor, although these preparations may be of synthetic or herbal origins.

When distilled, musk yields the principles muscone (muskone) (0.3% to 2%) and normuscone. Other compounds present in musk include steroids, paraffins, triglycerides, waxes, mucopyridine and other nitrogenous substances and fatty acids.[1,2]

Cyclopentadecanone is a synthetic compound that differs from muscone only in the absence of a methyl group.[2]

PHARMACOLOGY: Musk is reported to have anti-inflammatory and antihistaminic activity in animal models. Its anti-inflammatory activity has been reported to exceed that of phenylbutazone in rats with experimentally induced adjuvant arthritis.[1]

Musk has also been reported to have spasmolytic, CNS-depressant, stimulant and antibacterial activity.[1] In clinical studies, musk has been shown to have a beneficial effect in patients suffering from angina, with a therapeutic effect comparable to that observed with nitroglycerin.[1]

TOXICOLOGY: No significant reports of systemic toxicity have been associated with the use of musk.

As with many naturally derived compounds that are applied topically, there exists a potential for a dermal hypersensitivity reaction. Musk components are known to cause a variety of dermal reactions, including pigmented dermatitis following the application of musk-containing rouge[4] and photoallergic contact dermatitis following the use of musk-containing fragrances.[5] In a survey of dermatology clinics in Scandinavia, musk ambrette was among the leading topical photosensitizers reported.[6] This material was similarly cited as one of the most photosensitizing compounds reported by Mayo Clinic patients.[7]

SUMMARY: Musk is an odiferous material derived from a gland of the Asian musk deer. Its unique odor has made it an important component of perfumes. Although traditionally derived from deer that had been killed for the express purpose of musk collection, the material today is largely obtained from deer specifically raised for musk production.

PATIENT INFORMATION — Musk

Uses: Musk is used as a fragrance and component in herbal medicine. It reportedly shows anti-inflammatory and antihistaminic activity, and various other therapeutic effects as a stimulant, treatment for angina, etc.

Side Effects: Topical use may cause symptoms such as contact dermatitis, photosensitivity, etc.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MUSK

MUSTARD

DATE OF ISSUE: FEB 1992

REPLACES MONOGRAPH DATED: N/A

COMMON NAME(S): Brown mustard: *Brassica juncea* (L.) Czern. et Cross. and *B. nigra* (L.) Koch. White mustard: *Sinapis alba* L. synonymous with *Brassica alba*. Family: Cruciferae or Brassicaceae. Other common names by which mustards are known include Chinese mustard(*S. juncea*), Indian mustard (*B. juncea*), yellow mustard (*S. alba*), and *black mustard* (B. nigra).

BOTANY: The mustards are annual or bienniel herbs that grow from 3 to 9 feet in height. All common mustards are cultivated worldwide. The dried ripe seed is used commercially.

Ground mustard, derived from the powdered mustard seed, is known as mustard flour. It may consist of a mixture of brown, black or white seeds. The more pungent mustards are derived from seeds from which the fixed oil has been removed.[1]

HISTORY: Mustard and its oil have been used for the topical treatment of rheumatisms and arthritis and as foot baths for aching feet. Internally, they have been used as appetite stimulants, emetics and diuretics.[1] When black mustard is prepared as a condiment with vinegar, salt and water, the product is properly termed German prepared mustard. Sinapis alba seeds, prepared in a similar manner but without spices, are known as English mustard.[4] Mustards are grown extensively as forage crops.

CHEMISTRY: The volatile mustard oil is derived from steam distillation or by expression. The fixed oil does not contribute to the pungency of the mustard, and ground mustard does not have a pungent aroma.

The pungency is produced when the mustard is mixed with water and the enzyme myrosin hydrolyzes sinigrin (a glucoside found in black and brown mustards) or sinalbin (found in white mustard), releasing allyl isothiocyanate or p-hydroxybenzyl isothiocyanate, which are responsible for the pungent aroma.[2] Depending on the variety of mustard, the yield of allyl isothiocyanate is approximately 1%.[1,5]

Other components of the oil include sinapic acid, sinapine, fixed oil, proteins and a mucilage.

PHARMACOLOGY/TOXICOLOGY: Allyl isothiocyanate is a powerful irritant and blistering agent. It has counterirritant properties and induces lacrimation. It is one of the most toxic essential oils and should not be tasted or inhaled undiluted.[1]

Isothiocyanate compounds such as those found in mustard and other Brassicaceae have been implicated in the development of endemic goiter and have been shown to produce goiter in laboratory animals.[1]

Derivatives of allyl isothiocyanate have formed the basis for toxic agents such as the "mustard gasses" and antineoplastic agents.

Because of its topical irritant effects, mustard has been used as a rubifacient and irritant; mustard plasters are prepared by mixing mustard with flour or other material to make a paste for topical application.[3]

SUMMARY: The pungent flavor of the mustard seeds has made it one of the most widely used spices in the Western world. The mustards have been used in traditional medicine, primarily as topical counterirritants and continue to find some use in a poultice (commonly but inappropriately described as a mustard plaster).[4] The oil is highly irritating and should be considered toxic.

PATIENT INFORMATION — Mustard

Uses: Mustard is used as food, flavoring, forage, emetic, diuretic, topical treatment for arthritis and rheumatism, etc. It contains antineoplastic agents.

Side Effects: The oil is highly irritating and should be considered toxic. Mustard compounds have been implicated in development of goiter.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "M" MONOGRAPHS
  MUSTARD

MYRRH

DATE OF ISSUE: FEB 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Commiphora molmol* Engl. Synonymous with *C. myrrha*, *C. abyssinica* and other *Commiphora*species are used in commerce. Family: Burseraceae

COMMON NAME(S): African myrrh, Somali Myrrh (C. molmol), Arabian and Yemen myrrh (*C. abyssinica*), myrrha, gum myrrh[1] , bola, bal, bol, heerabol[2]

BOTANY: The Commiphora species that serve as sources of myrrh are trees that grow to heights of 30 feet. They are native to Africa and are found in the Red Sea region. A pale yellow-white viscous liquid exudes from natural cracks in the bark or from fissures cut intentionally to harvest the material. [2] This exudate hardens into yellow-brown tears that weigh up to 250 g that form the basis of myrrh resin.[1,2]

HISTORY: Myrrh has been used for centuries[2] for diverse effects as an astringent, antiseptic, emmenagogue and antispasmodic. It also has been used to treat a variety of infectious diseases (including leprosy and syphilis), and to treat cancers. [1] Myrrh played a key role in the religious ceremonies of the ancient Egyptians. [3] It finds use in African, Middle Eastern and Chinese traditional medicine. Today, myrrh is used as a component of fragrances, and as an astringent in mouthwashes and gargles.[1,4] It is sometimes used to flavor beverages and foods.

CHEMISTRY: Myrrh is an oleo-gum-resin[2] that contains from 1.5% to 17% (typically about 8%) of a volatile oil composed of heerabolene, limonene, dipentene and more than a half-dozen additional fragrant compounds.[1] Up to 40% (average 20%) of the resin consists of commiphoric acids and about 60% of the product is a gum that yields a variety of sugars upon hydrolysis.[1] The gum has been reported to contain an oxidase enzyme.[2] The related *C. guidottii* contains the sesquiterpene (+)-T-cadinol.[5]

PHARMACOLOGY: Myrrh is reported to have mild astringent properties.[6] It has been reported to exert antimicrobial activity in vitro.[1]

Myrrh has been found to have a locally stimulating action on smooth muscle tissue and may stimulate peristalsis. [7,8] By contrast, T-cadinol has been shown to have a concentration-dependent smooth muscle relaxing effect on the isolated guinea pig ileum and a dose-dependent inhibitory effect on cholera toxin-induced intestinal hypersecretion in mice.[5]

In addition, extracts of C. mukul have been shown to inhibit the maximal edema response and total edema induced by carrageenan in the rat paw. [9]

A mixture of plant extracts that includes an extract of myrrh has been shown to reduce the rate of gluconeogenesis in rats and may be of interest in the management of diabetes mellitus.[10] An ethylacetate extract of C. mukul significantly prevented the rise in serum cholesterol and triglycerides caused by an atherogenic diet. [11]

TOXICOLOGY: Although myrrh is generally considered to be nonirritating, nonsensitizing and nonphototoxic to human and animal skins, [1] several cases of dermatitis due to myrrh have been reported.[12]

SUMMARY: Myrrh is a fragrant plant exudate that has been used in traditional medicine and as part of religious ceremonies for thousands of years. Today, myrrh is used in fragrances and as a food flavoring. Myrrh posseses potentially useful pharmacologic activity, although the components that exert these actions have not been well characterized.

PATIENT INFORMATION— Myrrh

Uses: Myrrh has been used as a fragrance, flavoring, astringent, antiseptic, emmenagogue, antispasmodic, and treatment for cancer and infectious diseases.

Side Effects: It has reportedly been associated with dermatitis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "M" MONOGRAPHS
    MYRRH

"N" MONOGRAPHS

NEEM

DATE OF ISSUE: JUL 2003

REPLACES MONOGRAPH DATED: APR 1991

SCIENTIFIC NAME(S): *Azadirachta indica* A. Juss. Formerly known as *Melia azadirachta* L. Family: Meliaceae.

COMMON NAME(S): Neem, margosa, nim, nimba

BOTANY: The neem is a large evergreen tree that grows to 18 meters in height. The spreading branches of this tree form a broad crown. The plant is found commonly throughout India and the neighboring region, where it is often cultivated commercially. *Azadirachta indica* is often confused with *Melia azedarach* L. (the chinaberry or Persian lilac).

HISTORY: Almost every part of the neem tree is used in traditional medicine in India, Sri Lanka, Burma, Indochina, Java, and Thailand. [1] The stem, root bark, and young fruits are used as a tonic and astringent, and the bark has been used to treat malaria and cutaneous diseases. The tender leaves have been used in the treatment of worm infections, ulcers, and cardiovascular diseases, and for their pesticidal and insect-repellent actions. [2] The tree yields a high quality timber and a commercial gum.

CHEMISTRY: The seed kernels of neem yield about 10% of a fixed oil, comprised primarily of glycerides. The yellow, bitter oil has a garlic-like odor and contains approximately 2% of bitter principles including nimbidin, nimbin, nimbinin, nimbidol, and other related minor components. [3] All parts of the tree yield beta-sitosterol. Azadirachtin is the most active insecticidal component of neem, with a yield of about 5 g from 2 kg of seeds. [4] An antiulcer phenolicglycoside has been mentioned.

PHARMACOLOGY: The variety of components in neem give the plant and its extracts a number of pharmacologic activities. Neem has been investigated for its potential as a contraceptive agent. The oil has been shown to inhibit sperm motility in vitro, and its intravaginal application to rabbits did not induce mucosal irritation. [6] Sodium nimbinate and nimbidinate have weak spermicidal activity in vitro, and the oil immobilizes human sperm within 30 seconds of contact. [7] In women, the intravaginal application of 1 mL of neem oil prior to intercourse did not affect cycle regularity and provided effective contraception for 10 couples over 4 cycles. [7] Initial acceptance problems caused by the unpleasant smell of the oil were overcome by masking the odor with lemon grass scent.

When injected subcutaneously in rats, neem oil causes alterations in the luminal epithelium of the uterus, preventing pregnancy when administered for several days postcoitally; this appears to be a direct toxic effect and not hormonally dependent. [8] Therefore, it has been suggested that the lack of hormonal effect may offer a contraceptive alternative with fewer side effects than traditional steroidal contraceptives. [9] Neem oil exerts some contraceptive effect when administered orally to rats, but its efficacy by this route is insufficient to warrant further study. [10]

A 200 mg dose of seed oil administered orally to normoglycemic and diabetic rats produced reductions in mean glucose concentrations of up to 48% 6 hours after drug administration.[11] In rats, *A. indica* could be of benefit in diabetes mellitus in controlling blood sugar or also may be helpful in preventing or delaying the onset of the disease.[12]

The aqueous extract of neem bark exhibits antiulcer and antisecretory effects. The antiulcer effects may be caused by a phenolic glycoside that represents 10% of the raw bark extract. The bark extract is equally effective as ranitidine but more potent than omeprazole in inhibiting pylorus-ligation-induced acid secretion. Its mechanism of action has been suggested to be similar to that of omeprazole (ie, dose-dependent inhibition of H+-K+-ATPase activity in vitro). The gastroprotective mechanism involves preventing oxidative damage of the gastric mucosa by blocking lipid peroxidation and by removing endogenous hydroxyl radicals. [5]

Neem oil and azadirachtin are effective pesticides and insect repellents. Azadirachtin is one of the most potent insect antifeedant and ecdysis-inhibitory compounds known from a botanical source.[13] Because of the complex chemical structure of azadirachtin, only naturally derived products have been used commercially. This compound is effective in concentrations as low as 0.1 ppm and has been shown to be biodegradable, nonmutagenic, and nontoxic to warm-blooded animals, fish, and birds. The Environmental Protection Agency has approved the use of a neem formulation as a pesticide for limited use on nonfood crops. [14] Other insecticidal compounds from neem include deactyl-azadirachtinol and salannin.[15]

A neem seed extract may be used in integrated pest management programs of citrus. The extract produced a dose-dependent larval mortality against the root weevil *Diaprepes abbreviatus* (L.), which is an exotic insect pest of Florida citrus. The numbers of larvae hatching per egg mass were reduced by 27% and 68% at 30 and 90 mg/L of neem, respectively. A reduction in fresh weights among larval survivors was more pronounced than the mortality response. Larvae treated with 45 mg/L weighed 60% less than those in the control after 4 weeks. Larval growth was inhibited by more than 97% with 42.9 mg/L in the diet. A soil drench containing 30 mg/L reduced the survival and weight gain of newborn larvae of the root weevil added to potted citrus and provided protection to the roots in a greenhouse experiment. [16]

Azadirachtin is a potent inhibitor of insect cell replication, with an EC50 of 1.5×10^{10} M against *Spodoptera* cells and of 6.3×10^{9} M against *Aedes albopictus* cells. The major neem seed terpenoids, nimbin and salannin, inhibited insect cell growth by 23% and 15%, respectively. [17] Other insecticidal compounds from neem include 22,23-dihydronimocinol, desfurano-6alpha-hydroxyazadiradione, meliacin, 7alpha-senecioyl-(7-deacetyl)-23-O-methylnimocinolide. [15,18]

Gedunin and nimbolide, both isolated from neem, have shown antimalarial activity in vitro. [13] One survey of the in vitro antibacterial effect of neem oil against 200 clinical bacterial isolates resulted in 92% susceptibility. [19] Three natural repellents (1 eucalyptus based, 1 neem based, and 1 containing several repellent essential oils) was compared with 15% DEET in human-landing catches in Bolivia. The eucalyptus-based repellent gave about 97% protection for 4 hours and DEET gave 85% protection. However, Neem did not provide sufficient protection against mosquito bites. [20]

Neem oil has been used as a traditional dentifrice. The oil has been found to be anti-inflammatory, aseptic, and healing in gingivitis. In toothpaste, the extract has low abrasiveness and good antimicrobial activity against oral flora. [21] Neem mouthwashes inhibit *Streptococcus mutans*.[22]

TOXICOLOGY: Neem oil is nonmutagenic in the Ames mutagenicity assay.[23]

Neem oil traditionally has been considered to be a relatively safe product in adults. The LD50 of neem oil is 14 mL/kg in rats and 24 mL/kg in rabbits. In rats, a dose of up to 80 mL/kg caused stupor, respiratory distress, depression of activity, diarrhea, convulsions, and death. [24] Gross examination of all organs except the lungs was normal after acute dosing.

The seeds of neem, which are poisonous in large doses, resemble the more toxic drupes of *M. azadarach* and are sometimes confused. Severe poisoning in 13 infants who had received 5 to 30 mL doses of margosa (neem) oil has been reported. Toxicity was characterized by metabolic acidosis, drowsiness, seizures, loss of consciousness, and coma. Death occurred in 2 infants.[1] These infants exhibited Reye syndrome-like symptoms, with death from hepatoencephalopathy. Neem oil administered to mice can induce mitochondrial injury, resulting in similar hepatic damage. The toxin has not been identified, but may be a long-chain monounsaturated free acid, to which infants and small children are particularly vulnerable. [25]

A neem-based compound, *Vepacide*, was investigated for its effects on lactate dehydrogenase (LDH) in different tissues of male and female rats for a period of 90 days. Administration of *Vepacide* caused a significant increase of LDH activity in serum and lung tissues and decreased LDH activity in liver and kidney tissues after 45 and 90 days of daily treatment. Necrosis was observed in the liver and kidney tissues but not in the lung tissue, possibly because of the stress adaptive response

from the increase in LDH.[26]

SUMMARY: Neem oil has been used in traditional medicine in India for thousands of years, practically as a panacea. The oil and its extracts are insecticidal, can reduce blood sugar levels, and may be the source of a contraceptive substance. The antiulcer effect of the bark extract may help control gastric hyperacidity. Although it generally has not been associated with toxicity in adults, its use has resulted in Reye syndrome-like symptoms and mortality in infants.

PATIENT INFORMATION— Neem

Uses: Neem has been used as an insecticide, insect repellent, oral dentifrice, and in traditional medicine to treat malaria, diabetes, worms, and cardiovascular and skin diseases. It reportedly has contraceptive, antiulcer, antisecretory, and fungicidal potential; however, there are no clinical trials to support these uses.

Side Effects: It is toxic in large doses. In infants, it can produce symptoms like those of Reye syndrome.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "N" MONOGRAPHS
    NEEM

NETTLES

DATE OF ISSUE: APR 1997

REPLACES MONOGRAPH DATED: FEB 1989

SCIENTIFIC NAME(S): *Urtica dioica* L. Family: Urticaceae

COMMON NAME(S): Stinging nettle, nettle

BOTANY: Nettles are perennial plants native to Europe and found throughout the US and parts of Canada. This plant has an erect stalk and can stand up to 3 feet. It has dark green serrated leaves that grow opposite each other along the stalk. The plant flowers from June to September. The leaves contain bristles that transmit irritating principles upon contact. The nettle fruit is a small, oval seed about 1 mm wide. It is yellow-brown in color. [1]

HISTORY: This plant is known for its stinging properties. However, it has been used in traditional medicine as a diuretic, antispasmodic, expectorant and treatment for asthma. The juice has been purported to stimulate hair growth when applied to the scalp. Extracts of the leaves have been used topically for the treatment of rheumatic disorders. The tender tips of young nettles have been used as a cooked pot herb in salads.

CHEMISTRY: More than 24 chemical components have been identified in nettles. The primary structure of *Urtica dioica* agglutinin has been determined and found to be a two-domain member of the hevein family of proteins.[2] Compounds isolated from the roots and flowers include scopoletin, steryl derivatives, lignan glucosides and flavonol glycosides.[3] Sixteen free amino acids have been found in the leaves.[4] Nine flavonoid compounds have been isolated and identified. [5] Phenylpropanes and lignans from the roots have been isolated and described.[6] The plant also contains vitamins C, B-group and K, along with other various acids. [1] Mineral salts have also been found. Nitrate concentrations in nettle leaves have been reported. [7] Glucokinin (allegedly responsible for "antidiabetic activity") has been reported, but its presence in the plant is controversial. [1] In addition to sitosterol, at least six other related steroids have been identified. [8] The plant has been used as a commercial source of chlorophyll. The young shoots are rich in carotene and vitamin C. The stinging trichomes of nettle contain amines, such as histamine, serotonin and choline. Nettle fruit contains protein, mucilage and fixed oil. [1] Aqueous extracts of the plant have been studied.[10,11,12,13] Isolation and identification among nettles have been performed.[14] HPLC, GC and other methods have determined a specific lectin found only in *Urtica dioica* roots, which may help to standardize preparations.[15,16]

PHARMACOLOGY: Nettle herb is known to have mainly diuretic actions. Treatment over 14 days increases urine volume and decreases systolic blood pressure. [1] Nettle's "supposed" claims against diabetes, cancer, eczema, rheumatism, hair loss and aging have been reported [9,17] but are probably related to its "age-old" roles in folk medicine. Other folk medicine applications include wound healing, treatment of scalp seborrhea and greasy hair, and gastric juice secretion. [1] A combination product includes nettle to treat hyposecretory gastritis. [18]

Nettle in a combination product containing several other herbs has been tested in 22 patients for bladder irrigation. Post-operative blood loss, bacteriuria and inflammation were all reduced following prostatic adenomectomy.[19] *The German Commission E Monograph* supports this indication by its similar listing for "irrigation in inflammation of the urinary tract and in the prevention and treatment of kidney gravel." [1] Nettle's use in expelling bile has been studied. [20]

Urtica dioica in a combined extract to treat benign prostatic hyperplasia (BPH) in 134 patients was effective in reducing urine flow, noctura and residual urine. A 300 mg dose of the plant extract was as effective as 150 mg.[21] A possible mechanism may be caused by a hydrophobic constituent (eg, steroidal), which inhibits the sodium-potassium ATP-ase activity of the prostate, leading to suppressed cell growth in this area. [22] Another report explains a different mechanism but suggests the aqueous extract is the active component in BPH therapy to inhibit the sex hormone-binding globulin to its receptor. [23]

Freeze-dried nettle has been evaluated for allergic rhinitis. In a double-blind trial, 57% of 69 hay fever sufferers who completed the trial judged the nettle preparations to be moderately to highly effective in treatment vs placebo.[24]

CNS depressant effects of nettle extract in rats are described, suggesting diminished motor activity and reduced convulsions, along with hypothermic effects with its use.[27]

Animal reports on nettle pharmacology are available, including its dihydroergotamine-like effect on mouse uterine smooth muscle, probably caused by pyranocoumarin,[27] nettle's carbohydrate binding properties[28] and its ability *in vitro* to inhibit enzyme aromatase.[29] A study concerning a lectin present in nettle suggests a potent and selective inhibitor of HIV and cytomegalovirus replication *in vitro*. When evaluated for its anti-diabetic effect, *Urtica dioica* slightly increased glycemia, aggravating the condition in two reports. [25,26]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Nettles are known primarily for their ability to induce topical irritation following contact with exposed skin. This contact urticaria is accompanied by a stinging sensation lasting 12 hours or longer. A report closely associates mast cells and dermal dendritic cells. Immediate reaction to nettle stings is caused by histamine content, while the persistence of the sting may be caused by other substances directly toxic to nerves. [31]

The stinging hairs of the nettle plant comprise a fine capillary tube, a bladder-like base filled with the chemical irritant and a minute spherical tip, which breaks off on contact leaving a sharp-pointed tip that penetrates the skin. The irritants are forced into the skin as the hair bends and constricts the bladder at the base.

The topical irritation is treated by gently washing the affected area with mild soapy water. Treatment with systemic antihistamines and topical steroids may be of benefit. Other side effects of nettle are rare but include allergic effects such as edema, oliguria and gastric irritation. [1]

SUMMARY: Nettles have been part of our culture for thousands of years. They are more widely recognized for their irritation, but have been found to have many pharmacological benefits, proving some "folk remedies" to be effective. Its use in bladder irrigation, BPH treatment, hay fever relief and its CNS depressant effects have all been studied. Other than contact urticaria, side effects with plant ingestion are rare. The young herb (before stinging cells form) can be consumed as a pot vegetable.

PATIENT INFORMATION — Nettles

Uses: Prove as a diuretic, nettles are also being investigated as treatment for hay fever and irrigation of the urinary tract.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Internal side effects are rare and are allergic in nature. External side effects result from skin contact and take the form of burning and stinging that persist for 12 hours or more.

Dosing: The herb is used as a diuretic at doses of 8 to 12 g/day. In contrast, the root is used for urinary conditions such as benign prostate hypertrophy at 4 to 6 g/day.[32]

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "N" MONOGRAPHS
  NETTLES

NEW ZEALAND GREEN-LIPPED MUSSEL

DATE OF ISSUE: APR 1997

REPLACES MONOGRAPH DATED: APR 1987

SCIENTIFIC NAME(S): *Perna canaliculus*; *Mytilidae*

COMMON NAME(S): New Zealand Green-Lipped Mussel (NZGLM)

HISTORY: Early reports suggested that the daily ingestion of NZGLM extract alleviates the symptoms of rheumatoid arthritis and osteoarthritis in humans. Supported by a worldwide media campaign, claims were made that the extract was safe and effective in treating rheumatic diseases. The Arthritis Foundation responded by calling the product unproven and feared that the campaign could delude arthritis sufferers and raise false hopes. [1] Although the FDA issued an "Import Alert" in 1980 to stop the importation of the extract, it persists in the marketplace.

CHEMISTRY: Virtually nothing is known about the chemistry of the components of *P. canaliculus*. Lipid fractions have been found to contain arachidonic acid and its sterol ester, other unidentified sterols and the compound phaeophytin-a. Freeze-dried mussel preparations contain 9% nitrogen, 9% lipid and 20% carbohydrate, with less than 4 ppm heavy metals. Glutamine and aspartate are the most prevalent amino acids. [2] An extract contains amino acids, fats, carbohydrates and minerals. [3]

The New Zealand green-lipped mussel (NZGLM) is freeze-dried and ground into a capsule preparation for human consumption. The gonad comprises > 70% of the weight of the mollusk, and some investigators use gonadal tissue selectively in their preparations.

PHARMACOLOGY: Evidence for the anti-inflammatory activity of NZGLM extract is believed to have originated in the US during the screening of marine mollusks for antitumor activity. Animal data describing its activity have been conflicting.

Oral administration of the lipid fraction to rats concomitantly with the anti-inflammatory agents aspirin, indomethacin, tolmetin or diclofenac was found to reduce gastric mucosal damage by these drugs in some instances by 100%. Oral administration of the crude mussel preparation and its lipid extracts slightly reduced carrageenan-induced rat footpad edema; however, the changes were not statistically significant. [2]

Other investigators found that *P. canaliculus*extract reduced carrageenan-induced rat footpad edema only following intraperitoneal injection. A 500 mg/kg dose of crude preparation was the lowest effective dose, and the effect was noted within 2 hours. Oral administration of the material had no effect on inflammation. [4] This effect was also reported by investigators at the Royal Melbourne Institute of Technology, Australia, who showed that rat paws injected with carrageenan had swelled by 3% two hours after injection with the extract compared with 26% after injection with aspirin, ibuprofen or indomethacin. [5]

The oral administration of a marketed preparation of NZGLM to pregnant rats retarded fetal development and delayed parturition (the action of giving birth), suggesting that the product contains an orally active prostaglandin inhibitor. Other inhibitors, such as aspirin, indomethacin and naproxen, are known to interfere with ovulation and prolong gestation periods in rats. This consistency of similar effects from NZGLM are shown in this study. [6] Contrary to earlier work by this group, this experiment indicated that pharmacologic activity could be obtained when the extract was administered orally.

The results of several human clinical trials using NZGLM have been reported. The studies have been generally small, some poorly designed and the data conflicting. A highly publicized study heralded the benefits of oral administration of NZGLM extract in patients with classical rheumatoid arthritis and osteoarthritis. [7] Patients took 3 capsules a day (350 mg NZGLM extract per capsule or placebo) under double-blind conditions for 3 months. Both groups were then given NZGLM during months 4 to 6. At the end of the first 3 months of treatment, 39% of the patients (13/33) taking NZGLM and 18% (6/33) of the placebo-treated patients showed improvement. Although additional patients improved during the second 3 months of treatment, the analysis of the data was insufficient to draw conclusions about the extent of clinical benefit. The FDA and the National Institute for Arthritis, Metabolism and Digestive Diseases found that the study was small and poorly described, and that the extract was no more effective than the placebo.[7] In a follow-up study, 30 patients with rheumatoid arthritis were given the compound (300 mg 3 times/day) for one month.[8] There were no significant differences between the NZGLM group and placebo for any measurement. [8] The authors of the *Practitioner* report objected to the conclusions of this study, indicating that a 1-month trial period was too short to detect efficacy with *Seatone*; even in their trial, improvement was not noted before 3 months of therapy. Further, this improvement was maintained for days to several months after discontinuing treatment. They emphasized that NZGLM was the "safest and most effective preparation for both rheumatoid arthritis and osteoarthritis that [we] have yet come across." [9]

In another study, patients with rheumatoid arthritis and osteoarthritis received naproxen (750 mg/day) concomitantly with either NZGLM extract (1050 mg/day) or placebo for 6 weeks. From weeks 7 to 12, naproxen was replaced with placebo in both groups. During the first 6 weeks, there were no significant differences between the groups in any measurement or any change in measurement. After withdrawing naproxen, 15 or 22 patients in the NZGLM group and 15 of 19 in the placebo group discontinued because of a lack of efficacy. The addition of the mussel extract was not superior to adding placebo for alleviating symptoms in patients already receiving naproxen, and neither placebo nor mussel extract alone provided adequate symptomatic relief in the majority of patients, despite 6 weeks of pretreatment. [12]

TOXICOLOGY: All studies with NZGLM and its extracts have reported a low incidence of adverse effects, which generally consisted of GI symptoms (eg, diarrhea, nausea, flatulence); no significant changes in laboratory test results have been noted. [13]

One case report describes granulomatous hepatitis, jaundice, colickly epigastric pain, anorexia and malaise in a 64-year-old woman taking NZGLM. Liver biopsy and eosinophil presence were suggestive of a drug reaction. Discontinuation of all medications yielded normal liver function tests after a 3-month period. [14]

SUMMARY: NZGLM extract is promoted for the relief of symptoms of rheumatoid arthritis and osteoarthritis. Some anti-inflammatory activity has been found in animal tests, but this effect is inconsistent. The results of several human trials indicate that the initial findings of effectiveness reported in 1980 have not been reproducible. NZGLM extract cannot be recommended at this time for the treatment of inflammatory disease. A low incidence of adverse effects has been reported primarily consisting of possible GI symptoms. NZGLM delays parturition in animals and, therefore, should be avoided in pregnancy. A case report of drug-induced granulomatous hepatitis also exists. Additional research is needed to determine efficacy with this product.

PATIENT INFORMATION — New Zealand Green-Lipped Mussel

Uses: This product is being investigated as a treatment for rheumatoid arthritis and osteoarthritis. Although anti-inflammatory activity has been reported, this has not been proven.

Side Effects: Gastrointestinal discomfort has been reported, but the incidence is low. Animal studies suggest that this product could be dangerous to a fetus. Do not take during pregnancy.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "N" MONOGRAPHS
    NEW ZEALAND GREEN-LIPPED MUSSEL

NIGELLA SATIVA

DATE OF ISSUE: MAR 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Nigella sativa* L. Family: Ranunculaceae

COMMON NAME(S): Black seed, black cumin, charnushka, "black caraway" (not true caraway), baraka (the blessed seed), fitch (Biblical), "love in the mist"

BOTANY: *Nigella sativa* (NS) is an annual herb with terminal, grayish-blue flowers reaching between 30 to 60 cm in height. The toothed seed pod contains the distinctive tiny (1 to 2 mm long), black, 3-sided seeds, that are the plant parts used for medicinal purposes. [1,2,3]

HISTORY: NS is said to have been used for 2000 years, with some recordings of traditional uses of the seed dating back 1400 years. Its use began in the Middle East and spread throughout Europe and Africa. NS was found in the tomb of King Tutankhamen. Ancient Egyptians believed that medicinal plants such as these played a role in the afterlife. In the 1st century AD, Greek physician Dioscorides documented that the seeds were taken for a variety of problems including headache, toothache, nasal congestion, and intestinal worms.[1,3]

CHEMISTRY: Active ingredients in the seeds include thymoquinone, nigellone, and 40% fixed oils. Nigellimine N-oxide, an isoquinoline alkaloid, has been isolated from the seeds, as well. Other constituents include 84% fatty acids (linoleic and oleic); volatile oils (1.4%); alkaloids; saponin (melantin); palmitic, glutamic, ascorbic and stearic acids; arginine; methionine; lysine; glycine; leucine; and phytosterols. Crude fiber, calcium, iron, sodium, and potassium are also present. Nutritional composition of the seeds breaks down to 21% protein, 35% carbohydrate, and 36% fat. [1,2,3,4,5]

PHARMACOLOGY: NS has been used to benefit the GI system, as it eases gas and colic. [1] It has been used for diarrhea (dysentery) and constipation (hemorrhoids).[2]

At least 2 references claim that the respiratory effects of NS make it beneficial for allergies, cough, bronchitis, emphysema, asthma, flu, and chest congestion. [2,3] Constituent nigellone, in low concentrations, inhibits the release of histamine from mast cells. [6] Another report discusses volatile oil of NS (with the thymoquinone component removed) to provide a centrally acting respiratory stimulant when tested in guinea pigs. [7]

There are many studies available discussing immune/protective or anticancer effects of certain preparations of NS. One of these reports that a mixture of NS, including cysteine, vitamin E, and *Crocus sativus*, reduces cisplatin-induced side effects in rats, including nephrotoxicity. [8] In another report, NS protected against induced falls in hemoglobin levels and leukocyte counts. [9] NS also enhances production of certain human interleukins and alters macrophages, suggesting changes in immune response in vitro.[10] NS has inhibited stomach tumors in mice.[11] Antitumor activity against certain carcinoma cells in vitro has been shown. In vivo, Ehrlich ascites carcinoma was completely inhibited by NS.[12] Constituents thymoquinone and dithymoquinone have demonstrated cytotoxic actions in human cell lines, as well.[13] Thymoquinone protected against induced hepatotoxicity in mice in vivo, [14] and in rat hepatocytes.[15]

Traditional use (ground seeds in poultice form) for inflammatory ailments such as rheumatism, headache, and certain skin conditions is proven by modern studies. Topical application of an NS mixture delayed and reduced papilloma formation in mice. [16] A fixed oil preparation of NS demonstrated anti-eicosanoid and antioxidant activity, again supporting the seeds' use for anti-inflammatory actions. [17]

A mixture containing NS displayed hepatic gluconeogenesis in rats related to antidiabetic actions. This may be beneficial in non-insulin dependent diabetes mellitus patients.[18] However, NS was not proven to increase glucose tolerance as the other components of the investigational mixture. [19]

NS has been used as a vermifuge.[1] The essential oil of the seed has been reported as an effective antimicrobial and anthelmintic agent. [20] NS has eradicated staphlococcal infections in mice and has also displayed other gram negative and gram positive antimicrobial actions, some of which are synergistic with other antibiotics.[21] NS traditionally has been used for conjunctivitis,[2] abscesses, parasites, and other infections.[3]

NS also plays a role in women's health, stimulating menstruation and increasing milk flow. [1,3] One study reports NS to have an anti-oxytocic potential in rat uterine smooth muscle, inhibiting spontaneous contractions. [22] Another report discusses the use of a seed extract to prevent pregnancy in rats 1 to 10 days post-coitum. [23]

NS may also possess the ability to decrease arterial blood pressure as observed in rats, suggesting the possible use as an antihypertensive agent. [24]

NS has also been used as a flavoring or as a spice.[3]

TOXICOLOGY: One report discusses allergic contact dermatitis from topical use of the oil. [25]

SUMMARY: NS has a long history dating back to Biblical times. Its uses include therapy in digestive disorders, as a respiratory treatment, and for its immunological effects including anti-cancer properties, anti-inflammatory actions, and antimicrobial effects. Toxic effects include contact dermatitis. Use during pregnancy should be avoided.

PATIENT INFORMATION — Nigella Sativa

Uses: *Nigella sativa* has been used for GI disorders and respiratory problems. Studies have been performed researching its immune/protective or anticancer effects, anti-inflammatory actions, and antimicrobial and anthelmintic properties. More human studies are needed.

Side Effects: Contact allergic dermatitis can occur with topical use of the oil. Do not use NS during pregnancy.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "N" MONOGRAPHS
    NIGELLA SATIVA

NUTMEG

DATE OF ISSUE: NOV 1997

REPLACES MONOGRAPH DATED: SEP 1987

SCIENTIFIC NAME(S): *Myristica fragrans* Houtt. Family: Myristicaceae

COMMON NAME(S): Nutmeg, mace, nux moschata

BOTANY: The nutmeg tree is the source of the spices nutmeg and mace. This evergreen grows to over 60 feet. It is found in India, Ceylon, Malaysia and Granada. This slow-growing tree produces a fruit called a nutmeg apple, which is similar in appearance to a peach or apricot. When the fruit ripens, it splits to expose a bright-red, net-like aril wrapped around a shell, which contains the nut. The nut is removed and dried to produce nutmeg. The dried aril yields the spice mace, which possesses a flavor similar to that of nutmeg.[1,2]

HISTORY: Nutmeg is a widely used food spice that has received attention as an alternative hallucinogen. Both nutmeg and mace have been used in Indian cooking and folk medicine. The folk uses of nutmeg have included the treatment of gastric disorders and rheumatism, and it has been used as a hypnotic [3] and an aphrodisiac.[4]

Pliny, in the 1st century A.D., described a "comacum" tree with a fragrant nut and two perfumes. During the 6th century A.D., nutmeg and mace were imported by Arab traders. By the 12th century, these spices were well known in Europe. Chaucer writes of "nutmeg in ale" in *The Canterbury Tales* during the 14th century.[5]

At the turn of the 19th century, interest developed in the use of nutmeg as an abortifacient and a stimulant for menses. These properties have been largely discounted but remain a persistent cause of nutmeg intoxication in women with delayed menses.[6,7]

CHEMISTRY: Nutmeg seed contains 20% to 40% of a fixed oil called nutmeg butter, once used externally for sprains. Today, it has some commercial use in soaps and perfumes.[5] This oil contains myristic acid and glycerides of lauric, tridecanoic, stearic and palmitic acids. Nutmeg oil (also known as myristica oil) is produced from the steam distillation of the nut. Also present is starch, protein, saponin, catechins and others. [1]

The seed nut also contains 8% to 15% of an essential oil that is believed to be partially responsible for the effects associated with nutmeg intoxication. The aromatic oil contains d-camphene (60% to 80%), dipentene (8%), myristicin (4% to 8%), elemicin (2%) and small amounts of iso-elemicin; d,l-pinene; geraniol; eugenol; isoeugenol; safrole; and limonene.[8,9] Also present in the oil is sabinene, cymene alpha-thujene, gamma-terpinene and monoterpene alcohols in smaller amounts. Mace and mace oil contain many of the same components of nutmeg and its oil, but mace appears to have a higher myristicin content, with less fixed oil. [1,3]

Nutmeg constituents have been identified by thin-layer chromatography. [10] Quantitative determination has been performed on its active constituents in the oil (eugenol and isoeugenol).[11] High-performance liquid chromatography (HPLC) has also been performed in the determination of safrole and myristicin in the nut and the aril. [12] Other recent reports are available concerning chemical composition. [13,14] Nutmeg and mace responded similarly to marijuana in a "simple field test for marijuana." [15]

PHARMACOLOGY: Nutmeg was known for its psychoactive properties as early as 1525 and has gained a reputation among inmates and drug cultists as a hallucinogen.[16] Doses of 5 to 20 g appear to be required for any pharmacologic activity to occur. This is equivalent to one to three whole nuts; 2 tablespoons of commercial ground nutmeg weight, about 14 g; or two grated nuts.[17]

Debate surrounds the issue of whether myristicin is the psychoactive component of nutmeg. It does not appear that myristicin alone can induce hallucinations. [18] Because synthetic myristicin does not imitate nutmeg intoxication, it has been suggested that the presence of other compounds (eugenol, geraniol) may be needed for the characteristic pharmacologic effect.[19] It has been proposed that the structural similarities of the allyl benzene components of nutmeg to those of amphetamine-like compounds may be responsible for the CNS activity of the spice. Alternately, it has been theorized that myristicin and elemicin may be metabolized to their amino derivatives following ingestion. The probable derivatives include the psychotomimetics MMDA (3-methoxy-4,5 dimethylene-dioxyamphetamine) from myristicin and TMA (3,4,5-tri-methoxyamphetamine) from elemicin.[20] A structural similarity exists among these metabolites, amphetamine and mescaline. One report suggests nutmeg oil to antagonize amphetamine stimulatory effects in chickens.[21]

The effects of nutmeg intoxication are variable, and the loss of the volatile oil from the ground spice results in part in the variability of the experience. Generally, nutmeg for intoxication is chewed or the powdered nut is suspended in a liquid and drunk. Geraniol is approximately three times as potent as ipecac in inducing emesis; hence, users may combine ground nutmeg with cola syrup to reduce the chances of emesis. This mixture is appropriately referred to as "brown slime." [22]

Nutmeg has received attention for the treatment of diarrhea in calves.[23] It has also been used in the treatment of human diarrhea secondary to thyroid medullary carcinoma[24] and in the treatment of human diarrhea in doses of 4 to 6 tablespoons of nutmeg per day. A fall in serum calcium levels was also noted in this case report, improving chronic hypercalcemia possibly related to this therapy. [25] The hexane-soluble fraction of nutmeg was found to be most active in inhibiting secretory activity against *E coli* toxins in an antidiarrheal report in animals.[26] Inhibition of the synthesis and activity of prostaglandins appears to be additionally responsible for this effect.[27] Another study on this effect reports dose-related inhibition of contraction in rat tissue. In human colon resections, nutmeg similarly reduced prostaglandin-like activity in doses from 0.1 to 500 mcg/ml (however, at 5 mcg/ml, an increase, not understood, was noted). [28] Eugenol appears to be the most potent antiprostaglandin component of nutmeg oil.[9] A later study confirms this fact by quantitative determination, reporting eugenol and isoeugenol to be the active principles. The mechanism is their capacity to inhibit platelet aggregation. [11] An earlier report on two subjects found no differences in aggregation using 1.5 to 4 grams of freshly ground nutmeg, 3 to 4 times a day for a 2-day period.[29] Ground nutmeg administered orally to rats decreased renal prostaglandin levels to a degree similar to that produced by indomethacin.[30] Other reported uses of nutmeg include use as a larvicidal agent, a flavoring agent in many foods and a fragrance component in soaps and perfumes.[1] Ethnopharmacology employs nutmeg for mouth sores and insomnia.[31] Traditional medicinal use is also discussed. [12]

TOXICOLOGY: Symptoms appear 3 to 8 hours after ingestion of large amounts of the spice. The episodes are characterized by weak pulse, hypothermia, disorientation, giddiness, nausea and vomiting and a feeling of pressure in the chest or lower abdomen. For up to 24 hours, an extended period of alternating delirium and stupor persists, ending in a heavy sleep. There is often a sensation of loss of limbs and a terrifying fear of impending death. Death has been reported following the ingestion of a very large dose.[32] A case report reviews a 25-year-old male expressing psychotic symptoms upon ingestion of 120 to 650 mg nutmeg. Haloperidol therapy was necessary to stabilize the patient.[33] Another case report discusses similar findings in a 23-year-old with acute psychotic break and anticholinergic toxic episode symptoms, such as hallucinations and palpitations.[34] In a similar case, an acute anticholinergic hyperstimulation occurred in a pregnant woman after excessive nutmeg ingestion.[35] Gastric lavage and supportive therapy have been recommended for nutmeg toxicity.[36] Recovery usually occurs within 24 hours but may extend for several days.[37] Additional reports discussing misuse of nutmeg are also available. [38,39]

Safrole, a minor component of the oil, has been shown to promote hepatocarcinomas in mice.[40] The oil is moderately irritating when applied to rabbit skin for 24 hours under occlusion but was found to be nonirritating and nonsensitizing to human skin. [32]

SUMMARY: Nutmeg is a common spice that is used widely in cooking. It has been used pharmacologically for diarrhea treatment and is being studied for its role in inhibition of prostaglandin synthesis and inhibition of platelet aggregation. The ingestion of several tablespoons of the spice can lead to a stuporous intoxication that may be severe in its presentation.

PATIENT INFORMATION— Nutmeg

Uses: Nutmeg is used as a flavoring agent and a fragrance. It has also been used as a larvicidal, a hallucinogen and treatment for diarrhea, mouth sores and insomnia.

Side Effects: Side effects include weak pulse, hypothermia, disorientation, giddiness, nausea, vomiting, a feeling of pressure in the chest or lower abdomen, a sensation of loss of limbs, a fear of impending death and, after a very large dose, death.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "N" MONOGRAPHS
    NUTMEG

"O" MONOGRAPHS

OATS

DATE OF ISSUE: NOV 1997

REPLACES MONOGRAPH DATED: JAN 1991

SCIENTIFIC NAME(S): *Avena sativa* L. Family: Gramineae

COMMON NAME(S): Oats

BOTANY: Oats probably originated in three geographic regions: Abyssinia, the Mediterranean and China. Today, the grain is grown primarily in the US, Canada, Russia and Germany. The oat is derived from wild grasses and evolved into today's cultivated plant, which adapted to climate and locality. The plant grows to be about 1 meter tall. Its linear leaves are long and narrow, and its flowers are gathered at the top of the plant, which contain two to three florets. [1]

HISTORY: Rich in fat and protein, oats, compared with other cereals, have one of the highest food values for humans. [2] The majority of oat stocks are used for feeding livestock, but recent interest in the fiber content of oats has resulted in an increased demand for human consumption. Oat extracts have been used for more than a century as soothing topical emollients. Since 100 B.C., the oat has been grown mainly in northern latitudes. [1]

CHEMISTRY: Aside from polyphenols, mono- and oligosaccharides, iron, manganese and zinc are also present in the plant. Concentration of these minerals is higher in oats than in other cereals. Other constituents include flavones, triterpenoid saponins in the leaves, carotenoids and chlorophyll derivatives. [3] Composition and physical behavior of oats have been evaluated in another report. [4]

PHARMACOLOGY: Oats are a good source of energy, protein and fat for humans, especially children. [5] Because of its gluten content, oat plant derivatives have been effective in managing dry, itchy skin conditions. [6] Bath products, including colloidal oatmeal mixtures, bath soaps and gels, and powders containing oat extracts are available commercially. An overview of oat use in cosmetics, including gels, balms and powders is available. [7]

An extract of oats is used in traditional Ayurvedic medicine to cure opium addiction. A case report shows six out of 10 opium addicts giving up the drug after a treatment period of 27 to 45 days using a decoction of green oats. [8] Oats may also reduce the desire to smoke cigarettes. In one poorly blinded study, 26 smokers received either an alcoholic extract of oats or placebo for 28 days. Mean cigarette use in the oat group was 20 per day at baseline, which decreased to six cigarettes/day after therapy ($P < 0.001$). Consumption in the control group remained constant (17 cigarettes/day). The difference between groups was statistically significant at the end of therapy. The reduction in consumption continued to be observed 2 months after terminating treatment. [9] However, these results could not be confirmed in another 12-week blinded study that showed no overall group effect on cigarette consumption during oat extract therapy. [10]

Oat bran, the ground inner husk of the grain, has become popular as a dietary means of lowering blood lipids. Oat bran and oatmeal are available in various breakfast foods, laxatives and baked goods. In general, water-soluble dietary fiber has a greater lipid-lowering effect than insoluble fiber. Soluble fiber may bind cholesterol and bile acids in the intestines, preventing absorption, or may be fermented to short chain fatty acids by colonic bacteria. Upon absorption, these compounds may inhibit cholesterol synthesis. [11] A serving of Quaker Oat Bran hot cereal provides 4.1 g of total dietary fiber, of which 1.9 g is soluble and 2.2 g is insoluble.

A large number of clinical studies have been conducted to evaluate the effect of oat bran supplementation on blood lipid levels. [11] Typically, the results of controlled clinical trials indicate that supplementation with oat bran products for 6 to 8 weeks results in a decrease in total cholesterol levels of approximately 6 mg/dl, [12] although the addition of 100 g of oat bran and dried beans daily for 3 weeks resulted in a 23% decrease in total cholesterol, a 23% decrease in LDL-cholesterol, a 21% decrease in triglycerides and a 20% decrease in HDL-cholesterol. Low cholesterol levels were maintained for up to 2 years of supplementation in this study. [13] However, at least one well-publicized study refutes the inherent value of dietary oat bran to lower serum cholesterol. [14] Swain, et al claim the value of oat bran ingestion is caused by basic diet manipulation, rather than a "pharmacologic" effect of the fiber itself. The study has been criticized for many methodologic flaws. [15] A later study evaluated the mechanism of oat bran in lowering serum lipids. Beta-glucan present in oats mediates an increase in bile acid secretion, explaining its effect in nine ileostomy patients. [16] Oat extract has also been studied in animals fed a high-fat diet. Results of one report suggest oat extract plays an appreciable role in atherosclerosis prophylaxis and management. [17]

Antibiotic and antifungal properties of oats have been evaluated. [18] In folk medicine, oat-herb tea is used as a sedative and to lower uric acid levels; neither use has been scientifically proven. The tea has also been used as a diuretic. Baths prepared from oat straw are used to treat arthritis, paralysis, liver and skin disorders. [1]

TOXICOLOGY: Oat bran increases the stool bulk, which may be uncomfortable to patients [19] and increased defecation frequency may result in perineal irritation. Fiber digestion by colonic bacteria may cause gaseous distention and flatulence. Although epidemiologic studies suggest that ingestion of large amounts of dietary fiber may reduce incidence of colonic cancer, one report provides evidence that the increase in fecal bile excretion that occurs in the presence of soluble fibers may promote chemically induced colonic cancer in animals fed oat bran. [20] As with any fiber product, oat bran products should be taken with plenty of water to ensure hydration and dispersion of the fiber in the GI tract.

Contact dermatitis from oat flour has been reported, [21] and the oat prolamine, avenin, has been shown to raise antibodies in rabbits. [22] Gluten should be avoided by patients with celiac disease. Oat gluten has been used as a stabilizer, emulsifier and food extender. [23]

While some fibers have been used successfully in the adjunctive management of glycemic control in diabetic patients, oat-based meals appear to have a smaller effect on blood glucose and insulin levels than most fiber sources. [24] A protease inhibitor has been identified in *Avena sativa*, but its clinical significance is not known. [25] A multimycotoxin detection method for "aflatoxins, ochratoxins, zearalenone, sterigmatocystin and patulin" has been developed to detect their presence in oats and other grains. [26]

SUMMARY: Oat and its extracts are commercially important as grains and dietary supplements. The ingestion of large amounts of fiber (40 g/day) may contribute to the reduction of blood cholesterol levels, an effect that is observed in as few as 2 to 3 weeks. Other effects of oat extract include possible cures for opium addiction or smoking and atherosclerosis prophylaxis. Oats are effective for itchy skin conditions, and its presence in bath and beauty products is well known. No significant toxicity has been associated with the ingestion of oat products.

PATIENT INFORMATION— Oats

Uses: Oats are used to manage dry, itchy skin conditions, to cure opium addiction, to reduce the desire to smoke cigarettes and to lower blood lipids.

Side Effects: Oat bran increases bulk of stool and frequency of defecation resulting in perineal irritation. Fiber may cause distention and flatulence.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OATS

OCTACOSANOL

DATE OF ISSUE: JUN 1997

REPLACES MONOGRAPH DATED: APR 1988

SCIENTIFIC NAME(S): 1-octacosanol, n-octacosanol, octacosyl alcohol

COMMON NAME(S): 24 to 36 carbon alcohols isolated from wheat germ oil or other plants.

HISTORY: Studies in the 1930s and 1940s suggested that athletes who were given daily or weekly doses of raw, unrefined wheat germ oil outperformed subjects who received only vitamin E supplements. The biologic value of wheat germ was reconfirmed in a 1951 study in which college students received wheat germ oil for 18 weeks. Treated subjects improved their "all-out" bicycle riding times by 47%, while the untreated controls increased their average riding times by only 4%. All of these studies suggested that some component of unrefined wheat germ oil increased physical endurance, and that vitamin E was not entirely responsible. Further investigations culminated in a patent for the combination of "physiologically active" components of raw wheat germ oil. [1] No published scientific studies were provided that evaluated the physiologic activity of these "active constituents." [2]

CHEMISTRY: Octacosanol is a constituent of vegetable waxes and has been isolated from wax on green blades of wheat. [3] The name octacosanol specifically pertains to a 28-carbon alcohol, but it is commonly used to denote a mixture of 24-, 26-, 28-, and 30-36-carbon alcohols, that are believed to possess most of the physiologic activity of wheat germ oil. These compounds are present as alcohols or acetates and can also be isolated from plants other than wheat. [2] A number of reports are available, isolating octacosanol as one of many components in certain plants. A brief listing follows, with references listed for those interested in these specific species: octacosanol from leaves of *Pithecolobium dulce* V.,[4] *Cymbopogon citratus* (Dc.) Stapf (Poaceae);[5] whole plant of *Euphorbia myrsinitis* L.,[6] *Euphorbia tinctoria* boiss,[7] *Daemia extensa* R. Br.;[8] stem bark of *Acacia modesta*;[9] Heart wood of *Cassia javanica*;[10] fruits of *Serenoa repens* Bartram,[11] *Poinsettia pulcherrima*,[12] *Citrullus colocynthus*;[13] roots of *Talinum paniculatum* Gaertner,[14] *Acanthus illicifolius*;[15] crude drug "jungle pepper" *Vitex pubescens*;[16] and octacosanol from *Eupolyphaga sinensis* Walker.[17]

PHARMACOLOGY: Specific biologic activity has been described for triacontanol (30-C alcohol); its application to seedlings and growing plants increases growth rate and fruit yield.[18] It is being investigated in humans for use as an antiviral for herpes and for the treatment of inflammatory skin diseases. The biologic activity of tetracosanol (24-C) and hexacosanol (26-C) are poorly understood.

To understand mechanisms such as increased physical exercise and improved motor endurance by octacosanol, its pharmacokinetic characteristics were evaluated. Octacosanol was found to distribute mainly to adipose tissue when administered orally in rats. [19] After ingestion of octacosanol in rats that were exercised, however, results showed significantly higher distribution to muscle tissue, supporting a theory of octacosanol muscle storage in response to exercise. A similar report by the same authors evaluates muscle storage of serially administered (orally through stomach tubs) radioactive octacosanol. At first, highest concentration is in the liver, but rapidly disappears (even when doses are increased). The muscle was able to store a considerable amount of octacosanol, which may help to explain increased muscle endurance in exercise.[20]

Also proposed is the possibility that octacosanol increases mobilization of free fatty acids from fat cells in the muscle, having "adipokinetic" activity affecting the muscle's lipolysis process.[21] In another report, lipid metabolism was evaluated in rats receiving octacosanol and a high-fat diet. Results suggest octacosanol to suppress lipid accumulation in adipose tissue. Additionally, it decreased serum triacylglycerol concentration and enhanced serum fatty acid concentration. [22]

Absorption of octacosanol was found to be low, with excretion mainly via feces. Metabolites of the alcohol were found to be present in urine. [19]

Orally administered combinations of octacosanol compounds were shown to produce a physiologic response characteristic of androgenic activity in the chick-comb test. 1-Octacosanol increased the size of the testes and seminal vesicles in rats, compared to those fed a cottonseed oil control diet. Further, guinea pigs fed a diet containing 2.2 mg/kg octacosanol for 28 days had a better swimming performance than animals fed rations without the alcohol. Animals that were fed a 2% wheat germ oil diet also swam longer than those fed the control diet. Patent 3,031,376 provided limited evidence that daily doses ranging from 0.05 to 150 mg of these compounds are well tolerated by humans; it indicated that the usual "maintenance dose" is 40 to 80 mg total alcohols daily. [2]

In one single-blind study, 12 men received 1-octacosanol daily in cottonseed oil (dose not specified) and 10 received placebo. Both treatment groups were tested before the study and again at a later, unspecified interval, for ECG R-wave changes, the mile run, 466-yard swim, pushups and six other athletic events. Significant ($P < 0.05$) improvements were noted for all test parameters in the octacosanol-treated group; however, statistically significant improvement was also noted in the placebo group for the mile run, 466-yard swim and step-up test. The maximum percent mean improvement for any test was 18%, and this was observed in both test groups. In another test using four matched groups of boys (population size not specified), subjects given an unspecified quantity of octacosanol for 8 weeks completed the 600-yard run an average of 10% faster than before starting the supplement. Boys who received wheat germ oil improved their times by 9%, those receiving wheat germ by 6% and those receiving placebo by 4%.[2]

A recent review article discusses efficacy of nutritional supplementation by athletes. Octacosanol is mentioned to have ergogenic qualities, but with little or no scientific evidence supporting this.[23]

The patent proposes that, theoretically, octacosanol improves stamina and vigor by improving oxygen utilization during anaerobic glycolysis. At the onset of exercise, when the circulation is increasing to meet muscle oxygen demand, a period of relative oxygen deficiency exists, and blood lactate levels rise. It is believed that octacosanol and related compounds may aid in the removal of lactic acid by increasing the efficiency of the tricarboxylic acid cycle, which operates through reactions connecting to the oxygen supply. This may also result in an increased oxygen uptake or a decreased oxygen requirement. However, no data exist to confirm this mechanism of action.

A small study suggests that octacosanol benefits patients with Parkinsonism. In a double-blind, placebo controlled trial, 10 patients received six weeks of treatment with 5 mg octacosanol in wheat germ oil or placebo, three times daily with meals. Three of the patients showed significant symptomatic improvement during the octacosanol phase of treatment. None of the patients showed worsening of their conditions during octacosanol treatment. Overall, the treated group showed a slight improvement in performance of activities of daily living. [24]

The promising results in Parkinson patients led to a double-blind, crossover study involving 11 patients with amyotrophic lateral sclerosis. Patients received either 40 mg/day of each of the 28-C, 30-C, and 30-36-C alcohols or a placebo for 3 months. Although 3 patients in the drug phase and 3 in the placebo phase reported subjective improvement, neurological evaluations showed progression of the disease in all cases. Some patients showed some improvement in certain test scores, but there was no significant difference between the octacosanol and placebo groups. [25,26]

TOXICOLOGY: There are no data on the long-term toxicity of products containing octacosanol. [2] In the Parkinson's disease study, side effects were infrequent but included position-related nonrotational dizziness, mild increase in nervous tension, and worsening of carbidopa/levodopa-related dyskinesias. These effects suggested an interaction with levodopa.[25,26]

SUMMARY: Octacosanol commonly denotes a mixture of 24- to 36-carbon alcohols isolated from wheat germ oil. It is also found in many other plants. They have been touted as improving the stamina of athletes, but scientific proof of this is lacking. Animal studies on pharmacokinetic parameters may help to explain possible theories of increased muscle endurance and mobilization of free fatty acids from fat cells, but more research is needed for proof in the human population. There is preliminary evidence that octacosanol may benefit patients with Parkinsonism, but trials in patients with amyotrophic lateral sclerosis have shown no therapeutic value. The long-term safety of octacosanol is not known.

PATIENT INFORMATION— Octacosanol

Uses: Octacosanol is being investigated as a herpes antiviral and as a treatment for inflammatory diseases of the skin. It also has demonstrated enhanced physical endurance in some studies.

Side Effects: There have been no reported side effects with the use of octacosanol except for a suggestion of interaction with levodopa/carbidopa in Parkinson's disease patients.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OCTACOSANOL

OLEANDER

DATE OF ISSUE: AUG 2003

REPLACES MONOGRAPH DATED: SEP 1993

SCIENTIFIC NAME(S): *Nerium oleander* L. Synonymous with *Nerium indicum* Mill. Family: Apocynaceae

COMMON NAME(S): Oleander, adelfa, laurier rose, rosa laurel, rose bay, rosa francesa. [1] Should not be confused with yellow oleander (*Thevetia neriifolia*), a related toxic plant.

BOTANY: The oleander is a shrub that grows to about 6 to 7 meters in height. It has long, narrow leaves that attain almost a meter in length, and these are typically grouped in threes around the stem. The red, pink, or white fluffy flowers form in small clusters. Cultivated plants rarely produce fruits. [1] Although native to the Mediterranean, the oleander is widely cultivated throughout warm, tropical climates.

HISTORY: Despite its well-recognized toxic potential, the oleander has been used in traditional medicine for centuries. It was used by primitive people as arrow and dart poisons.[2] Its uses included the management of such diverse ailments as cardiac illnesses, asthma, corns, cancer, and epilepsy. [3]

A number of uses for oleander have been reported, although in most cases, evidence supporting these indications is lacking. In the Narni area of Umbria, in the Italian countryside, the farmers and shepherds still use medicinal plants. *N. oleander* leaves are ground and mixed with honey to form a poultice and then applied topically to treat scabies.[4] In certain regions of Morocco, phytotherapy represents an integral part of health care. Diabetes mellitus, hypertension, and cardiac disorders are conditions "treated" with oleander.[5]

CHEMISTRY: The plant contains a number of related cardiac glycosides similar in activity to digitalis. The main glycosides are oleandrin and neriine. [2] Cardenolides gentiobiosyl oleandrin and odoroside also are present. [3] In addition, a variety of other pharmacologically active compounds, including folinerin, rosagenin, rutin, and oleandomycin, have been identified in the plant. [3]

PHARMACOLOGY: More recently, research has focused on the anticancer effects of oleander and its constituent compounds. Oleandrin inhibits certain kinases, transcription factors, and inflammatory mediators, including tumor necrosis factor. This may provide a molecular basis for the ability of oleandrin to suppress inflammation and perhaps tumorigenesis. The authors of this in vitro study suggest that oleandrin may have applications for various diseases, including arthritis, but all require further investigation.[6]

TOXICOLOGY: The entire oleander plant contains toxic cardiac glycosides. However, the highest levels are found in the roots and seeds. Even smoke from the plant and water in which the plant has been immersed can be toxic.[1]

In birds, as little as 0.12 to 0.7 g of the plant has caused death. [7] As few as 15 to 20 g of fresh leaves can be fatal to a horse, and 1 to 5 g can be lethal to a sheep. [3] Deaths have been reported in children who ingested a handful of flowers and in adults who used the fresh twigs as meat skewers; the nectar makes honey toxic. [3,8] Additionally, oleander reportedly was used in a case of deliberate poisoning by chronic administration of the roots of the plant over an 8-week period. [9]

Symptoms of oleander toxicity include pain in the oral cavity, nausea, emesis, abdominal pain, cramping, and diarrhea. Special attention must be given to cardiac function. The cardiac glycosides may induce conduction defects. Most common are defects affecting the sinus or AV nodes with PR interval prolongation and progression to atrioventricular dissociation. [10] Additionally, systemic hyperkalemia induced by the plant may worsen cardiac function. [1]

Oleander toxicity should be managed aggressively. Gastric lavage or induced emesis should be performed. Some experts have reported that activated charcoal may be administered orally. ECG monitoring for cardiac impairment and monitoring of serum potassium levels should be performed frequently. [1] The conduction defects can usually be managed with atropine and isoproterenol, which contain similar compounds. [11] Anti-digoxin Fab fragments have been shown to be a safe and effective treatment for serious cardiac arrhythmias induced by yellow oleander. Administration of anti-digoxin antibodies can restore sinus rhythm and rapidly correct bradycardia and hyperkalemia. However, the lower affinity of digoxin-specific Fab for nondigoxin cardiac glycosides in oleander results in a larger dose requirement than for usual digoxin toxicity.[12]

In a patient who ingested oleander, the serum digoxin levels were high (4.4 ng/mL) and were associated with bradyarrhythmias and tachyarrhythmias, which decreased as the serum concentration of the toxin decreased.[13] Another patient who ingested 7 oleander leaves in a suicide attempt had digoxin serum levels of 5.69 nmol/L, using a digoxin radioimmunoassay. This assay confirmed the toxicity, but did not predict the severity of the toxicity. [14]

Phytodermatitis caused by contact with oleander has been frequently reported. The dermatitis may result when crushed leaves of the shrub come into contact with the skin of a person who is sensitive because of previous exposure. The crushed leaves and stems have been reported to be irritating, but the allergenic properties have not been adequately studied. Generally, no positive patch test can be obtained. [15]

SUMMARY: The oleander is an extremely toxic plant that is grown widely as an ornamental. Its toxicity precludes widespread medicinal use. It has been used in traditional medicine and is still used in certain cultures.

PATIENT INFORMATION — Oleander

Uses: Oleander has been used in the treatment of cardiac illness, asthma, diabetes mellitus, corns, scabies, cancer, and epilepsy. However, in none of these conditions is there good evidence for use.

Side Effects: Oleander is extremely toxic. Major toxicity includes disturbances in heart rhythm and death. Other signs of toxicity include pain in the oral cavity, nausea, emesis, abdominal pain, cramping, and diarrhea.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OLEANDER

OLIVE LEAF

DATE OF ISSUE: JULY 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Olea europaea* L. Family: oleaceae.

COMMON NAME(S): Olive leaf

BOTANY: The olive tree is an evergreen, growing to approximately 10 m in height. Native to the Mediterranean regions, the trees are also cultivated in areas of similar climates in the Americas. The small, leatherly leaves are gray-green on top, and the underside contains fine, white, scale-like hairs. The leaves are gathered throughout the year.[1,2,3]

HISTORY: The olive tree was cultivated in Crete as far back as 3500 BC, where the leaves had been used to clean wounds. Symbolically, the olive branch stands for peace. The leaves were worn by athletes in ancient Olympic games.[1] Medicinal properties of the plant in the 1800s include malaria treatment. In the 1900s, the leaf constituent oleuropein was found to resist disease. The plant has also been reported to possess some hypotensive properties. [2]

CHEMISTRY: Olive leaf contains the active constituent oleuropein (chief constituent 60 to 90 mg/g). This iridoid has been pharmacologically analyzed. [4] Other secoiridoids include 11-demethyloleuropein, 7,11-dimethyl ester of oleoside, ligustroside, oleuroside, and unconjugated secoiridoid-type aldehydes; triterpenes and flavonoids are also present, and include rutin, and glycosides of apigenin and luteolin. [3] Other sources list oleasterol, leine, and glycoside oleoside as being present in olive leaf.[1,2] A report on peroxidase and ethylene formation in olive leaves is available. [5] A comparison of organelles from young and mature olive leaves has been performed, finding no remarkable differences.[6]

PHARMACOLOGY: In animal experimentation, oleuropein has always produced a reproducible reduction in blood pressure. [2] It has been shown to increase coronary flow and left intraventricular pressure in rabbit myocardium. [3] A decoction of olive leaves caused relaxation of rat aorta preparations in another report. [7] Oleuropein exerts hypotensive action in cats and dogs as well. The hypotensive action of this iridoid depends on specific animal species. [4]

Also in animal experimentation, olive leaf has demonstrated antispasmodic, coronary dilator, and antiarrhythmic properties in addition to its hypotensive effects. [8] A proposed mechanism as to how oleuropein may exert its effects may be a result of its direct action on smooth muscle.[4] Oleuropeoside was found to be responsible for vasodilator activity in another report.[7]

Documentation regarding olive leaf's use as an antihypertensive in humans is insignificant. [8] Other sources state no definite proof of the therapeutic efficacy in this area.[3,9] In contrast, Italian folk medicine employs dried olive leaf as a remedy for high blood pressure. [9] Other sources state that olive leaves do lower pressure and help to improve circulatory function as well.[1] Another report mentions the hypotensive activity of olive leaves to be slight, but existent, and suggests their use only in mild cases of hypertension.[2]

Olive leaf has other documented properties. Hypoglycemic activity was demonstrated in animals. Mechanisms were stated as being potentiation of glucose-induced insulin release, and increased peripheral uptake of glucose. [10] Olive leaf is also said to be mildy diuretic. It enhances renal and digestive elimination functions, along with renal excretion of water.[3] It may be used to treat cystitis as well.[1] Oleuropein was also listed as a good antioxidant.[3] Many unsubstantiated claims and "cure-alls," except for "testimonial-type" proof, exist for olive leaf. Some of these claims include therapy for chronic fatigue syndrome, herpes and other viral infections, arthritis, yeast infection, skin conditions, and others. More research and clinical trials are necessary to validate these claims.

TOXICOLOGY: Potential toxicity of olive leaf is not well known. [3] Oleuropein in doses up to 1 g/kg body weight in albino mice did not provoke lethality in an analysis on olive leaf.[4] The German Commission E monographs list no known risks associated with the plant.[9] One source states the drug as causing gastric symptoms, and suggests that it be taken with meals because of this irritant effect. [2]

SUMMARY: The olive tree dates back to 3500 BC. The leaves possess hypotensive properties in animal experimentation, probably as a result of vasodilator activity. The leaves have been used in humans for hypertension, but the leaf's effects may only be useful in mild cases. Olive leaf also exhibits hypoglycemic, renal, and antimicrobial effects. Toxicity of the plant is not well known, but there seems to be little risk with its use.

PATIENT INFORMATION— Olive Leaf

Uses: The olive leaves possess hypotensive properties in animal experimentation and have been used in humans for hypertension (possibly only for mild cases). The olive leaves also have hypoglycemic, renal, and antimicrobial effects.

Side Effects: Toxicity is not well known, but the leaf may cause gastric symptoms. Use in diabetic patients should be followed carefully due to the hypoglycemic effects of olive leaf.

Dosing: Olive leaves are used to make a tea for rheumatism, gout, and diabetes; however, there is no dosage information available on these uses. [11]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OLIVE LEAF

OLIVE OIL

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Olea europaea* (fruit), *Oleum olivae* Family: Oleaceae

COMMON NAME(S): Olive oil, sweet oil, salad oil

BOTANY: The olive is technically a fruit, ellipsoid and drupaceous in character, measuring 2 to 3 cm in length. The fruits grow from an evergreen tree, which seldomly exceeds 10 or 12 m in height. The plants were first cultivated in Greece but are now widely grown in Mediterranean countries and the US. Many cultivated varieties are the result of its geographic diversity.

Olive oil is a fixed oil, expressed from ripe olive fruits. It is pale-yellow and may have a greenish tint, depending on the ratio of chlorophyll to carotene. Taste has been described as characteristic but slight or bland to faintly acrid. Olive oil is offered in several grades of purity, including "virgin" oil (initial unrefined oil from first fruit pressing) or "pure" (lower quality from subsequent pressings). Chemically, the difference between "extra virgin" and "virgin" oils involve the amount of free oleic acid (ie, virgin allows 4% free oleic acid, and extra virgin allows 1%). [1,2,3,4]

HISTORY: "Olea" comes from the Latin "oliva" meaning olive.[2] The fruit dates back to the 17th century BC and appears to be native to Palestine.[4] One source mentions that Ramses ??, Egyptian ruler between 1300 and 1200 BC, used olive oil for every ailment.[5]

CHEMISTRY: Olive oils of different varieties and from varied climatic areas differ in composition. Oleic acid (a monounsaturated fatty acid) for example, can range from 65% to 86%. Linoleic acid can vary as well, from 0% to 15%. Palmitic and stearic acids range from 9% to 15%.[1,4,6,7] Oleuropein, a phenolic compound, is found in the fruits.[8,9]

TLC and GC analyses are employed to detect adulteration of the oil with foreign oils (eg, sesame, cottonseed, peanut oils). Certain percentage limits are set for the amounts of saturated fatty acid chain lengths and number of sterols.[4]

PHARMACOLOGY: Recent computer literature searches found > 1800 citations on olive oil, hence the following is only a brief outline of some main points.

Olive oil is classed as a pharmaceutic acid.[2] It is used as a vehicle for oily suspensions for injection.[3] Olive oil is also employed in the preparation of soaps, plasters, ointments, and liniments.[3,4] In addition, it is a good drug solvent.[3,6] Externally, olive oil is a demulcent and emollient. It is used to soften the skin in eczema and psoriasis.[3] It is useful as a lubricant for massage or for prevention of stretch marks. It also has been used as a wound dressing and for minor burns. In addition, olive oil softens ear wax and is helpful for ringing or pain in the ears. Effectiveness of certain applications is not documented.[10]

Olive oil is a nutrient, widely used as a salad oil and for cooking.[2] It is a common element in the Mediterranean diet.[11,12,13]

Olive oil is a mild laxative as an intestinal lubricant.[6] It is also claimed to be useful for gall bladder problems, including cholecystitis and cholelithiasis.[10]

A number of articles concerning olive oil's role against heart disease exist. Constituent oleic acid has been shown to lower blood cholesterol levels.[1] Monounsaturated fatty acids replacing saturated fatty acids in the diet decrease serum cholesterol as discussed in a review of population and clinical studies.[14] Olive oil supplementation in hypercholesterolemic patients was shown to reduce susceptibility of LDL to oxidation, which contributes to atherosclerotic processes.[15] Olive oil improves the good HDL-cholesterol ratios and combats arterial build-up of cholesterol as well. In middle-aged Americans, the oil decreased cholesterol by 13% and LDL-cholesterol by 21%. Four to five tablespoons per day of olive oil administered to heart surgery patients improved their blood profiles.[5] A comparative study of olive oil vs fish oil on blood lipids and atherosclerosis has been performed.[16]

Olive oil and cancer prevention have been correlated in experimental animals. In rats, olive oil had no colon tumor-enhancing effects as compared with other fatty-type diets.[17] A nutrition review of dietary fat and chronic disease risk finds monounsaturated oils, such as olive oil, to be a weak promoter of certain cancers (including breast and colon) as opposed to such strong promoters as n-6 polyunsaturated oils.[18] This author claims evidence for an enhancing effect of the latter strong promoters in increased breast cancers in western diets.

Other effects of olive oil include the following: Decreased tendency to develop spontaneous osteoarthritis in mice compared with other fats,[19] reduction of blood pressure,[5] and antimicrobial properties including gram-negative bacteria, fungi, and enterotoxin B production by *Staphylococcus aureus*.[8,9]

TOXICOLOGY: Ingestion of excessive amounts of olive oil has resulted in temporary mild diarrhea.[5] In rare cases, topical use of olive oil has caused allergic reactions.[10]

SUMMARY: Olive oil has been used for centuries as a food and pharmacological agent. It is an ingredient in certain preparations such as ointments. It is used to soften skin and ear wax. Olive oil is useful as a laxative and may be useful for gall bladder ailments. It also is beneficial as a nutrient, especially in the Mediterranean diet. It plays an important role against heart disease as it lowers cholesterol levels. Olive oil does not promote certain cancers compared with other fats. Toxicities from olive oil include mild diarrhea and rare skin reactions.

PATIENT INFORMATION— Olive Oil

Uses: Olive oil is used for cooking, as a salad oil, and as a vehicle for oily suspensions for injections. It is used to prepare soaps, plasters, ointments, and liniments and is used as a demulcent and emollient. It is a mild laxative, and it lowers cholesterol.

Side Effects: Olive oil has caused temporary mild diarrhea and allergic reactions from external use.

Dosing: Olive oil is used as a laxative at a typical dose of 30 mL.[20]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
      OLIVE OIL

ONION

DATE OF ISSUE: JUN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Allium cepa* Family: Liliaceae, Alliaceae.

COMMON NAME(S): Onion

BOTANY: The onion plant is a perennial herb growing to about 1.2 m, with 4 to 6 hollow cylindrical leaves. On top of the long stalk, greenish-white flowers are present in the form of solitary umbels growing up to 2.5 cm wide. The seeds of the plant are black and angular. The underground bulb, which is used medicinally, is made up of fleshy leaf sheaths forming a thin-skinned capsule. The onion is one of the leading vegetable crops in the world. [1,2,3,4]

HISTORY: Central Asia is believed to be the region of origin of the onion. [4] Onions were used as early as 5000 years ago in Egypt, as seen on ancient monuments. Ancient Greek and Roman recordings also refer to the onion. During the Middle Ages, onions were consumed throughout Europe. They were later thought to guard against evil spirits and the plague, probably because of their strong odor. Onion "skin" dye has been used for egg and cloth coloring for many years in the Middle East and Europe. Columbus was said to have brought the onion to America. Folk healers used the onion to prevent infection. The combination of onions and garlic cooked in milk is a European folk remedy used to clear congestion. Onions are also used in homeopathic medicine. [1,2,5,6]

CHEMISTRY: Onions contain 89% water, 1.5% protein, and vitamins, including B_1, B_2, and C, along with potassium.[1,2] Polysaccharides such as fructosans, saccharose, and others are also present, as are peptides, flavonoids, and essential oil. [3,4] The alliums, like onion, contain alliin and similar sulfur compounds, including allylalliin and methyl and propyl compounds of cysteine sulfoxide. [3,4,6] Sulfur and other compounds of *A. cepa* have been analyzed.[7] The flavor components of onion have been evaluated by TLC.[8] Prostaglandins have also been identified in onion. [9] Onion cell wall analyses have also been performed.[10,11] The chemical analysis of onion seed oil is available. [12]

PHARMACOLOGY: The main properties of onion include antimicrobial activity, cardiovascular support, hypoglycemic action, antioxidant/anticancer effect, and asthma protection.

Antimicrobial effects: Onion has had antibacterial,[3] antiparasitic,[13] and antifungal actions.[14,15] *Salmonella typhimurium* mutagenicity was reduced in hamburger when onions were added.[16] Growth of oral pathogenic bacteria, including *Streptococcus mutans*, *S. subrinus*, *Porphyromonas gingivalis*, and *Prevotella intermedia*, the main causes of dental caries and periodontitis, was prevented by onion extracts. [17] Either onion juice or onion oil has also been shown to inhibit growth of other gram-positive bacteria and gram-negative bacteria *Klebsiella pneumoniae*.[14,15,18] Antifungal actions of onion include certain yeasts, [14] *Microsporum canis*, *M. gypseum*, *Trichophyton simii*, *Chrysosporium queenslandicum*, *T. mentagrophytes*, *Aspergillus flavus*, and *Penicillium rubrum*.[15] One source identifies thiosulfinate principle in the onion as one of the main antimicrobial agents. [4]

Cardiovascular disease: Onion may also be of benefit in cardiovascular disease. The hypolipidemic effects of sulfur-containing principles in onion, including s-methyl cysteine sulfoxide and allylpropyl disulfide, have been demonstrated in several studies in rats and rabbits. [19,20,21,22,23] Examples include onion's protective effects against diet-induced atherosclerosis[22] and onion's marked actions in controlling lipids [23] and triglycerides.[21] One report evaluates onion's hemostatic effects in humans,[24] but certain lipid-reducing and blood pressure-lowering effects in humans have not yet been clinically proven. [4] Cardiovascular disease risk factors also involve blood coagulability. Several reports confirm the onion's inhibitory effects on platelet formation. Raw onion (vs. cooked) demonstrated antithrombotic effects in rats.[25,26] Dose-dependent inhibitory effects on platelet aggregation were seen in rabbits also with raw onion. [27] Boiling onion may cause decomposition of the antithrombotic ingredient.[25] Certain onion genotypes containing higher contents of sulfur in the bulb correlated with greater antiplatelet activity. [28] Thiosulfinates dimethyl- and diphenylthiosulfinate, for example, are known to retard thrombocyte biosynthesis. [4,29] The least polar fraction of onion extract was associated with the most inhibitory activity toward platelet aggregation, thus a greater inhibition of thromboxane synthesis was reported. [30] Synthesis of thromboxanes and prostaglandins in vitro has been shown with onions, as well as with garlic and other liliaceae family members. [31] Onion's benefits relating to cardiovascular disease have been reviewed.[5,32]

Diabetes: Although more research is needed on the use of onion as a treatment for diabetes in humans, many articles describe onion's benefits in improving glucose levels.[33] Studies from 1965 to 1975 report antidiabetic activity, "hypoglycemic principles," and blood sugar level reduction in diabetic rabbits. [34,35,36] Recent reports confirm many of these claims, finding similar outcomes. Onion decreased the hyperglycemic peak in rabbits. [37] In addition, onion amino acid s-methyl cysteine sulfoxide (SMCS) contributed to antidiabetic effects in affected rats, controlling blood glucose and other diabetic effects comparable to insulin. [23,38]

Cancer: Onion has also proven to be an antioxidant and may be beneficial in certain cancers. The organosulfur compounds contained in onion exert chemopreventive effects on chemical carcinogenesis. The constituent diallyl disulfide possesses inhibitory properties against colon and renal cancers. [39] People consuming diets high in allium vegetables including onion suffer from fewer incidences of stomach cancer. [1,40] Onion's protective factors for breast cancer have been evaluated in a French case-control study.[41] Oil of onion is an effective antioxidant against nicotine-induced damage in rats. [42] Another report compares the antioxidant activity of onion polyphenols with those of other fruits and vegetables. [43] The quercetin component in onion, however, was found to be absorbed by humans from dietary sources but provided no direct protective effect during LDL oxidation. [44]

Respiratory problems: Folk medicine has used the onion for treatment of asthma, whooping cough, bronchitis, and similar ailments. [4,33] The onion is used in homeopathic medicine.[5] Onion juice administration protected guinea pigs from asthma attacks. An ethanol extract of onion reduced "allergy-induced" bronchial constriction in certain patients.[4] The thiosulfinates present in the onion are said to inhibit bronchoconstriction, but definite efficacy remains unproven in this area. [29]

Other uses: Onions have been used in the treatment of stingray wounds,[45] warts, acne,[2] appetite loss,[1,3] urinary tract disorders,[5] and indigestion.[1] Onion cell extract was ineffective in treating postsurgical scarring.[46] General reviews of therapeutic uses of onion are available. [47,48]

Dosage: The *German Commission E Monographs* lists the average daily dose as 50 g of fresh onion, the juice from 50 g of fresh onion, or 20 g dried onion. A maximum of 35 mg diphenylamine/day is recommended if onion preparations are used over several months.[3]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Certain sulfur compounds (eg, propanethial-s-oxide) escape from the onion in vapor form and hydrolyze to sulfuric acid when it is cut, causing the familiar eye irritation and lacrimation. [1,6] Corneal swelling from onion exposure has been reported. [49] Using a sharp knife also minimizes the crushing of onion tissue and liberation of volatiles, and cutting an onion under running water avoids lacrimation. Ingestion of onion seems relatively safe, as the *German Commission E* lists no contraindications, side effects, or interactions from the plant. [3] Onion can be taken frequently in low doses without any side effects as seen with rat experimentation. [25] Food colorant extracted from the tan onion bulb covering had no acute or subacute toxic effects in mice. [50] With large intake, the stomach may be affected, and

frequent contact with onion rarely may cause allergic reaction.[4] The onion seeds have been reported as an occupational allergen.[51] Onion toxicity is only accociated with high intake.

A review of onion discussing ingestion of large amounts of the bulb finds toxicity unresolved.[32] Low doses of onion (50 mg/kg) given to rats had little effect on the lung and liver tissues. High doses (500 mg/kg) resulted in histological changes in these organs. IP administration was more damaging than oral, resulting in 25% mortality in rats.[52] Eighty-five young cattle were given 1000 kg of onions per day, affecting approximately 26%, with 1 fatality. New illnesses continued to occur for 5 days after the withdrawal of the onions, including lack of appetite, tachycardia, staggering, and collapse, all probably due to adverse red blood cell effects.[53]

SUMMARY: Onions have been used for thousands of years. The bulb contains certain sulfur compounds that are known to be antimicrobial. The onion may also be of benefit in cardiovascular disease, as it possesses hypolipidemic effects and has antiplatelet actions, retarding thrombosis. Some studies have been performed concerning diabetes treatment by onion with promising results in animal experimentation. The onion is also a proven antioxidant and may be helpful in treating certain cancers. More research is needed in the area of asthma treatment, although certain compounds are said to inhibit bronchoconstriction. Toxicology of onion is usually associated with high intake, but if taken properly it has few side effects. The proper dose for beneficial properties remains to be determined, particularly because newer, sweeter, and less potent varieties have been developed in recent years.

PATIENT INFORMATION — Onion

Uses: Onion is used as an antimicrobial, cardiovascular-supportive, hypoglycemic, antioxidant/anticancer, and asthma-protective agent. In folk medicine, onion has been used for asthma, whooping cough, bronchitis, and similar ailments. Other uses include the treatment of stingray wounds, warts, acne, appetite loss, urinary tract disorders, and indigestion. Onion skin dye has been used as an egg and cloth coloring.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: The toxicity of large doses of onion has been unresolved, but the stomach may be affected. Frequent contact with onion seeds has been reported as an occupational allergen.

Dosing: Fresh onion bulbs are used at daily doses of 50 g; dried onion is used at a dose of 20 g/day for dyspepsia.[54]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
      ONION

OREGANO

DATE OF ISSUE: MAY 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Origanum vulgare* L., family Lamiaceae (mints), is the scientific name for the herb oregano used in cooking. [1] A number of different species of *Origanum* exist including *O. compactum*,[2] *O. dictamnus*, and *O. onites*.[3]

COMMON NAME(S): Wild marjoram, mountain mint, winter marjoram, wintersweet,[1] Mediterranean oregano[4]

BOTANY: Common or wild oregano is a perennial plant that grows in the Mediterranean region and Asia and is cultivated in the US. Its creeping rootstock produces a square, downy, purplish stem with opposite ovate leaves (on stems up to 76.2 cm high) that are dotted with small depressions. Purple, two-lipped flowers grow in terminal clusters from July to October.[1]

The *Origanum vulgare* subspecies *hirtum*, which has a spicy flavor (other species have little flavor), has furry leaves on stems up to 45.7 cm high and floppy white flowers.[5]

HISTORY: Oregano has been a common ingredient in Spanish, Mexican, and Italian dishes as a spice and flavoring agent for hundreds of years. Its initial purpose was as a warming digestive and circulatory stimulant.[6] It also has been used in perfumery, especially in the scenting of soaps and for its volatile oil contents. [7]

The antiseptic qualities of aromatic and medicinal plants and their extracts have been recognized since antiquity, while attempts to characterize these properties in the laboratory date back to the early 1900s. [8]

CHEMISTRY: Oregano contains oleanolic and ursolic acids, flavanoids and hydroquinones, rosemarinic acid, tannins, and phenolic glycosides. [7] The polar phenols thymol and carvacrol are responsible for many of the properties of the essential oil. [2] Phenolic compounds represent 71% of the total oil.[9]

PHARMACOLOGY: Antispasmodic, calmative, carminative, diaphoretic, expectorant, stomachic, and tonic actions have been reported from oregano use. It has been suggested that an infusion of the fresh herb has beneficial effects on an upset stomach and indigestion, headache, colic, and nervous complaints, as well as on coughs and other respiratory ailments. An infusion of the flowers is said to prevent seasickness and have a calming effect. The oil also is used externally in liniments and lotions and to ease toothache. Reports also discuss its use as an insect repellent against ants. [1]

Progestin bioactivity: Oregano has been used traditionally to relieve abdominal cramps in women and to regulate the menstrual cycle. [1] The content and in vitro bioactivity of plant progestins in a number of herbs have been studied. Oregano was found to bind to estrogen- and progestin-binding sites, resulting in an agonist and antagonist (or neutral) effect, respectively. The dried herb (2g) contains 8 mcg of progesterone. It was concluded that oregano might be expected to have mild estrogenic effects in foods.[10]

Appetizer effect: In a small study (n = 54), human subjects were fed pasta with a tomato sauce, with palatability adjusted by the addition of 3 levels of oregano: bland, palatable, and strong. The addition of a small amount of oregano increased palatability and food intake, whereas addition of excess oregano tended to reduce intake.[11]

Antioxidant/Preservative activity: Dry oregano and its various extracts have been studied as inhibitors of autoxidation for many years. Reports have shown that extracts of oregano have antioxidant effects on lard that may be partly attributed to the presence of essential oils. The active components of the oils are thymol and carvacrol. However, high concentrations of tocopherols also are present in the extract and have antioxidant properties. [3] Herbs with antioxidant properties thus have been used as stabilizers of fat in order to increase shelf-life. Indeed, a-tocopherol protects against free radical damage. In food systems, free radicals cause oxidative rancidity. Oregano has been shown to delay the onset of rancidity. [12] One report in the literature compared the antioxidant properties of all the Mediterranean herbs; rosemary and oregano rated highest and produced stabilizing effects on olive oil. [13]

Antifungal activity: Aflatoxins are fungal metabolites contaminating many food products. There is a natural occurrence of aflatoxins in foodstuffs of cereal origin, especially when they are stored over long periods. A number of studies have attempted to determine whether herbs and spices have any antifungal properties. In these studies, various species of *Aspergillus* were incubated with different herbs and spices as substrates. Oregano inhibited aflatoxin and prevented growth of *Aspergillus* at concentrations as low as 0.1%.[14,15,16] Further studies have compared the effects of oregano versus the phenols in its essential oil, thymol and carvacrol. All 3 completely inhibited fungal growth (*Aspergillus* and *Penicillium* species).[17]

Antibacterial activiity: The volatile oils of oregano have demonstrated antibacterial activity against a wide range of gram-positive and gram-negative microorganisms including *Listeria*, *Pseudomonas*, *Proteus*, *Salmonella*, and *Clostridium*.[8,18,19,20,21,22] It appears this is caused by the phenolic structure of thymol and carvacrol, components of the volatile oil. Depending on the concentration used, these agents are known to be bactericidal or bacteriostatic. Oregano appears to be able to inhibit organisms at concentrations less than 2% (v/v). [23]

Antispasmodic effects: *O. compactum* has been used in Morocco as a spasmolytic, prepared as a tea with the flowers and leaves of the plant. In vitro experiments using acetylcholine on smooth muscle preparations to produce contraction demonstrated the rapid spasmolytic action of *O. compactum*. It is thought that the herb stabilizes the muscle membrane by interfering with the influx of calcium and its regulatory proteins. [2] The active components in *O. compactum* appear to be thymol and carvacrol in the essential oil. [24]

Antiparasitic action: The oil of *O. vulgare* has been shown to eradicate common fowl parasites in infected chickens and pheasants. In a small human study performed in the US, 14 patients with known parasites were administered 200 mg emulsified *O. vulgare* oil for 6 weeks. The *Entamoeba hartmanni*, *Endolimax nana*, and *Blastocystis hominis* parasites were eradicated from 13 patients.[4]

TOXICOLOGY: Although oregano is frequently consumed, there are few reports in the literature of adverse effects or systemic reactions. However, one report comments on a patient with an anaphylactic reaction. A 45-year-old man developed pruritus, swelling of the lips and tongue, dysphagia, dysphonia, upper respiratory difficulty, hypotension, and facial and palpebral edema occurring a few minutes after ingestion of food containing oregano. Subsequent skin tests showed oregano as the responsible agent. Cross-sensitivity with other members of the Labiateae family also was noted.[25] Allergic contact dermatitis caused by spices is well documented. In one study, 55 patients with contact dermatitis were patch-tested with spice preparations. Four patients tested positive to oregano. [26] An additional case report of a 45-year-old woman notes an eczematous reaction that developed within 20 minutes of ingestion of large quantities of oregano. [26]

SUMMARY: Oregano is a spice commonly used in cooking. It possesses antibacterial, antifungal, and antioxidant properties that appear to be caused by the phenols (thymol and carvacrol) present in the essential oil. There also is limited evidence for antispasmodic and estrogenic activity. Although oregano is consumed by many, there have been few studies of adverse effects or reactions.

PATIENT INFORMATION— Oregano

Uses: Oregano is an antibacterial, antifungal, and antioxidant agent and has possible activity as an antispasmodic and estrogenic agent.

Side Effects: Oregano has caused allergic contact dermatitis when applied locally, eczematous rash, and, rarely, anaphylactic reactions when ingested.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OREGANO

OSTRICH FERN

DATE OF ISSUE: DEC 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Matteuccia struthiopteris* (L.) Tod. Family Aspleniaceae (Athyroideae)

COMMON NAME(S): Ostrich fern

BOTANY: The ostrich fern is a common fern that grows in the northeastern US and in large parts of Canada.

HISTORY: Fiddleheads (the young shoot tops) of the ostrich fern are a seasonal delicacy, harvested commercially throughout the northeastern US and coastal Canadian provinces. This spring vegetable had been a regular part of the diet of Canadian settlers by the early 1700s. [1] Unlike some ferns that have been considered carcinogenic or toxic, this fern had been considered to be nontoxic. Recent experience, however, indicates that it has the potential to induce severe food poisoning when not cooked properly. The ferns are available canned, frozen or fresh.

CHEMISTRY: Little is known about the chemistry of the ostrich fern. As described in the Toxicology section, poisonings due to this fern are believed to be caused by a heat-labile toxin that has not been characterized. The ostrich fern has been reported to accumulate heavy metals. [2]

A protein identified as matteuccin has been characterized in the fern. It is a small basic protein consisting of two small disulfide-linked polypeptides, [3] but there is no indication that this protein is responsible for the toxicity of the plant.

PHARMACOLOGY: The fiddleheads of the ostrich fern are generally considered to be edible following steaming. One field guide indicates that wild greens may have laxative properties and recommends boiling them and discarding the first water, to limit this effect. [4] No other significant pharmacologic properties have been ascribed to the fern.

TOXICOLOGY: Boiling the yound fiddleheads of the fern is believed to deactivate the potentially toxic properties of the plant. Recently, several outbreaks of severe food poisoning were reported by the Centers for Disease Control and Prevention (CDC). Affected individuals had eaten raw or lightly cooked fiddleheads of the ostrich fern in New York and western Canada.[5] The ferns associated with toxicity had often been eaten in restaurants, where the fiddleheads had been blanched or sauteed for only two minutes or less. However, when the ferns had been boiled for ten minutes prior to being sauteed, no illness occurred at the same restaurants. Symptoms were repoted within 12 hours; nausea, vomiting and abdominal cramping were the most commonly reported adverse events. Consumption of fiddlehead soup was also associated with gastrointestinal illness.

SUMMARY: Fresh fiddlehead ferns have only recently become widely available in restaurants. Because many vegetables are now only lightly sauteed or blanched (rather than being fried or boiled), patrons may be at risk for developing severe gastrointestinal illness if they eat undercooked ostrich fern fiddleheads. The CDC recommends that they should be cooked thoroughly (eg, boiling for 10 minutes) before eating.

PATIENT INFORMATION — Ostrich Fern

Uses: Ostrich fern has been used as a seasonal delicacy.

Side Effects: Adverse effects due to undercooking ostrich ferns include nausea, vomiting, abdominal cramping, and GI illness.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "O" MONOGRAPHS
    OSTRICH FERN

"P" MONOGRAPHS

PAPAYA

DATE OF ISSUE: JUN 2003

REPLACES MONOGRAPH DATED: AUG 2001

SCIENTIFIC NAME(S): *Carica papaya* L. Family: Caricaceae

COMMON NAME(S): Papaya, pawpaw, melon tree[1]

BOTANY: Papaya grow as small trees in the Americas and Africa. The common name pawpaw is sometimes given to an unrelated plant *Asimina triloba* (L.) Dunal. Family: Annonaceae.[2] The papaya produces large leaves and smooth-skinned edible melons.

HISTORY: *C. papaya* is cultivated for its milky juice or latex (obtained from the fruit), which is the source of the proteolytic enzyme papain. The fruits are eaten fresh and are also the source of a flavoring used in candies and ice cream. Shallow cuts on the surface of fully grown but unripe fruits cause the exudation of a milky sap that is collected, dried, and termed crude papain.[3] Papain has been used widely in folk medicine for the treatment of digestive disorders, particularly those associated with the ingestion of protein-rich foods. Teas brewed from fermented papaya leaves are said to produce a richer mixture of proteolytic enzymes than teas from fresh leaves. Papain has been used as a vermifuge and as a component of facial creams to soften skin. Papain is sold commercially as a meat tenderizer. [3]

CHEMISTRY: Papain (also known as vegetable pepsin) is found not only in the fruit latex but also in the leaves. Papain is a mixture of protein-degrading enzymes. [4] Chymopapain has been fractioned into subcomponents designated "A" and "B".[5] It is very similar to papain in the spectrum of its proteolytic activity, although it is less potent with respect to protein degradation.[6] Other components of papain degrade carbohydrates and fats. The seeds contain caricin, a glycoside. When caricin is combined with myrosin, it produces a mustard-like odor. Papaya seeds and pulp contain benzyl glucosinolate. This glucosinolate is hydrolyzed by the enzyme myrosinase to produce benzyl isothiocyanate.[7] The major cyanogenic glycoside in papaya is (2R)-prunasin; small amounts of sambunigrin are also present. [8] The alkaloid carpaine has been identified in the leaves. [9]

PHARMACOLOGY: Papain is used in digestive aids and in preparations to control edema and inflammation associated with surgical or accidental trauma. [6] Papain solutions have produced therapeutic effects in patients with inflammatory disorders of the genitals, intestine, liver, and eye. [10] Papain (0.1% to 1%) solutions also have decreased the weight of burn crust in vitro and accelerated experimental burn healing in vivo. [10]

Papain is unstable in the presence of digestive juices, which may account for its general lack of efficacy as a vermifuge. [3] One study alludes to the in vitro activity against helminths; benzyl isothiocyanate is considered to be the sole anthelmintic in papaya seed extracts. [5] Bacteriostatic activity of papaya is documented against several enteropathogens such as *Bacillus subtilis*, *Enterobacter cloacae*, *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.[11]

Papaya also contains antioxidant components such as vitamin C, malic acid, and citric acid. [11,12]

In the early 1980s, chymopapain[13] was approved for intradiscal injection in patients with documented herniated lumbar intervertebral discs and who had not responded to conservative therapy. This procedure is effective but remains the focus of controversy, particularly regarding the safety of the administration of the enzyme.[14] Anaphylactic shock was initially reported in about 1% of those receiving the drug; a number of fatalities also were reported. [15] More recent statistics, however, indicate that anaphylaxis occurs in less than 0.5% of patients, [13,16] and other adverse events, such as neurological problems, occur rarely. [13]

Diuretic activity is associated with the aqueous extracts of *C. papaya*. Adult male Sprague-Dawley rats were given an oral dose of 10 mg/kg of *C. papaya* root extracts. The demonstrated increased urine output ($P < 0.01$) was similar to receiving 10 mg/kg of hydrochlorothiazide. [17]

Benzyl isothiocyanate found in the pulp and seeds of papaya is a potent inducer of glutathione s-transferases, a phase II enzyme involved in the cellular detoxification of xenobiotics and reactive metabolites.[18]

TOXICOLOGY: A 1978 report suggested that papain was teratogenic and embryotoxic in rats. [3] Several studies have investigated whether papaya consumption is safe during pregnancy. Rats given a ripe papaya blend in place of water showed no difference in the number of implantation sites and viable fetuses. [16] However, unripe or semi-ripe papaya, which contains a higher concentration of latex, could be unsafe during pregnancy. The crude papaya latex induced spasmodic contraction of the uterine muscles similar to oxytocin and prostaglandin F2a. [19] No adverse effects on prenatal development was observed in female Sprague-Dawley rats administered a low-dose crude aqueous extract of papaya seeds.[20] Some writers promote clinically unsupported data that eating unripe papaya for 3 consecutive days may induce abortion. They also believe that when consumed daily, the papain in the ripe fruit may have contraceptive-like activity. They believe that papain suppresses progesterone, which is needed for conception and pregnancy. Lastly, they believe papain also may affect a vital membrane involved in the development of the fetus.[21]

Ingestion of large amounts of papain or papaya has been associated with perforation of the esophagus. [6]

Papaya seed extract may exert potentially toxic effects on mammalian vascular smooth muscle. Benzyl isothiocyanate, the chief bioactive ingredient in seeds, irreversibly inhibits the contraction of dog carotid artery. [22] Papaya extract, when present in high concentration, was found to be cytotoxic by increasing the membrane permeability to calcium.[22]

The enzyme may induce severe allergic responses in sensitive persons. The latex can be a severe irritant and vesicant. Internally, it may cause severe gastritis. [13]

Carpaine has been shown to cause paralysis, decreased heart rate and central nervous system activity, [13] and may have some amebicidal activity.[6]

SUMMARY: Papain is a mixture of natural enzymes derived from the papaya fruit. Papain is used as a meat tenderizer and chymopapain is employed in the chemical degradation of herniated vertebral disks. Consumption of fully ripened papaya during pregnancy is safe; however, semi-ripe and unripened papaya should be avoided. Papaya seed extract may have adverse effects on vascular contraction. The latex from the plant may induce dermatitis, and allergic hypersensitivity reactions have been associated with the ingestion of the plant and its extracts.

PATIENT INFORMATION— Papaya

Uses: Papaya has been used in patients with herniated discs, as a digestive aid, and in preparations to control edema and inflammation associated with surgical or accidental trauma, although very limited information is available to support these uses.

Side Effects: Enzymes related to papaya (eg, carpaine and other related compounds) have been associated with perforation of the esophagus, severe gastritis, paralysis, decreased heart rate and CNS activity, and may inhibit some amebicidal activity. Consumption of semi-ripe and unripened papaya should be avoided during pregnancy.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PAPAYA

PARSLEY

DATE OF ISSUE: JUN 2003

REPLACES MONOGRAPH DATED: FEB 1991

SCIENTIFIC NAME(S): *Petroselinum crispum* (Mill.) Nyman ex A. W. Hill. Family: Umbelliferae

COMMON NAME(S): Parsley, rock parsley, garden parsley

BOTANY: Parsley is an annual herb indigenous to the Mediterranean region, but now cultivated worldwide. It has erect stems and bright green leaves. Two cultivars of parsley exist, a curly leaf type and a flat leaf type.[1] Parsley produces an umbel of tiny flowers and characteristic ribbed seeds. [1]

Caution must be used when gathering wild parsley because of the general similarity of its leaves and flowers to those of 3 common poisonous plants. The first, *Aethusa cynapium* (dog poison, fool's parsley, small hemlock) can be distinguished from parsley by the shiny yellow-green underside of the leaves, which are dull in parsley, and the white flowers, which are yellowish in parsley. Similarly, collectors should be aware of *Conium maculatum* (poison hemlock, water hemlock, poison parsley) and *Cicuta maculata* (water hemlock). Poison hemlock is a much larger plant than common parsley. Poisonings have occurred when the leaves of *Conium* were mistaken for parsley and the seeds for anise. Symptoms of *Conium* and *Cicuta* poisoning include vomiting, diarrhea, weakness, paralysis, weak pulse, dilated pupils, convulsions, and death.

HISTORY: Parsley leaves and roots are popular as condiments and garnish worldwide. In Lebanon, parsley is a major ingredient in a national dish called tabbouleh. An average adult may consume as much as 50 g of parsley per meal.[2]

Parsley seed was used traditionally as a carminative to decrease flatulence and colic pain. The root was used as a diuretic and the juice to treat kidney ailments. Parsley oil has also been used to regulate menstrual flow in the treatment of amenorrhea and dysmenorrhea, and is purported to be an abortifacient. Bruised leaves have been used to treat tumors, insect bites, lice, skin parasites, and contusions.[3,4] Parsley tea at one time was used to treat dysentery and gallstones.[3] Other traditional uses reported include treatment of diseases of the prostate, liver, and spleen, in the treatment of anemia, arthritis, and cancers, as an expectorant, antimicrobial, aphrodisiac, hypotensive, laxative, and as a scalp lotion to stimulate hair growth. [3,5]

CHEMISTRY: The concentration of parsley oil varies throughout the plant. The roots contain 0.1% oil, whereas the leaf contains about 0.3%. [6] The fruit contains the largest percentage of oil, between 2% to 7%.[6] The oil contains 2 components, apiol and myristicin, which are pharmacologically active. Myristicin is chemically related to apiol and has also been identified in nutmeg. More than 30 varieties of parsley are recognized and their relative content of apiol and myristicin vary. For example, "German" parsley oil contains about 60% to 80% apiol, whereas "French" parsley oil contains less apiol but more (50% to 60%) myristicin. [7] Parsley has a high carotenoid content, with 25.7 mg per 100 g edible portion.[8]

Parsley contains psoralen and related compounds that can induce photosensitivity (see Toxicology); these include ficusin, bergapten, majudin, and heraclin. [9] The plant also contains several antimicrobial furocoumarins-psoralen, 8-methoxypsoralen, 5-methoxypsoralen, oxypeucedanin, and isopimpinellin. [10] Parsley contains the estrogenic flavone glycosides, 6?-acetylapiin and petroside. [11]

PHARMACOLOGY: Nutritionally, parsley is a good natural source of vitamins and minerals. These include: calcium, iron, carotene, ascorbic acid, and vitamin A.[3,6]

Myristicin, a compound found in parsley oil, is suggested to be in part responsible for the hallucinogenic effect of nutmeg. It is not known whether parsley oil induces hallucinations, but the practice of smoking parsley as a cannabis substitute was well known during the 1960s. Parsley may have been smoked for a euphoric effect or as a carrier for more potent drugs such as phencyclidine.[12]

Apiol is an antipyretic and, like myristicin, is a uterine stimulant. Apiol was once available in capsules for use as an abortifacient. Although the effectiveness of this compound as a uterotonic has not been substantiated, a Russian product has been used containing about 85% parsley juice to stimulate uterine contractions during labor.[13] Data regarding the safety and efficacy of this drug are not readily available.

Apiol and myristicin may be responsible for the mild diuretic effect of the seed and oil. [14] Rats given an aqueous parsley seed extract in place of drinking water eliminated a higher volume of urine compared with controls.[15] An in situ kidney perfusion technique also supports this finding. [15] Research suggests that the diuretic effect of parsley is mediated through an inhibition of the Na+-K+ pump.[15] The laxative effect of parsley seed extract is also attributed to the inhibition of sodium and of the Na+-K+ pump.[16] Parsley extracts have shown slight antibacterial and antifungal activity when tested in vitro, [17] but is not known to what extent this activity is retained in vivo. Furocoumarins extracted from 4 varieties of fresh and freeze-dried parsley leaves inhibited *Escherichia coli* 0157:H7, *Listeria monocytogenes*, *Erwinia carotovora*, and *L. innocua*.[10]

A methanolic extract of the aerial parts of parsley showed potent estrogenic activity in the MCF-7 breast cancer cell line. [11] The activity was attributed to two different compounds, 6?-acetylapiin and petroside. The estrogenic activities of these compounds are very similar to the isoflavones found in soybeans. [11]

One study indicates that parsley extracts may affect the pharmacodynamic activity of certain drugs. Parsley juice may alter the activity of drugs affected by the cytochrome P450.[18] A decrease of cytochrome P450 in liver homogenate was observed in mice administered parsley juice 2 hours prior to decapitation. [18]

TOXICOLOGY: Adverse effects from the use of parsley are uncommon. Persons allergic to other members of the Umbelliferae family (ie, carrot, fennel, celery) may be sensitive to the constituents (especially in the flowers) of parsley. Because of the potential uterotonic effects, parsley oil, juice, and seed should not be taken by pregnant women. Adverse effects from the ingestion of the oil have included headache, giddiness, loss of balance, convulsions, and renal damage.

The psoralen compounds found in parsley have been linked to a photodermatitis reaction found among parsley cutters. The skin reaction is usually only evident if the areas that have contacted the juice are exposed to very strong sunlight; it can be minimized by the use of protective clothing and sunscreens. [19]

SUMMARY: The leaves, roots, seed, and oil of parsley have been used medicinally in the treatment of arthritis, diseases of the liver and spleen, and as expectorants. There is no evidence to justify their use in these disorders. The use of parsley as a diuretic and for the control of dysmenorrhea stems from the presence of apiol and myristicin. Parsley has diuretic and laxative effects. These compounds may stimulate the uterine muscles and, therefore, the seed, juice, and oil of parsley should not be administered to pregnant women. The safety of the herb is limited primarily by potential photodermatitis reactions. There are no specific drug interactions with parsley; however, evidence suggests that parsley juice may have an effect on drugs involving cytochrome P450 metabolism.

PATIENT INFORMATION — Parsley

Uses: Parsley, in addition to being a source of certain vitamins and minerals, has been used in the treatment of prostate, liver and spleen diseases, as well as anemia, arthritis, and microbial infections. It has also been found useful as a diuretic and laxative. However, there have been no clinical trials to confirm these uses.

Side Effects: Adverse effects from the ingestion of parsley oil include headache, giddiness, loss of balance, convulsions, and renal damage. Pregnant women should not take parsley because of possible uterotonic effects.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PARSLEY

PASSION FLOWER

DATE OF ISSUE: MAR 1999

REPLACES MONOGRAPH DATED: MAY 1989

SCIENTIFIC NAME(S): *Passiflora* sp. Most often *P. incarnata* is used medicinally. Family: Passifloraceae

COMMON NAME(S): Passion flower; passion fruit, granadilla (species with edible fruit); water lemon; Maypop, apricot vine, wild passion flower(*P. incarnatus*); Jamaican honeysuckle (*P. laurifolia*).

BOTANY: The term "passion flower" connotes many of the ˜ 400 species of the genus *Passiflora*, which includes primarily vines. Some of the species are noted for their showy flowers, others for their edible fruit. Common species include *P. incarnata*, *P. edulis*, *P. alata*, *P. laurifolia*, and *P. quadrangularis*. Those with edible fruit include *P. incarnata*, *P. edulis*, and *P. quadrangularis*, the last being one of the major species grown for its fruit.[1] *Passiflora* species are native to tropical and subtropical areas of the Americas. In the US, *P. incarnata* is found from Virginia to Florida and as far west as Missouri and Texas. The flowers of *Passiflora* have 5 petals, sepals, and stamens, 3 stigmas, and a crown of filaments. The fruit is egg-shaped, has a pulpy consistency, and includes many small seeds.[1,2]

HISTORY: The passion flower was discovered in 1569 by Spanish explorers in Peru, who saw the flowers as symbolic of the passion of Christ, and therefore a sign of Christ's approval of their efforts. This is the origin of both the scientific and common names.[3] The folklore surrounding this plant possibly dates further into the past. The floral parts are thought to represent the elements of the crucifixion (3 styles represent 3 nails, 5 stamens for the 5 wounds, the ovary looks like a hammer, the corona is the crown of thorns, the petals represent the 10 true apostles, and the white and bluish purple colors are those of purity and heaven).[2,4] In Europe, passion flower has been used in homeopathic medicine to treat pain, insomnia related to neurasthenia or hysteria, and nervous exhaustion. Other indications have included bronchial disorders (particularly asthma), in compresses for burns, and for inflammation, inflamed hemorrhoids, climacteric complaints, pediatric attention disorders, and pediatric nervousness and excitability.[5]

CHEMISTRY: Researchers have identified a number of constituents in different passion flower species. "Official passion flower" is considered to be *P. incarnata*, which is the plant used for the drug.[6] Key constituents in *P. incarnata*generally include flavonoids, maltol, cyanogenic glycosides, and indole alkaloids (harmans).[2] Flavonoid content (2.5%) includes flavone di-C-glycosides shaftoside, isoshaftoside, isovitexin (found to be at highest concentration between pre-flowering and flowering stages in 1 report),[7] iso-orientin, vicenin, lucenin, saponarin, and passiflorine (similar to morphine).[8] Free flavonoids include apigenin, luteolin, quercetin, and campherol.[6] Another report confirms similar constituents above by mass spectral analysis.[9] Flavonoid determination by HPLC and other methods has been extensively reported.[10] The stability of dried extract also has been studied.[18] *P. incarnata* components also include phenolic, fatty, linoleic, linolenic, palmitic, oleic, and myristic acids, as well as formic and butyric acids,[5,19] coumarins, phytosterols, essential oil, maltol (0.05%;[6] which has been isolated and studied in 1 report),[20] and harman and its derivatives (0.03%). "Harmala" alkaloids include harmine, harmaline, and harmalol. Quantitative determination of harman and harmin in *P. incarnata* has also been performed.[21]

Other *Passiflora* species also have been studied in detail.

***P. edulis*:** In this species, fatty acid from seed oil has been analyzed,[22] aroma precursors have been isolated from its fruits,[23] flavor analysis has been performed,[24] flavonoid and alkaloid compositions have been determined both by chromatographic and spectrometric methods,[25,26] and harman content of the leaf parts has been evaluated.[26,27]

***P. bryonioides*:** Flavone compounds vitexin, quadrangularis, pulchella, and apigenin-7-monoglucosides have been identified.[28] Alkaloidal constituents also have been determined.[29]

***P. palmeri*:** Isolation of 17 flavonoids and flavone tricetin 4'-methyl ether has been determined.[30]

***P. coerulea*:** Constituent chrysin has been identified from this species and was found to be a ligand for benzodiazepine receptors.[31]

***P. sexflora*:** Leaf parts of this Mexican species yield flavonoids luteolin, an aurone, and sulphuretin.[32]

***P. pavonis*:** Flavonoids from this species have been isolated and identified.[33]

***P. serratifolia*:** Five C-glycosylflavonoids have been isolated from this species' leaves.[34]

***Comparative studies*:** C-glycoslyflavonoids from *Passiflora*species, *P. pittieri*, *P. alata*, *P. ambigua*,[35] *P. cyanea*, *P. oerstedii*, *P. menispermifolia*,[36] and *P. foetida*[37] have been reported. Thin layer chromatographic methods to differentiate *P. incarnata* from *P. edulis*and *P. caerulea* are described.[38] Quantitative analysis of different plant parts from *P. incarnata* and *P. edulis*indicate that *P. edulis* leaves have the highest alkaloid content, and that fruit rinds contain ˜ 0.25% alkaloids. Seeds and root tissue have the lowest alkaloid content. These findings may have economic importance. *P. edulis* fruit rinds, by-products of passion fruit juice production, may provide an economical source of alkaloids.[39] The cyclopentenoid cyanogenic compounds pasicapsin and linamarin have been isolated and identified from *P. capsularis* and *P. warmingii*.[40] Flavonoids from *P. trinervia* and *P. sanguinolenta*also have been reported.[41] A review of the chemical constitution of *Passiflora* species is available.[42]

PHARMACOLOGY: Animal studies have shown that *Passiflora*extracts have a complex action on the CNS, inducing dose-dependent stimulation and depression.[43] A report describes CNS-receptor binding sites of *P. incarnata*.[44]

Passion flower has been researched for its sedative and anxiolytic effects.[2,6,8] A 1986 survey of British herbal sedatives revealed passion flower as the most popular species (*P. incarnata*). Other popular species included *Valeriana officinalis*, *Humulus lupulus*, and *Scutellaria lateriflora*.[45,46] Martindale also lists many multi-ingredient preparations from other countries.[47]

The pharmacological activity of *Passiflora* is attributed primarily to the alkaloids and flavonoids. The harmala alkaloids have been found to inhibit monoamine oxidase and this may account for part of their pharmacologic effect.[20]

Passiflora species exhibit sedative activity in animals[48] and anxiolytic activity in mice.[49] The species *P. incarnata*when given to rats, showed diminished general activity when tested in a 1-arm, radial maze.[50] In mice, *P. incarnata*'s sedative and anxiolytic properties were confirmed to be caused by aqueous extracts of aerial plant parts.[51] The sedative effect of *Passiflora* may occur only when complexes of alkaloids and flavonoids are present.[39] Mice injected SC with 400 mg/kg of maltol and ethyl maltol showed reduced spontaneous activity, bradycardia, hypothermia, relaxation of skeletal muscle, and diminished pinna, corneal, and ipsilateral flexor reflexes. An ethylene chloride-soluble fraction at 2 mg/ml significantly reduced brain oxygen consumption and the effect with the acid-soluble fraction was even greater. Both maltol and ethyl maltol potentiated the sleep-inducing effect of hexobarbital and counteracted the convulsive effects of pentylene or strychnine. These findings indicate that maltol and ethyl maltol may mask the stimulant effects of harmala alkaloids in *Passiflora*.[20]

Human studies in the sedative/anxiolytic areas of *Passiflora* species are reported. A case report using the plant in a combination natural product, "calmanervin," for successful sedation before surgery is discussed.[52] In 91 patients, *Passiflora* (in combination, "Euphytose") exhibited statistically significant differences when

compared to placebo in the treatment of adjustment disorder with anxious mood, in a multicenter, double-blind trial. [53] *Passiflora* in the combination product Compoz contradicts these last 2 studies. It was not possible to differentiate from either aspirin or placebo when tested as a daytime sedative. However, this report was from the early 1970s and was only 2 weeks in duration.[54]

Other *Passiflora* species exhibit similar effects. *P. coerulea* has sedative actions.[31] Constituent chrysin, isolated from this same species (a central benzodiazepine [BDZ] ligand) has anxiolytic effects, due in part to this role as a partial agonist of central BDZ receptors. [55] Tranquilizing effects have been seen from alkaloids from the harman group in *P. edulis* species as well.[25]

Passion flower's ability to reduce anxiety makes it useful for asthma, palpitations, and other cardiac rhythm abnormalities, high blood pressure, insomnia, neurosis, nervousness, pain relief, and other related conditions. [2,6,8]

In vitro experiments have demonstrated that *Passiflora* kills a wide variety of molds, yeasts, and bacteria. Group A hemolytic streptococci are much more susceptible than *Staphylococcus aureus*, with *Candida albicans* being intermediate in susceptibility. The antimicrobial activity of *Passiflora* disappears rapidly from dried plant residues and fades gradually in aqueous extracts. Addition of dextran, milk, or milk products has a stabilizing effect on dry *Passiflora*.[56,57] A later report discusses *P. tetrandra* component, "4-hydroxy-2-cyclopentenone," to exhibit antipseudomonal actions. This consituent was also found to be cytotoxic to P388 murine leukemia cells.[58]

Other uses of passion flower include herbal treatment for menopausal complaints[59] and as a flavored syrup to mask drug taste.[60]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Little information is available on the clinical toxicity of *Passiflora*. Extracts produced no adverse effects in mice when administered intravenously.[56] Cyanogenesis from species *P. edulis* has been suggested.[61] The plant's known depressant actions may reduce arterial pressure affecting circulation and increasing respiratory rate.[8] There are no controlled human trials on single herb preparations of *Passiflora* extracts since the mid 1990s.[62] Some cases report vasculitis[63] and altered consciousness in 5 patients taking the herbal product Relaxir, produced mainly from *P. incarnata* fruits.[64] Induced occupational asthma and rhinitis may occur from the species *P. alata*, proven by skin testing and Western blot in vivo and in vitro studies. [65] *P. adenopoda* fruits may produce some toxic effect.[66]

Use of passion flower is contraindicated during pregnancy because of the uterine stimulant action of its alkaloids harman and harmaline, and the content of the cyanogenic glycoside gynocardin.[67]

SUMMARY: Passion flower denotes 1 of several species of the genus *Passiflora* that grow wild or are cultivated for their ornamental flowers and, in some species, for their edible fruit. In folk medicine, passion flower extracts have been used for their sedative and anxiolytic effects, which have been confirmed by animal and human studies. Edible passion fruit is used as food and in the production of juice. Some *Passiflora* species contain constituents that are active against molds, yeasts, and bacteria. No major clinical trials have been conducted to assess the plant's toxicities, although a few case reports are available.

PATIENT INFORMATION — Passion Flower

Uses: Passion flower has been used to treat sleep disorders and historically in homeopathic medicine to treat pain, insomnia related to neurasthenia or hysteria, and nervous exhaustion.

Interactions: Passion flower may interact with MAOI therapy.[68]

Side Effects: lthough no adverse effects of the passion flower have been reported, large doses may result in CNS depression.

Dosing: No clinical trials of passion flower as a single agent have been reported; therefore, the daily dose of 4 to 8 g currently is not supported.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PASSION FLOWER

PAWPAW

DATE OF ISSUE: APR 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Asimina triloba* (L.) Dunal. Family: Annonaceae (Sometimes confused with *Carica Papaya*.)

COMMON NAME(S): Pawpaw, Custard apple, Poor man's banana

BOTANY: The pawpaw is a small, North American tree which grows from ~ 3 to 12 meters high. It is common in the temperate woodlands of the eastern US. Its large leaves are "tropical looking" and droopy in nature. The dark brown, velvety flowers (~ 5 cm across) grow in umbrella-like whorls, similar to some magnolia species, and can bloom for up to 6 weeks. Pawpaw fruit is smooth-skinned, yellow to greenish-brown in color, measuring from ~ 8 to 15 cm long. It can reach up to 0.45 kg in weight. It resembles that of a short, thick banana, and is also similar in nutrient value. The yellow, soft, "custard-like" pulp is edible but sickly sweet in flavor and contains dark seeds.[1,2,3,4]

HISTORY: One source states that the pawpaw was introduced to the US in 1736.[3] It has been used as food for Native Americans. The thin, fibrous, inner bark has been used to make fish nets.[1,3] The bark was also used as medicine because it contains useful alkaloids. [3]

CHEMISTRY: The bark, roots, twigs, and seeds of the pawpaw plant contain the majority of acetogenins. Acetogenins are long-chain, aliphatic compounds with 35 to 39 carbon atoms ending with a gamma-lactone, cyclized in tetrahydrofuran rings. [5] They are polyketide-derived molecules and are unique to the Annonaceae family. Thus far, > 230 acetogenins from Asimina and other genera have been identified. [6] Acetogenins are known for their cytotoxic, antitumor (ie, asimicin, bullatacine), immunosuppressive antimalarial, pesticidal (ie, asimicin), antibacterial, and antifeedant properties. [5,6]

Known bioactive compounds from pawpaw bark include asimicin, bullatacin, bullatacinone, N-p-coumaroyltyramine, N-trans-feruloyltyramine, and (+)-syringaresinol. Trilobacin, a highly cytotoxic acetogenin, and trilobalicin and its ketolactones (2,4-cis and 2,4-trans-trilobacinone) have also been identified. [7,8] In addition, acetogenins cis- and trans-annonacin-a-one, cis- and trans-gigantetrocinone, trans-isoannonacin, and squamolone have been determined. [9] The acetogenins asimin, asiminacin, and asiminecin (all structural isomers) from pawpaw stem bark extracts were determined and also found to have highly cytotoxic properties. [10] Similar findings were described for acetogenins bis-tetrahydrofurans,[11] asiminocin ([30s]-hydroxy-4-deoxyasimicin),[12] (2,4-cis)- and (2,4-trans)-asimicinone.[13] In addition, acetogenins asimilobin, cis- and trans-murisolinones, and cis- and trans-bullatacinones have been isolated from pawpaw seeds. [14] Asiminine and analobine alkaloids have also been found.[3] A variation of essential oils and other extracts from the plant has been reported. [15]

PHARMACOLOGY: The pawpaw acetogenins have consistently exhibited cytotoxic (antitumor) and pesticidal (antimicrobial) activities.

Brine shrimp lethality bioassay or "test" (BSLT) is a screening tool used to predict cytotoxic and pesticidal activity. Tiny shrimp, *Artemia salina*, are placed in brine where their eggs hatch within 48 hours. Extracts of test-plant material are then put in shrimp-containing vials where survivors are microscopically counted. LC_{50} values are then calculated to determine the potential killing activity of, in this case, pawpaw extracts. [16]

In several studies performed in this manner it was found that specific acetogenins exhibited potent cytotoxicities. [7,9,11,14] Examples include acetogenin's cytotoxic potential against lung carcinoma, breast carcinoma, and colon adenocarcinoma. [9] Certain seed extracts also possessed cytotoxic actions comparable with doxorubicin against 6 human solid tumor cell lines.[14]

Of all the acetogenins, the adjacent-bis-THF-ring compounds are the most potent, showing cytotoxic activity aganist human lung and breast tumor cell lines with up to a million times the potency of doxorubicin.[8] Compound asiminocin, a pawpaw acetogenin isolate from stem bark was highly inhibitory against 3 human cell lines, with over a billion times the potency of doxorubicin.[12] The mechanism of action is via potent inhibitors of mitochondrial NADH:ubiquinone oxidoreductase, thus causing a decrease in cellular ATP levels.[6,10]

Various pawpaw tree parts were tested for pesticidal potential. It was found that small twigs yielded the most potent extract, while the leaves were the least potent. Unripe fruits, seeds, root wood and bark, and stem bark were also notably potent.[17] A caterpillar-laden tree was sprayed with a pawpaw bark extract and 30 minutes later the majority of insects had died and fallen from the tree. Phlox plants infested with mildew fungus were also sprayed with pawpaw preparation and 10 days later improvement was markedly observed. Pawpaw tree samplings were collected, expressing monthly variation in pesticidal activity. All of these are examples of the plant's beneficial (and natural) properties. The pawpaw tree is usually insect- or disease-resistant because of its acetogenin content, which prevents the feeding of many organisms.[6]

TOXICOLOGY: Handling the fruit may produce a skin rash in sensitive individuals. [3] The sensitizing potential of the pawpaw was examined in guinea pigs; the crude extract of the stem bark was found to be a weak sensitizer and to elicit allergic contact dermatitis. This report also determined the active compound asimicin to be a weak irritant.[18]

SUMMARY: The pawpaw is a North American plant bearing an elongated fruit. The plant parts and seeds contain acetogenins that possess cytotoxic and pesticidal actions. Certain extracts are comparable to, or are a million or over a billion times more potent than, doxorubicin. The plant may cause contact dermatitis in certain individuals.

PATIENT INFORMATION— Pawpaw

Uses: Pawpaw has historically been used for food, fishing nets, and medicine. It exhibits cytotoxic and pesticidal activities.

Side Effects: May cause contact dermatitis in certain people.

Dosing: Pawpaw has been used in homeopathy. Higher doses run a substantial risk of toxicity; therefore, pawpaw cannot be recommended.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PAWPAW

PECTIN

DATE OF ISSUE: FEB 2002

REPLACES MONOGRAPH DATED: JUN 1995

SCIENTIFIC NAME(S): Pectin

COMMON NAME(S): Pectin

HISTORY: Pectin is found in the cell walls of all plant tissue where it acts as an intercellular "cement," giving the plant rigidity. The compound is found at concentrations of 15% to 30% in the fiber of fruits, vegetables, legumes, and nuts. [1] Lemon and orange rinds are among the richest sources of the compound, containing up to 30% of this polysaccharide. [2] Pectin is also found in the roots of most plants. [3]

Pectin has been used in the food industry to add body and texture to jellies, jams, puddings, and other gelatinous products. It has also been added to antidiarrheal products and has been particularly effective when combined with adsorbing clays such as kaolin.

CHEMISTRY: Pectin is a polysaccharide with a variable molecular weight ranging from 20,000 to 400,000 depending on the number of carbohydrate linkages. [2] The core of the molecule is formed by linked D-polygalacturonate and L-rhamnose residues. The neutral sugars D-galactose, L-arabinose, D-xylose, and L-fucose form the side chains on the pectin molecule. Once extracted, pectin occurs as a coarse or fine yellowish powder that is highly water soluble and forms thick colloidal solutions. Pectin forms a gel in the presence of calcium ions that is more resistant to breakage in the gut than alginate gel. [3] The parent compound, protopectin, is insoluble, but is readily converted by hydrolysis into pectinic acids (also known generically as pectins). [4]

Pectin that has been pH-modified into smaller, less complex molecules is called modified citrus pectin. This modification allows better dissolution in water and more complete absorption by the body. [5]

PHARMACOLOGY: One of the best-characterized effects of pectin supplementation is its ability to lower human blood lipoprotein levels. [6] Most studies have evaluated its ingestion in combination with other gums. For example, a mixture of guar and apple pectin in combination with apple pomace was evaluated in 15 diabetic women. Ingestion of the mixture before meals resulted in a decrease in total cholesterol level (from 11.3% to 12.6%) and triglycerides (from 15.5% to 19.2%), although HDL cholesterol levels remained relatively stable. [7] Other combinations exhibiting cholesterol-lowering effects include the following: Guar gum/pectin mixture, acacia, pectin, guar gum-based fiber supplement, and a water-soluble dietary fiber (WSDF) mixture of psyllium, pectin, guar gum, and locust bean gum. [8,9,10] However, a study using different concentrations of a low-viscosity gum arabic and pectin fruit juice supplement failed to lower cholesterol in hypercholesterolemic patients. [11]

Addition of 15 g/day pectin supplement to fish oil-treated patients with type 2 diabetes mellitus decreased total and low-density-lipoprotein-cholesterol concentrations. [12] Intake of 15 g/day pectin has beneficial effects on both lipid metabolism and fibrin network architecture. These networks are believed to be less atherogenic. [13] A meta-analysis of cholesterol-lowering effects of dietary fiber (comparison of pectin, oat bran, guar gum, and psyllium) showed that increasing soluble fiber can make only a small contribution to dietary therapy to lower cholesterol. Reasons for variations in the effect of fiber on cholesterol include the following: Small sample sizes, different dosages of fiber, different background of diets, concurrent changes in body weight, varying dietary control, and different types of subjects. [14]

Dietary fiber has been associated with a reduction in the risk of colon cancer, and this may also apply to pectin. Possible direct mechanisms include the binding of carcinogens to undegraded dietary fiber and the absorption of water by these fibers to increase stool bulk and to shorten GI transit time. [15]

Modified citrus pectin was studied in a rat prostate cancer model for its effectiveness against prostate cancer metastasis. Rats were injected with prostate adenocarcinoma cell lines and given drinking water containing various modified citrus pectin concentrations. Although primary tumor growth was not affected, the 0.1% and 1% concentrations reduced metastasis when compared with control. [16] One human study in 7 prostate cancer patients examined the effect of modified citrus pectin on prostate specific antigen (PSA) doubling time. Four of 7 patients exhibited > 30% lengthening of PSA doubling time, representing a decrease in cancer growth rate. [5]

Pectin has also been investigated for its ability to reduce the consequences of exposure to radiation. People exposed to radiation after the Chernobyl accident were given pectin supplements, which were found to have a beneficial effect on the antioxidant level of their hematologic systems, as well as normalizing their triglyceride and albumin levels. [17] Pectin supplements appear to act as "enterosorbents," protecting against the accumulation of ingested radioactivity. [18]

A combination of alginate-pectin-polylysine particulates shows promise as a vehicle for controlled-release medications. The presence of a rigid pectin gel inside the particulates imparts a stronger and more stable vehicle in acidic and alkaline solutions, which could prolong drug release. This particulate system may have potential use as a carrier for drugs that are poorly absorbed after oral administration. [3]

Pectin supplementation was as effective as green bananas in the management of persistent diarrhea in children. Both pectin and banana reduced the volume of stool, improved stool quality, decreased the amount of oral replacement solutions and IV fluids for hydration needed, and shortened the duration of illness. [19] Pectin stimulates epithelial growth in the colon, thus reducing diarrhea. [20] In a study of 44 critically ill tube-fed adults receiving antibiotics, there was a trend toward decreased diarrhea in those receiving fiber and pectin. [20] More studies are needed to ascertain the dosage of pectin to be used to prevent and treat diarrhea.

A pectin-based, raft-forming, antireflux agent available in Europe has been studied for use in patients with heartburn. This product reduces the amount of food and acid concentration reaching the esophagus, thus reducing heartburn. [21,22] The pectin-based agent also has been shown to delay the recurrence of moderate or severe heartburn and erosive esophagitis when used as maintenance treatment. [23] However, in a study of patients with an ileal pouch-anal anastomosis, neither pectin nor fiber had any effect on stool frequency. [24]

INTERACTIONS: Concomitant administration of pectin with beta-carotene-containing foods or supplements can reduce the blood levels of beta-carotene by > 50%. [25] There is some evidence that concomitant ingestion of pectin with high energy diets may reduce the nutritional benefits of these diets, as demonstrated in a controlled trial of undernourished children; urea production also was shown to be lower in children who ingested pectin with their caloric supplement. [26]

In 3 patients with hypercholesterolemia, concomitant use of 15 g of pectin and 80 mg of lovastatin daily produced an increase in LDL cholesterol compared with taking lovastatin alone. [27] When pectin was stopped, the LDL cholesterol decreased. Pectin may decrease the GI absorption of lovastatin. Based on pharmacologic and pharmacokinetic considerations, a similar interaction may be expected to occur with concurrent use of pectin and other HMG-CoA reductase inhibitors (eg, atorvastatin).

TOXICOLOGY: Pectin is a fermentable fiber that results in the production of short-chain fatty acids and methane. [28]

Occupational asthma associated with the inhalation of pectin dust is a well-recognized hazard. [29,30,31,32] Positive skin test results for pectin indicate that an IgE-mediated hypersensitivity reaction is probably involved. [32] A case report involved a woman with occupational rhinitis and urticaria from pectin dust who presented with an anaphylactic reaction to cashew nut. An extensive skin prick test produced a positive reaction to cashew, pistachio, and pectin. [33]

Pectin in doses of 50 to 100 mg/kg increased the number of gastric mucosal lesions produced by ethanol or aspirin when studied in rats. No increase was produced

by application of 25 mg/kg pectin.[34] Whether these pectin-induced physicochemical changes are reproducible in humans has yet to be studied.

SUMMARY: Pectin is a natural polysaccharide that forms thick colloidal solutions in water. It is added to processed foods to create texture. Medicinally, the compound has been widely used alone and in antidiarrheal products as a stool-forming agent. Modified citrus pectin is being studied for decreasing prostate cancer growth rate. Pectin is generally well tolerated, although it may interfere with the absorption of dietary nutrients such as beta-carotene. Occupational asthma has been documented along with cross-sensitivity to cashew and pistachio nuts.

PATIENT INFORMATION— Pectin

Uses: Pectin has been used in antidiarrheal products and to lower blood lipoprotein levels. Pectin also has been investigated for its ability to reduce the consequence of exposure to radiation and for decreasing prostate cancer growth rate, but more study is needed.

Interactions: Coadministration of pectin with beta-carotene-containing foods or supplements can reduce the blood levels of beta-carotene by > 50%. Concomitant use of pectin and lovastatin, as well as other HMG-CoA reductase inhibitors, may decrease absorption of the HMG-CoA reductase inhibitor.

Side Effects: Pectin is generally well tolerated when ingested. Occupational asthma has been associated with the inhalation of pectin dust, along with cross-sensitivity to cashew and pistachio nuts.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PECTIN

PENNYROYAL

DATE OF ISSUE: JUL 1998

REPLACES MONOGRAPH DATED: JAN 1992

SCIENTIFIC NAME(S): *Hedeoma pulegeoides*(L) Persoom and *Mentha pulegium* L. Family: Labiatae

COMMON NAME(S): American pennyroyal, squawmint, mosquito plant, pudding grass

BOTANY: Both plants are members of the mint family and both are referred to as pennyroyal. *H. pulegeoides* (American pennyroyal) grows in woods through most of the northern and eastern United States and Canada while *M. pulegium* is found in parts of Europe. Pennyroyal is a perennial, creeping herb that possesses small, lilac flowers at the stem ends. It can grow to be 30 to 50 cm in height. The leaves are grayish green and, like other mint family members, are very aromatic. [1,2]

HISTORY: Pennyroyal has been recorded in history as far back as the 1st century AD, where it was mentioned by Roman naturalist Pliny and Greek physician Dioscorides. In the 17th century, English herbalist Nicholas Culpeper wrote about some uses for the plant including its role in women's ailments, venomous bites and digestion. European settlers used the plant for respiratory ailments, mouth sores and female disorders. [1] The plant's oil has been used as a flea-killing bath, hence the name *pulegeoides* (from the Latin word meaning flea), and has been used externally as a rubefacient. In addition, the oil has found frequent use among natural health advocates as an abortifacient and as a means of inducing delayed menses. The oil and infusions of the leaves have been used in the treatment of weakness and stomach pains.[3]

CHEMISTRY: The leaves and flowering tops are the source of pennyroyal oil, which is found in a concentration of 1% to 2% depending on the genus. The oil contains 80% to 92% of the cyclohexanone pulegone.[4,5] Other constituents include: Methone, iso-methone, octanol, piperitenone, pinene, limonene, dipentene and formic, acetic, butyric, salicylic and other acids. [6,7]

Quantitative determination of pulegone from Chilean *M. pulegium* oil has been performed.[8] Using mass spectrometry, biliary metabolites of pulegone, glucuronide, glutathione and conjugates have been detected. [9]

PHARMACOLOGY: Pennyroyal has been used as an insect repellent and antiseptic. [1,2,6,7] It has been employed as a flavoring agent for food and spice [7] and also as a fragrance in detergents, perfumes and soaps.[2,7]

The plant has been reported to be of use for female problems as an emmenagogue (to induce menstruation). It has also been used as a carminative, stimulantand antispasmodic, and for bowel disorders, skin eruptions, pneumonia and other uses. [1,2,6,7]

TOXICOLOGY: Pennyroyal herb teas are generally used without reported side effects (presumably because of low concentration of the oil), [6] but toxicity for pennyroyal oil is well recognized, with many reports of adverse events and fatalities documented.

American or European pennyroyal can cause dermatitis and, in large doses, abortion, irreversible renal damage, severe liver damage and death. A teaspoonful of the oil can produce delirium, unconsciousness and shock. [7]

One case of pennyroyal oil ingestion resulted in generalized seizures and auditory and visual hallucinations following the ingestion of less than 1 teaspoonful (5 ml) of the oil; the patient recovered uneventfully.[10] Other symptoms of plant ingestion may also include: Abdominal pain, nausea, vomiting, lethargy, increased blood pressure and increased pulse rate.[6]

The major component, pulegone, is oxidized by hepatic cytochrome P450 to the hepatotoxic compound menthofuran.[11] Pulegone, or a metabolite, is also responsible for neurotoxicity and destruction of bronchiolar epithelial cells. [5,12]

Pulegone extensively depletes glutathione in the liver, and its metabolites are detoxified by the presence of glutathione in the liver. Hepatic toxicity has been prevented by the early administration of acetylcysteine following ingestion of pennyroyal oil. [13] Various metabolite studies are available regarding hepatotoxicity. [14,15]

Pennyroyal toxicity in animals has been documented; intraperitoneal injections of pulegone in mice caused extensive liver injury. [16]

Rats given oral doses of pulegone for 28 days (80 or 160 mg/kg/day) developed encephalopathic changes characterized by cyst-like spaces in the cerebellum without concomitant demyelination. This resembles the neuropathy induced in rats by administration of hexachlorophene. [17] LD_{50} values for pennyroyal oil have been reported in rats and rabbits.[6] A dog treated for fleas with pennyroyal application suffered vomiting and, despite treatment, died within 48 hours. [18]

Case reports in humans are also widely reported: One woman who ingested up to 30 ml of the oil experienced abdominal cramps, nausea, vomiting and alternating lethargy and agitation. She later exhibited loss of renal function, hepatotoxicity and evidence of disseminated intravascular coagulation. She died 7 days after ingesting the oil. Another woman ingested 10 ml of the oil and only experienced dizziness. [19] Two infants (8 weeks of age and 6 months of age) who ingested mint tea containing pennyroyal oil developed hepatic and neurologic injury. One infant died, the other suffered hepatic dysfunction and severe epileptic encephalopathy. [20] A review of 18 previous cases reported moderate to severe toxicity in patients exposed to at least 10 ml of the oil, concluding that pennyroyal continues to be an herbal toxin of concern to public health.[21] Another review concluded that pennyroyal oil is toxic as well.[22]

Pennyroyal is contraindicated in pregnancy. It possesses abortifacient actions (because of pulegone content) and irritates the genitourinary tract. [6] The abortifacient effect of the oil is thought to be caused by irritation of the uterus with subsequent uterine contraction. Its action is unpredictable and dangerous. [23] The dose at which the herb induces abortion is close to lethal, and in some cases it is lethal. [2,7] However, one letter does report a pregnancy unaffected by pennyroyal use.[24]

SUMMARY: Pennyroyal oil and teas made from the plant continue to find use in a variety of herbal self-treatment practices. Despite this use, these products are potentially toxic to both animal and man and should not be ingested. The principle toxic assaults appear to be on the central nervous system and the liver. The plant is contraindicated in pregnancy because of its abortifacient actions.

PATIENT INFORMATION — Pennyroyal

Uses: Pennyroyal may be used as an insect repellent, antiseptic, fragrance, flavoring, as an emmenagogue, carminative, stimulant, antispasmodic and for bowel disorders, skin eruptions and pneumonia.

Side Effects: Pennyroyal can cause abdominal pain, nausea, vomiting, lethargy, increased blood pressure and increased pulse rate, dermatitis and, in large portions, abortion, irreversible renal damage, severe liver damage and death. A small amount of oil can produce delirium, unconsciousness, shock, seizures and auditory and visual hallucinations.

Dosing: Pennyroyal usually is used as the volatile oil as an abortifacient. Because of severe toxicity at doses of 5 g, it should not be used. [19]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PENNYROYAL

PEPPERMINT

DATE OF ISSUE: JUL 2002

REPLACES MONOGRAPH DATED: JUL 1990

SCIENTIFIC NAME(S): *Mentha x piperita* L. Peppermint is a hybrid of *M. spicata* L. (spearmint) and *M. aquatica* L. Family: *Labiatae*

COMMON NAME(S): Peppermint

BOTANY: This well-known perennial is a prototypical member of the mint family. Like all mints, it has a squarish purple-green stem with leaves of dark or light green, with purple and lilac-colored flowers. The plant is generally sterile and spreads by means of stolons (basal branches). A variety of types of peppermint exist, which are cultivated worldwide. Pharmaceutical oil is derived from 2 varieties, white (light green leaves) and black (dark green leaves) peppermint. [1] This is not to be confused with Japanese peppermint oil, which is similar in odor but derived from a different species. [1]

HISTORY: First described in England in 1696,[1] peppermint and its oil have been used in Eastern and Western traditional medicine as an aromatic, antispasmodic, and antiseptic in treating indigestion, nausea, sore throat, colds, toothaches, cramps, and cancers. Today, the oil is used widely as a flavoring in chewing gum, toothpastes, mouthwashes, cigarettes, and pharmaceuticals.[1] It also is used as an ingredient in cough and cold preparations, and a carminative for use in irritable bowel syndrome.[1] As the menthol component, it also is found in numerous antiseptic, antipruritic, and local anesthetic preparations. [1]

CHEMISTRY: Peppermint oil is extracted from the plant parts by steam distillation.[1] The chemistry of peppermint oil is complex and highly variable as more than 100 components have been found in the oil. Their relative concentrations vary between climate, cultivars, and geographic location. [2,3,4] Peppermint yields 0.1% to 1% of a volatile oil that is composed primarily of menthol (29% to 48%), menthone (20% to 31%), and methyl acetate (3% to 10%). [5] Pulegone, contained in various forms of peppermint, should not exceed a concentration of 1%, because it can be toxic.[6] Other pharmacologically active ingredients include tannins, bitter substances, caffeic acid, and flavonoids.[7] Mints also shift their monoterpene profile later in growth to produce more menthofuran, which is an off-flavor.

PHARMACOLOGY

Dermatologic: In low concentrations, topical application of menthol causes a cooling sensation, while in high concentrations it causes local anesthesia and irritation. [8] The coolant action of menthol can be observed as an ingredient in shaving creams.[8] The irritant effect of menthol causes local vasodilation; this has been used to aid penetration of topical drugs.[8] Menthol is used as a local anesthetic agent in topical products that are used to treat musculoskeletal pain. [8]

Antiemetic: In a placebo-controlled study of gynecological surgery patients, there was a statistically significant effect of peppermint oil in reducing postoperative nausea by antagonizing emetic sensory receptors.[9]

Biliary disorders: The flavonoids in peppermint leaves reportedly have choleretic (bile stimulating) effects in dogs. [5] A related effect was confirmed in one study in which guinea pigs were administered the essential oil of peppermint in IV doses of 0.1 to 50 mg/kg. Prior to dosing, the sphincter of Oddi had been occluded by the administration of morphine. Following a single dose of 1 mg/kg of peppermint oil, a rapid and complete opening of the sphincter was observed. However, in doses of 25 or 50 mg/kg, peppermint oil again constricted the sphincter.[10]

Colon spasm: Addition of 40 mL of peppermint oil to barium suspension, in a double-blind, placebo-controlled, randomized study of 141 patients receiving a barium enema, was shown to reduce the incidence of colonic spasm and decrease the use of IV spasmolytics.[11] A different study administered 8 mL of peppermint oil intraluminally by means of a hand pump system during colonoscopy. This produced a rapid and strong effect on colonic muscle relaxation and inhibition of motility. [12]

Diffuse esophageal spasm (DES): DES is a relatively rare motility disorder of the esophagus that results in chest pain, regurgitation, and dysphagia. [13,14] Peppermint oil was shown to significantly reduce the number of simultaneous contractions and increase the uniformity of contractions. [14]

Dyspepsia: Nonulcer dyspepsia patients exhibit a slower rate of gastric emptying, leading to a postprandial feeling of fullness, nausea, vomiting, and epigastric pain. Six patients with nonulcer, nonobstructive dyspepsia and 20 healthy male volunteers ingested a radiolabeled solid test meal with 0.2 mL peppermint oil in 25 mL of water or water without peppermint oil. Gastric emptying rate was accelerated in both volunteers and patients with dyspepsia after administration of peppermint oil. [15]

Enteric-coated capsules containing a fixed combination of 90 mg peppermint oil and 50 mg caraway oil were compared with placebo in patients with functional dyspepsia. Intensity of pain, sensation of pressure, heaviness and fullness, and global improvement were all shown to be significantly and clinically improved with the fixed combination product.[16]

Irritable bowel syndrome (IBS): Patients should be administered peppermint oil only after examination has definitely diagnosed the presence of IBS with no associated organic lesions and other diagnoses have been ruled out. [17]

Peppermint oil has been shown to exhibit spasmolytic activity on smooth muscles. Commercial preparations are available for use in the treatment of irritable bowel, abdominal pain, and related symptoms. Peppermint oil, alone in enteric-coated capsules or in combination with other herbs, is available for use in irritable bowel syndrome. *Peppermint Plus*, *Mintec*, *Colpermin*, *PeppermintZ*, *Enteroplant*, and *Herb-a-Calm* are examples of preparations.[18,19,20,21]

Generally administered as enteric-coated capsules,[19,21] these preparations release their contents in the large intestine and colon. [22] Therefore, peppermint appears to act directly on this smooth muscle.[23] The spasmolytic activity is related to menthol content.[18,24] Conflicting reports of the mode of action of peppermint oil have shown that a rise in intracellular cyclic adenosine monophosphate, as opposed to its action as a calcium channel blocker, mediates its spasmolytic effect. [25] As these studies were performed on animal tissue, the exact mechanism of action of peppermint oil in relieving symptoms of IBS in humans is still unknown. Peppermint oil also has been shown to affect intestinal transport by inhibiting enterocyte glucose uptake via a direct action at the brush border membrane. [26]

When administered orally, peppermint-containing drugs appear to be effective. [27] A meta-analysis of 5 placebo-controlled, double-blind, randomized trials indicates that peppermint oil is effective in the symptomatic treatment of IBS.[28] Three studies showed that treatment with peppermint oil was significantly superior to placebo.[27,29] However, 2 studies did not demonstrate a difference.[30,31] Three trials were included in the descriptive review. [31,32,33] One small trial, over 6 months, suggested that stress management was more effective than peppermint oil.[28,33] The authors noted that there are some limitations and methodological flaws in the studies included in this meta-analysis that prevent conclusively establishing beyond reasonable doubt the effectiveness of peppermint oil in the treatment of IBS.[27,28,29,30,31,32,33,34]

A systematic review evaluated the efficacy of pharmacologic agents, including peppermint oil, for treatment of IBS. [35,36] Three randomized, double-blind, placebo-controlled trials were evaluated. [35] Two crossover trials did not demonstrate efficacy of enteric-coated peppermint oil. [30,31] However, one high-quality parallel trial demonstrated improvement in symptoms of abdominal pain, distention, and stool frequency.[37] A definitive conclusion for the treatment of IBS with peppermint oil is still elusive. However, the Cochrane Inflammatory Bowel Disease Group is reviewing medications, including peppermint oil, used for the treatment of IBS. [38]

A randomized, double-blind, placebo-controlled trial of enteric-coated capsules in 42 children between 8 and 10 years of age demonstrated reduced severity in pain with no effect on other symptoms.[39]

Antibacterial: Peppermint oil possesses antibacterial activity in vitro. Substantial variation in the commercial peppermint oils display varying antimicrobial activity. [4] Peppermint oil and 15 of its constituents (eg, menthol, menthone) were shown to have significant antibacterial activity against *Escherichia coli* 0157:H7.[40] In another study, the essential oils of peppermint and spearmint exhibited bactericidal activity against *E. coli* 0157:H7, *Helicobacter pylori*, methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus*, and *Salmonella enteritidis*.[41] The potential role of these oils in the control of pathogenic infections has yet to be proven.

Antiviral: Peppermint extracts have been reported to have antiviral activity against Newcastle disease, herpes simplex, vaccinia, and other viruses in culture. [5]

Dementia: The Cochrane Dementia and Cognitive Improvement Group is assessing the use of aromatherapy to help relieve health problems and improve quality of life. Peppermint oil is one of the essential oils being studied as aromatherapy for dementia. [42]

Headache: In a double-blind, placebo-controlled, randomized crossover study in 32 healthy patients, 4 different topical preparations (peppermint and eucalyptus oil with ethanol, peppermint with ethanol, eucalyptus with ethanol, and ethanol alone) were tested for their effect on experimental headache mechanisms. The peppermint oil and ethanol combination exerted a significant effect and reduction in sensitivity to the pain experienced with headaches. [43]

Mental fatigue: Intraperitoneal administration of peppermint oil in mice caused a significant dose-dependent increase in measured ambulatory activity. [44]

Allergic rhinitis: Oral administration of peppermint extract in rats inhibited the nasal symptoms and nasal vascular permeability induced by a histamine challenge. [45]

Antitussive: Menthol is available in a variety of over-the-counter products (eg, chest rubs, lozenges, syrups, inhaled as a steam vapor) for the treatment of cough. Forty-two healthy children 10 and 11 years of age showed a decrease in cough when inhalation of menthol was compared with placebo. [46] The mechanisms by which menthol may act as an antitussive are still speculative.[8]

Asthma: In a 4-week study, 23 patients with chronic mild asthma were randomized to receive either nebulized menthol (10 mg twice daily) or placebo. Although there was no effect on forced expiratory volume in 1 second (FEV1), the menthol group used fewer bronchodilators and had fewer wheezing episodes. [47]

Nasal decongestant: Menthol is available in many common cold preparations for use as a decongestant. Menthol inhalation can cause a subjective nasal decongestant effect without any objective decongestant action.[8] In lozenges, the main action of menthol appears to be a subjective sensation of improved nasal airflow.[8]

Other uses: Azulene, which is found in small quantities in peppermint oil, is known to have anti-inflammatory and antiulcerogenic effects in animals.

INTERACTIONS: Inhibition of oxidative metabolism with cimetidine has been shown to result in increased menthol glucuronide excretion. The significance of this is unknown; however, menthol conjugation with glucuronic acid might be dose-dependent. [48]

In rats, peppermint oil has been shown to enhance cyclosporine oral bioavailability. [49]

In a crossover investigation involving 12 healthy subjects, peppermint oil increased the bioavailability of felodipine and simvastatin. [50]

TOXICOLOGY: Peppermint is generally recognized as safe for human consumption as a seasoning or flavoring, as are other mints from which menthol is derived as a plant extract.[6]

Adverse events: Menthol, the major component of peppermint oil, may cause allergic reactions (characterized by contact dermatitis, flushing, and headache) in certain individuals (eg, those with aspirin-induced asthma). [5,51,52] Delayed patch test reaction to menthol and peppermint oil may occur 6 days to 2 weeks after application.[53]

Patients presenting with oral symptoms, including ulceration, experienced improvement with discontinuation and avoidance of menthol/peppermint-containing products.[54] Excessive use of mint-flavored sweets caused stomatitis with oral papillary hypertrophy. [55]

Rats fed peppermint oil in daily doses of up to 100 mg/kg for 28 days developed dose-related brain lesions. A similar study for 90 days demonstrated identical pathology, with no additional aggravation of the cyst-like spaces in the cerebellum. [56] These were similar in nature to the neuropathy induced by hexachlorophene and attributed to the pulegone component of peppermint oil.[6,57] However, doses of this magnitude would be considered to be an overdosage with the oil.

A case of delirium from oral ingestion of topical *Mentholatum* intoxication required hospitalization in a chronic alcoholic female patient. [58] Delirium also was experienced in a chronic alcoholic male patient after possible oral ingestion of a topical menthol/alcohol-containing analgesic. [59]

Enteric-coated capsules may cause a burning sensation during defecation caused by unabsorbed menthol reaching the rectum. [19] This can be prevented by reduction of dose.[19]

Cautions: Because of the oil's ability to relax GI smooth muscle, people with hiatal hernia may experience worsening of symptoms while ingesting peppermint-containing preparations. Enteric-coated capsules should be swallowed whole and not broken or chewed, as peppermint oil can irritate the mouth, esophagus, and stomach. Take 30 to 60 minutes before meals on an empty stomach. Do not take after meals or with food.[17]

Peppermint leaf or oil is available in combination with many different constituents. Instruct patients to read the list of ingredients and excipients as some capsule preparations may contain arachis (peanut) oil that can cause anaphylaxis in susceptible people. [17]

Do not use for more than 14 days, except on the advice of a physician. The safety of peppermint oil for long-term use has not been established. [17]

Contraindications: There are no data available on the safety of peppermint in pregnancy.

Peppermint oil should not be administered to patients with heartburn or active gastric ulcers, as symptoms may be exacerbated. [17] Peppermint oil can decrease esophageal sphincter pressure, thus contributing to gastroesophageal reflux. [21] Patients with active hepatic disease, inflammation of the gallbladder, gallstones, or obstruction of bile ducts should consult a physician before using peppermint oil. [20]

Peppermint oil should not be applied to the face, especially under the nose of children and infants. [8] The application of menthol-containing ointment to the nostrils of an infant for the treatment of cold symptoms has been reported to have caused instant collapse.[5] Enteric-coated capsule preparations have not been studied in children younger than 8 years of age; thus, they are not recommended for use in very young children.

SUMMARY: Peppermint and its oil are used extensively in foods and drugs. The oil is a complex mixture of more than 100 compounds. Menthol, which is found in the highest concentration, is pharmacologically active in relatively small doses. Extracts have been used with preliminary success in the treatment of certain GI disorders. Various preparations of enteric-coated peppermint oil are now available over-the-counter for the treatment of IBS. A definitive diagnosis for IBS should be obtained before use. Instruct patients to swallow enteric-coated capsules whole, and administer 3 to 60 minutes before a meal. Peppermint oil may cause allergic

reactions characterized by contact dermatitis, flushing, and headache, and worsen the symptoms of hiatal hernias, heartburn, and stomach ulcers.

PATIENT INFORMATION— Peppermint

Uses: In addition to being recognized as a seasoning and flavoring, peppermint has been used to treat irritable bowel syndrome and abdominal pain. Menthol is available in numerous over-the-counter preparations for topical use for both cooling and warming.

Interactions: Peppermint oil has been shown to interact with cyclosporine, felodipine, and simvastatin. Consult your health care provider before using.

Side Effects: Peppermint oil may cause allergic reactions characterized by contact dermatitis, flushing, and headache, and worsen the symptoms of hiatal hernias, heartburn, and stomach ulcers.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PEPPERMINT

PERILLA

DATE OF ISSUE: AUG 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Perilla frutescens* (L.) Britt. Family: Lamiaceae

COMMON NAME(S): Beefsteak plant, perilla, wild coleus

BOTANY: The broad oval leaves are reminiscent of the leaves of the common ornamental coleus. It is widely cultivated in the Orient.

HISTORY: The leaves and seeds of perilla are eaten in the orient and form part of the native Japanese dish known as "shisho." [1] Dried leaves are used as components of herbal teas. The seeds are expressed to yield an edible oil. This oil is also used in commercial manufacturing processes for the production of varnishes, dyes and inks. The leaf oil has a delicate fragrance and is used in food flavoring.

In oriental folk medicine, the plant has been used as an antispasmodic, to induce sweating, for asthma treatment, to quell nausea and to alleviate sunstroke, among other uses.[1]

CHEMISTRY: Apigenin and luteolin are the major flavones in the seeds. These also are found in the leaves together with many additional flavones, the primary one being shishonin. The leaves contain anthocyanin and perillanin chloride. Perillartine is reported to be 2000 times sweeter than sugar. [1] The oil is rich in citral, l-limonene and alpha-pinene.

PHARMACOLOGY: Perilla oil is receiving attention because it is high in alpha-linolenate, which may result in beneficial health effects. Serum cholesterol and triglyceride levels decreased in rats fed perilla oil. Similarly beneficial changes in the levels of eicosapentaenoic acid and arachidonic acid were observed [2] in these animals.

Perilla oil dietary supplementation to laboratory animals has been found to reduce the incidence of mammary tumor development compared to diets rich in safflower oil.[3] Perilla oil supplementation in animals also limits the development of colonic tumors. [4]

Perilla extracts may have an immunosuppressant effect that preferentially attenuates IgE production, and it has been postulated that this extract may be useful for the management of certain allergic disorders.[5]

TOXICOLOGY: The volatile perilla oil contains aldehyde antioxide, which has been used in the tobacco industry as a sweetener, however, this compound may be toxic.

Perilla ketone is a potent agent for the induction of pulmonary edema in laboratory animals. [6] Animals grazing on the plant have also developed pulmonary edema and respiratory distress. This ketone is chemically related to the toxic ipomeanols derived from moldy sweet potatoes. Intravenous doses of this compound can result in death secondary to pleural effusion and edema.[1] The ketone acts by increasing the permeability of endothelial cells and does not appear to require the presence of cytochrome P-450 to increase vascular permeability.[7]

Dermatitis has been reported in perilla oil workers and patch testing suggests that 1-perillaldehyde and perillalcohol contained in the oil are responsible for the effect.[1,8]

SUMMARY: Perilla oil is a valued product for both food flavoring and commercial applications. Preliminary evidence suggests that the oil may have beneficial antilipidemic effects and potential cancer-protective activity.

PATIENT INFORMATION — Perilla

Uses: Perilla has been used for food flavoring and may be useful for the management of certain allergic disorders. Preliminary research suggests that perilla may also have beneficial antilipemic effects and potential cancer-protective activity.

Side Effects: Perilla may cause dermatitis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PERILLA

PERIWINKLE

DATE OF ISSUE: JUL 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Catharanthus roseus* G. Don. Also referred to as *Lochnera rosea*Reichb., *Vinca rosea* L., and *Ammocallis rosea* Small. The related plant *Vinca minor* (common periwinkle, Myrtle) is used as a ground cover. Family: Apocyanaceae

COMMON NAME(S): Periwinkle, red periwinkle, Madagascar or Cape periwinkle, old maid, church-flower, ram-goat rose, "myrtle," magdalena [1]

BOTANY: Although the plant is said to be native to the West Indies, it was first described in Madagascar. [1] The periwinkle is a perennial herb that grows to about 2 feet.[2] It is highly branched and develops a woody base. The flowers can bloom throughout the year, depending on the climate. These are often bred for their unique colors ranging from white to green-yellow and lavender. The seed pod dries, splits and releases numerous tiny seeds, of which there are about 350,000/lb. [1]

HISTORY: The plant was introduced in Europe during the mid-1700s during which time it was cultivated as an ornamental. Today it grows throughout much of the world and plantations have been established on most continents in the warmer climates. The plant has been widely used in tropical folk medicine. Decoctions of the plant have been used for maladies ranging from ocular inflammation, diabetes and hemorrhage to treating insect stings and cancers.

CHEMISTRY: All parts of the plant contain alkaloids. By 1977, 73 unique alkaloids had been isolated and named, and today the number exceeds 100. The concentration of alkaloids varies with the part of the plant and the region of harvest. Roots collected in India have yielded up to 1.22% total alkaloids. The hypotensive alkaloids reserpine and alstonine have been isolated from the root in concentrations less than 0.03%. [1] The alkaloid designated ajmalicine, raubasine,[3] vinceine or vincaine appears to be structurally similar to yohimbine. The most well known of the "vinca" alkaloids derived from *C. roseus* are vinblastine (vincaleukoblastine) (eg, *Velban*)[4] and vincristine (leurocristine) (eg, *Oncovin*),[4] which are now widely used antineoplastic agents.

The leaves also contain a complex volatile oil. [1]

PHARMACOLOGY: A number of pharmacologic activities have been ascribed to the periwinkle plant. Injection of a concentrated aqueous extract was shown to lower blood sugar levels in cats and tended to moderate blood sugar levels in humans according to a treatise on African plant uses. [1]

Investigations by the Lilly company into the antidiabetic activity of the plant found no effect on blood sugar levels but uncovered the antineoplastic effects of plant extracts. Vincristine and vinblastine appear to bind to or crystallize important proteins in cellular microtubules, thus preventing proper polymerization, arresting cellular division and killing the cell. These drugs may also exert some immunosuppressant activity and may interfere with other components of the cell cycle to induce cellular death. These drugs are used for the treatment of leukemia, Hodgkin's disease, malignant lymphomas, neuroblastoma, Wilms tumor, Kaposi's sarcoma and mycosis fungoides, among others. An extensive body of literature exists on the clinical uses of the various purified alkaloids of *Catharanthus*.

Catharanthine has demonstrated diuretic properties.[3] Ajmalicine may improve cerebral blood flow and has been used to treat high blood pressure when given in combination with rauwolfia alkaloids.[3]

TOXICOLOGY: The periwinkle plant has been reported to have caused poisonings in grazing animals. [1] Severe systemic adverse events are associated with the prolonged use of vincristine and vinblastine, and fatalities have been associated with the use of these alkaloids. Acute dyspnea has been reported following antineoplastic treatment with the related alkaloids vindesine (*Eldisine*)[4] and vinorelbine (*Navelbine*).[4,5]

There has been at least one report of persons attempting to smoke periwinkle leaves as an hallucinogenic substitute for marijuana, but this appears to have passed in fancy because of a lack of any significant pharmacologic effect. [1]

The related *Vinca minor* has been declared "unsafe" for human consumption by the FDA.[2]

SUMMARY: Members of the periwinkle group are well known as ornamentals. The Madagascar periwinkle has a long history of folk use and today is an important source of antineoplastic alkaloids. The plant should not be ingested because of concerns of potential toxicity.

PATIENT INFORMATION — Periwinkle

Uses: Periwinkle has been used in the treatment of leukemia, Hodgkin's disease, malignant lymphomas, neuroblastoma, Wilms tumor, Kaposi's sarcoma, mycosis fungoides, to improve cerebral blood flow, and treat high blood pressure.

Side Effects: Periwinkle is potentially toxic and has been known to cause acute dyspnea.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PERIWINKLE

PERU BALSAM

DATE OF ISSUE: NOV 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Myroxylon pereirae* (Royle) Klotzsch. Syn. with *M. balsamum* var. *pereirae*. Family: Leguminosae or Fabaceae

COMMON NAME(S): Peru balsam, Peruvian balsam, Indian balsam, black balsam, balsam Peru

BOTANY: Peru balsam is a large tree that grows 50 to 75 feet in height in Central America. It is often cultivated as a shade tree. [1] Crude Peru balsam is a dark brown, thick liquid with an aromatic smell of cinnamon and vanilla and bitter taste. [2,3] To remove it from the tree, the bark is alternately scorched and beaten. The balsam in the bark is obtained by boiling. Following removal of strips of bark from the tree, the exposed wood also secretes balsam. The material is soaked up by rags wrapped around the tree, which are then boiled in water. The balsam sinks to the bottom and is collected. Approximately two pounds is the annual yield per tree.

HISTORY: The drug was first imported from Spain through Peruvian ports, from which the material derives its name. [3] Peru balsam has been used for the treatment of topical wounds and infections and as a flavoring in the food industry. Indians used the material to stop bleeding and to promote wound healing. They also used the material as a diuretic and to expel worms. [1] Today, the material is in a number of pharmaceutical preparations and plays an important role in perfumery. The material has no use as an internal medication.

CHEMISTRY: The balsam contains 50% to 65% of a volatile oil called cinnamein along with about 25% resin. The volatile oil contains primarily benzyl cinnamate and benzoic and cinnamic acid esters, with small amounts of benzyl alcohol and related compounds. In addition, traces of styrene, vanillin and coumarin have been identified in the material. Oil distilled from the wood is about 70% nerolidol. [4] Considerable variations exist in the balsam based on the source of the material. [3]

PHARMACOLOGY: Peru balsam has mild antiseptic properties and is said to promote the growth of skin cells. [2] The balsam has been used in dentistry in the treatment of dry socket (postextraction alveolitis) and as a component of dental impression material. Topically it is included in preparations for the treatment of wounds and ulcers. [2] It was formerly used widely as a treatment for scabies, and it has been used in suppositories for hemorrhoids. [6]

TOXICOLOGY: Peru balsam is a contact allergen and contact dermatitis occurs frequently with the product. Systemic toxicity following application of Peru balsam to nipples of nursing mothers has been described. [5]

SUMMARY: Although Peru balsam is not used widely in American medicine, its use persists in topical applications and as a food flavoring. Its topical use is somewhat limited by contact dermatitis that occurs frequently with the product.

PATIENT INFORMATION — Peru Balsam

Uses: Peru balsam has been used in the treatment of dry socket, topically as a treatment of wounds and ulcers, and in suppositories for hemorrhoids.

Side Effects: Peru balsam may cause contact dermatitis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PERU BALSAM

PINEAPPLE

DATE OF ISSUE: JUL 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Ananas comosus* (L.) Merr. Family: Bromeliaceae

COMMON NAME(S): Pineapple

BOTANY: The plant grows to heights of 2 to 4 feet. The well-known fruit of the pineapple is actually a complex flowerhead that forms around the stem. The pineapple is the only cultivated fruit whose main stem runs completely through it.[1] Each of the eyes on the surface is the dried base of a small flower. The top crown of leaves contains a bud, which when mature, indicates the fruit is ready for cutting. Pineapples contain no seeds but are grown from their crowns.

HISTORY: Pineapples originated in South America and likely did not reach Hawaii until the 19th century.[2] Europeans spread the plant throughout much of the world. Because of rising labor costs, today the bulk of pineapple production no longer occurs in Hawaii, but in regions of South America and the Philippines.[1] The pineapple is cultivated for use as a fruit from which juices, syrups and candies are prepared.[3] The plant has a long history in traditional tropical medicine for the treatment of ailments ranging from constipation to jaundice.[3]

CHEMISTRY: The fruit is rich in citric acid, with some cultivars exceeding concentrations of 8%.[3] Malic acid also is found in significant quantities.[1] The ascorbic acid content also varies with the cultivar, but is generally in the low range.[1] The essential oil is rich in a variety of aromatic compounds. A steroidal component of the leaves possesses estrogenic activity.[3] The residue left after juice extraction is rich in vitamin A and is used as a component of livestock feed.

This residue, along with the juice and entire plant, also is used as a commercial source of the proteolytic enzyme bromelain. At least four proteolytic enzymes have been identified in pineapple, the most well studied of which is bromelain.[4] Bromelain is a mixture of protease and is used as a meat tenderizer, in the food and beverage industries, and has been used to treat edema and inflammation.[3] Slight differences in the composition of "stem" and "fruit" bromelain have been reported,[5] and the amino acid sequence has been identified.[6] Although products containing bromelain are available as nutritional supplements, therapeutic products are no longer available to the medical profession because the efficacy of these treatments could not be substantiated by well-designed trials.

PHARMACOLOGY: An antiedemic (diuretic) substance has been reported to be present in the rhizome, and the ripe fruit is said to have diuretic activity.[3] The juice from unripe pineapples can act as a violent purgative.[3]

Bromelain is a proteolytic enzyme that has been used to tenderize meat. Bromelain is absorbed unchanged from the intestine at a rate of about 40%. The product has been used for burn debridement and to reduce soft tissue inflammation and irritation. It also has been used to prevent ulcers and to enhance fat excretion as a component of some fad diets, but these effects have not been well substantiated.[3] The pharmacologic effects of bromelain are caused by an enhancement of serum fibrinolytic activity and inhibition of fibrinogen synthesis, as well as by direct degradation of fibrin and fibrinogen. Bromelain lowers kininogen and bradykinin serum tissue levels and has an influence on prostaglandin synthesis.[7] Topical application of pineapple-derived enzymes has been shown to enhance wound healing in animal models.[8] Bromelain is reported to have nematicidal activity.[3]

Ingestion of pineapple has been shown to result in the inhibition of endogenous nitrosation in human volunteers, suggesting that the ascorbic acid content of the fruit can limit the formation of potentially toxic digestive by-products.[9] Pineapple juice limits the mutagenic activity of carcinogens in the Ames' Salmonella/microsome assay test by approximately 50%.[10]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Repeated exposure of pineapple cutters to bromelain can result in the obliteration of fingerprints,[3] and the hooked margins of the leaves can cause painful injury. Ethyl acrylate, an aromatic component of the juice can produce dermal sensitization.

Angular stomatitis can result from eating large amounts of the fruit.[3] Large quantities of the juice have been reported to cause uterine contractions.

Bromelain ingestion has been associated with nausea, vomiting, diarrhea, skin rash and menorrhagia.[3]

SUMMARY: The pineapple is a widely cultivated fruit. It is the source of the proteolytic enzyme bromelain, which is used in commercial meat tenderizers, and which continues to be used in medical practice as a soft tissue anti-inflammatory and for topical debridement.

PATIENT INFORMATION — Pineapple

Uses: Pineapple has been used to prevent ulcers, enhance fat excretion, burn debridement, and to reduce soft tissue inflammation and irritation.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Pineapple extracts may produce dermal sensitization, uterine contractions, nausea, vomiting, diarrhea, skin rash, and menorrhagia.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
      PINEAPPLE

PLANTAIN

DATE OF ISSUE: JAN 1998

REPLACES MONOGRAPH DATED: AUG 1988

SCIENTIFIC NAME(S): *Plantago lanceolata*L., P. major L., *P. psyllium* L., *P. arenaria* Waldst. & Kit. (*P. ramosa* Asch.) (Spanish or French psyllium seed), *P. ovata* Forsk. (Blond or Indian plantago seed) Family: Plantaginaceae. (Not to be confused with *Musa paradisiacae*, or edible plantain.)

COMMON NAME(S): Plantain, Spanish psyllium, French psyllium, blond plantago, Indian plantago, psyllium seed, flea seed, black psyllium.

BOTANY: Plantain is a perennial weed with almost worldwide distribution. There are about 250 species, of which 20 have wide geographic ranges, 9 have discontinuous ranges, 200 are limited to one region, and 9 have very narrow ranges. *P. lanceolata* and *P. major* are among the widest distributed.[1] Plantain species are herbs and shrubby plants characterized by basal leaves and inconspicuous flowers in heads or spikes. They grow aggressively. Plantain is wind-pollinated, facilitating its growth where there are no bees and few other plantain plants. It is very tolerant of viral infections. *P. major* produces 13,000 to 15,000 seeds per plant, and the seeds have been reported to remain viable in soil for up to 60 years. *P. lanceolata* produces 2500 to 10,000 seeds per plant and has a somewhat shorter seed viability. Plantain seeds can survive passage through the gut of birds and other animals, facilitating their distribution further. [1] Plantain, or psyllium seeds, are small (1.5 to 3.5 mm), oval, boat-shaped, dark reddish-brown, odorless and nearly tasteless. They are coated with mucilage, which aids in their transportation by allowing adhesion to various surfaces.[1,2]

HISTORY: Plantain has long been associated with man and with agriculture. Certain species have been spread by human colonization, particularly that of Europeans. As such, North American Indians and New Zealand Maori refer to plantain as "Englishman's foot," because it spread from areas of English settlement. *P. lanceolata* and *P. major*have been used in herbal remedies and were sometimes carried to colonies intentionally for that purpose. Psyllium seed has been found in malt refuse (formerly used as fertilizer) and wool imported to England. It has been commonly used in birdseed. [1] Pulverized seeds are mixed with oil and applied topically to inflamed sites; decoctions have been mixed with honey for sore throats. The seeds and refined colloid are used commonly in commercial bulk laxative preparations.[1,3]

CHEMISTRY: Plaintain constituents include acids (eg, benzoic, caffeic, chlorogenic, cinnamic, p-coumaric, fumaric, salicylic, ursolic, vanillic, ascorbic), alkaloids (boschniakine) and amino acids (eg, alanine, asparagine, histidine, lysine). [4] An analysis of 8 of 21 Egyptian species of plantain, including *P. major*, has identified a variety of sugar and polysaccharide components of the seed mucilage. These include galactose, glucose, xylose, arabinose, and rhamnose. In addition, galacturonic acid, planteose, plantiobiose, sucrose, fructose, and an unidentified sugar (in *P. ovata*) have been identified.[5] Other plant carbohydrates such as saccharose, stachyose, sorbitol and tyrosol have also been reported. [4] The mucilage of the seed's testa epidermis constitutes 20% to 30%.[2] Seed mucilage of one species, *P. ovata* was found to have better suspending and emulsifying power compared to tragacanth and methylcellulose. [6] Leaf mucilage has been reported as well and includes such polysaccharides as rhamnose, L-arabinose, mannose, galactose and dextrose. [7] The seeds also contain fixed oil, protein, iridoids and tannins. [2,3] The gel-forming fraction of the seed was found to be effective in prolonging release rates of tetracycline in vitro. [8]

Flavonoids found in plantain include apigenin, baicalein, scutellarein and others. [4] Isolation and identification of flavonoids and saponins from related species *P. tomentosa* have been reported.[9]

Iridoids found in plantain are aucubin, plantarenaloside and aucuboside. [4] The main iridoids (eg, aucubin) and catalpol, have been isolated from *P. lanceolata*, *P. major* and *P. media* leaves using HPLC analysis.[10] Iridoid glycosides and phenolic acids have been found in leaf extracts of *P. lanceolata*and *P. media*.[11]

Other components of the plant include choline, fat, resin, steroids and vitamins. [3,4]

Reports on related species *P. asiatica*list constituents as: A "new" phenylethanoid glycoside, [12] aucubin,[13] plantaginin and plantamajoside.[14]

PHARMACOLOGY: The pharmacology of plantain involves gastrointestinal tract therapy, hyperlipidemia treatment, anticancer effects, respiratory and other actions.

GI: Psyllium seed is classified as a bulk laxative. Mixed with water, it produces a mucilaginous mass. The indigestible seeds provide bulk for treatment of chronic constipation, while the mucilage serves as a mild laxative comparable to agar or mineral oil. The usual dose is 0.5 to 2 g of husk (5 to 15 g of seeds) mixed in 8 oz of water. A study of 10 healthy volunteers examined the effects of a 3 g ispaghula mixture (dried psyllium seed husks) given three times daily. It decreased intestinal transit time.[15] Effectiveness of psyllium seed on 78 subjects with irritable bowel syndrome (IBS) has been reported. [16] *P. ovata* fiber is also effective in regulating colon motility in a similar set of patients. [17] A postcholecystectomy patient with chronic diarrhea was given a 6.5 g dose of a 50% psyllium preparation, and symptoms resolved in 2 days.[18,19] Plantago seed as a cellulose/pectin mixture was as effective as a bulk laxative in 50 adult subjects. [20] The effects of different dietary fibers on colonic function, including plantago seed have been evaluated. [21] Gastroprotective action from plantago extract (polyholozidic substances) has also been reported. [22]

In a triple-blind, crossover study of 17 female patients, *P. ovata* seed preparation was investigated on appetite variables. The preparation was deemed useful in weight control diets where a feeling of fullness was desired. Total fat intake was also decreased, again, suggesting the product to be a beneficial weight control diet supplement.[23]

A trial involving 393 patients with anal fissures found conservative treatment with psyllium effective. After 5 years of follow-up, 44% of the patients were cured without surgery within 4 to 8 weeks. There were complications (abscesses and fistulas requiring surgery) in 8% of the cases. The recurrence rate was 27%, but about one third of these were fistulas that responded to further conservative management. [24]

A double-blind study of 51 patients with symptomatic hemorrhoids showed *Vi-Siblin*, a psyllium-containing preparation, to be effective in reducing bleeding and pain during defecation: 84% of the patients receiving the preparation reported improvement or elimination of symptoms, compared to 52% taking placebo. [25]

Hyperlipidemia: Many reports on psyllium have concluded that it can be helpful in treating various hyperlipidemias. [26,27]

In animal studies, plantain lowered total plasma lipids, cholesterol and triglycerides in arteriosclerotic rabbits. [4] Other animals may be less sensitive to psyllium's hypo-cholesterolemic actions.[28]

Attention has been focused on the cholesterol-lowering effects of psyllium preparations in human trials. Psyllium hydrophilic mucilloid (*Metamucil*, Procter & Gamble) was found to lower serum cholesterol in a study of 28 patients who took 3 doses (3.4 g/dose) per day compared with placebo for 8 weeks. After 4 weeks, the psyllium-treated patients showed decreases in total serum cholesterol levels compared with the placebo group. Decreases were also seen in LDL cholesterol and the LDL/HDL ratio. At the end of 8 weeks, values for total cholesterol, LDL cholesterol and the LDL/HDL ratio were 14%, 20% and 15%, respectively below baseline (all, $p < 0.01$). This study suggested that high cholesterol levels could be managed safely and easily by including psyllium preparations in the diet. [29]

Similar results of cholesterol reduction have been reported, including: Psyllium colloid administration for 2 to 29 months, reducing cholesterol levels by 16.9% and triglycerides by 52%,[30] a trial of 75 hypercholesterolemic patients, evaluating adjunct therapy of psyllium seed to a low cholesterol diet, [31] a 16-week, double-blind trial, proving plantago seed improved in both total and LDL cholesterol in 37 patients, [32] and increased tolerance of psyllium seed in combination with colestipol

(rather than monotherapy alone) in 105 hyperlipidemic patients.[33]

Psyllium seed was found to be more effective than *P. ovata* husk in reducing serum cholesterol in normal and ileostomy patients.[34] A report on 20 hypercholesterolemic pediatric patients on low-fat diets, however, found psyllium seed to be ineffective in lowering cholesterol or LDL levels.[35]

Issues of cereal companies including plantago seed in their products and claims of "cholesterol reduction," have been addressed.[36]

A polyphenolic compound (from *P. major*leaves) was found to exhibit hypocholesterolemic activity,[37] but in addition, the mechanism by which plantago reduces cholesterol may also include enhancement of cholesterol elimination as fecal bile acids.[38]

Anticancer: The antitumor effects of plantain have been studied in animals. The isolate "plantagoside," from seeds of related species *P. asiatica*, has been found to suppress immune response in mouse tissue.[39] *P. major*has also inhibited carcinogen synthesis in induced toxic liver damage and has decreased tumor incidence in rats.[40] In mice given *P. major* subcutaneous injections, mammary cancer tumor formation frequency was 18%, as compared to 93% with placebo, suggesting prophylactic therapy for cancer of this type.[41] Immunotropic activity of *P. lanceolata* extract on murine and human lymphatic cells in vivo and in vitro has also been demonstrated.[42]

Respiratory: An aqueous extract of plantain may possess bronchodilatory activity in guinea pigs; however, it is less active and of shorter duration than salbutamol or atropine.[4] In human studies, plantain has been effective for chronic bronchitis,[4] asthma, cough and cold.[3]

Other actions: A report by a physician described the topical use of crushed plantain leaves to treat poison ivy in 10 people. Although the trial was not conducted scientifically, the treatment eliminated itching and prevented spread of the dermatitis in all cases, one to four applications being required.[43] Fresh leaves of the plant have been poulticed onto herpes, sores, ulcers, boils and infections. Plantain has been used for insect bites and gout.[3] Leaf extracts have wound healing activity in rabbits, caused by chlorogenic and neochlorogenic acid content.[4]

Plantain oils may exhibit therapeutic action on chemical burns of rabbit eyes.[44]

Aqueous extracts of plantain leaves possess antimicrobial activity caused by aglycone and aucubigenin.[2]

Aerial parts of plantago have been used as an anti-inflammatory and as a diuretic in folk medicine.[45] A report on *P. lanceolata*'s phenylethanoids, acteoside and plantamajoside has been evaluated for inhibitory effects on arachidonic acid-induced mouse ear edema.[46] Plantain extract has decreased arterial blood pressure by 20 to 40 mm Hg in normotensive dogs.[4] Reports such as these and others may help support plantain's use in folk medicine.

Psyllium administration had no effect on postprandial plasma glucose in one report.[47]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Plantain pollen has been found to contain at least 16 antigens, of which 6 are potentially allergenic. The pollen contains allergenic glycoproteins that react with concanavalin A, as well as components that bind IgE.[48] Antigenic and allergenic analysis has been performed on psyllium seed. All three fractions, husk, endosperm and embryo, contained similar antigens.[49] Formation of IgE antibodies to psyllium laxative has been demonstrated.[50] In addition, IgE-mediated sensitization to plantain pollen has been performed, contributing to seasonal allergy.[51]

There are many reported incidences of varying degrees of psyllium allergy including: Nurses experiencing symptoms such as anaphylactoid reaction, chest congestion, sneezing and watery eyes (some of these reactions taking several years to acquire);[52,53] a case report describing severe anaphylactic shock following psyllium laxative ingestion, linked occupational respiratory allergies in pharmaceutical workers exposed to the substance;[54] consumption of plantago seed in cereal, responsible for anaphylaxis in a 60-year-old female (immunoglobulin E-mediated sensitization was documented, and patient was successfully treated with oral diphenhydramine);[55] and a report on workers in a psyllium processing plant evaluated for occupational asthma and IgE sensitization to psyllium.[56]

Another unusual adverse situation involves the occurrence of a giant phytobezoar composed of psyllium seed husks. The bezoar, located in the right colon, resulted in complete blockage of gastric emptying.[57] All psyllium preparations must be taken with adequate volumes of fluid. The seeds contain a pigment that may be toxic to the kidneys,[14] but this has been removed from most commercial preparations.[58]

Drug interactions reported with psyllium involve lithium and carbamazepine. Psyllium may inhibit absorption of lithium in the GI tract, decreasing blood levels of the lithium, as seen in a 47-year-old woman with schizo-affective disorder.[59] Plantago seed also has decreased the bioavailability of carbamazepine in 4 male subjects.[60]

Economic significance: As a weed, plantain is important because of its competition with commercial crops and small fruits. The presence of plantain seeds can make adequate cleaning of crop seed difficult, especially with small-seed legumes. Plantain, because of its tolerance of viral infection, can serve as a reservoir for economically important infections of crops including beets, potatoes, tomatoes, tobacco, turnips, cucumbers and celery. Commercially, plantain is grown for use in forage mixtures and, primarily, for use in bulk laxatives.[1]

SUMMARY: Plantain is an aggressive weed found almost worldwide. It can have negative agricultural effects by competing with crops, contaminating crop seeds, and serving as a reservoir for viral plant diseases. Medicinally, the plant is used in bulk laxatives for GI tract health, hyperlipidemia treatment, anticancer effects, respiratory actions, infections and edema. There are many antigenic components in the seed and the pollen; these may affect sensitive individuals. Drug interactions of psyllium with lithium and carbamazepine have been reported.

PATIENT INFORMATION — Plantain

Uses: The psyllium in plantain has been used as GI therapy, to treat hyperlipidemia, as a topical agent to treat some skin problems, as an anti-inflammatory and diuretic, for anticancer effects, and for respiratory treatment.

Interactions: Plantain may interact with lithium and carbamazepine, decreasing their plasma concentrations.

Side Effects: Adverse events include anaphylaxis, chest congestion, sneezing and watery eyes, occupational asthma, and a situation involving the occurence of a giant phytobezoar composed of psyllium seed husks.

Dosing: Plantain leaves have been given as a tea for cold and cough at 3 to 6 g/day.[61]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PLANTAIN

PODOPHYLLUM

DATE OF ISSUE: JAN 1992

REPLACES MONOGRAPH DATED: FEB 1986

SCIENTIFIC NAME(S): *Podophyllum peltatum*L., *P. hexandrum* Royle syn *P. emodi* Wall. Family: Podophyllaceae (formerly Berberidaceae)

COMMON NAME(S): Mayapple, mandrake, American podophyllum (*P. peltatum*), Indian podophyllum *P. hexandrum*). Other common names include wild or American mandrake, devil's apple, vegetable mercuryand duck's foot. The plant should not be confused with the European mandrake (*Mandragora officinarum* L.) which contains the anticholinergics hyoscyamine, scopolamine and mandragorine.

BOTANY: A perennial plant with one or two large lobed leaves that grows in moist shaded areas throughout North America, *P. hexandrum*is found primarily in Tibet and Afghanistan.[1] A single white or cream-colored flower grows between the two leaves from May to August. It bears a fruity berry that turns yellow when ripe.

HISTORY: Podophyllum resin was used by the American Indians and colonists as a cathartic and anthelmintic, as an antidote for snake bites and as a poison. [2] Podophyllum was a common ingredient in many proprietary medicines including Carter's Little Liver Pills. [1] It has been used for almost 40 years in the treatment of topical warts, especially condylomata. The resin had long been thought to possess anticancer activity; derivatives have been used successfully in controlled clinical trials. An FDA advisory panel has established that because of its drastic effect and great potential for toxicity, podophyllum resin is not considered a safe laxative. [3]

CHEMISTRY: Podophyllum resin is obtained from the dried roots and rhizomes of the plant. The major active constituents of podophyllum are the lignan derivatives, which occur in free or glycosidic form in the resin. [1] The resin constitutes 3% to 6% of *P. peltatum* and up to 12% of *P. hexandrum*. The resin is a mixture of more than a dozen compounds, including podophyllotoxin, picropodophyllum and podophyllic acid. Alpha- and beta-peltatin are the major lignans in American podophyllum.[4] Podophyllum tincture is often combined with benzoin for topical use.

PHARMACOLOGY: Podophyllum resin is a drastic cathartic used as a veterinary and human purgative. Its effects are believed to be due to colonic irritation attributed to the peltatins.[5] The activity depends on the presence of a lactone ring in the *trans* configuration.

Podophyllum is highly lipid soluble and is readily absorbed through the gastrointestinal tract. Topical administration to large areas can also result in significant absorption. Little is known about the distribution of the active compounds. A podophyllic acid preparation was eliminated predominantly in the urine with a half-life of 30 minutes; podophyllotoxin is eliminated in the bile with a half-life of 48 hours. [6]

Podophyllin acts as a spindle poison, blocking cell division in metaphase. It has a direct effect on mitochondria, reducing the activity of cytochrome oxidase and succinoxidase. Several components of podophyllin have tumor-inhibiting properties including the peltatins, podophyllotoxin and its derivatives. Several semisynthetic analogs have been investigated clinically. [7] Teniposide and etoposide are active orally and parenterally. [8] Etoposide is available commercially (*VP-16, VePesid*/ Bristol-Myers Oncology) for the parenteral treatment of refractory testicular tumors and for the treatment of small cell cancers of the lung. [9,10] Teniposide is available under a treatment IND for use with cytarabine in the management of patients with acute lymphoblastic leukemia; it has also been used for a variety of lymphomas and other neoplastic diseases.[10]

The resin is used in the treatment of warts, especially condyloma. Alcoholic solutions (10% to 20%) of *P. peltatum* were as effective as those of *P. hexandrum* in the treatment of genital warts.[11] A topical solution of podophyllotoxin 0.5% twice daily for 3 days was more effective than repeated applications of topical podophyllin 20% ethanolic solution for the treatment of penile warts.[12] The use of these preparations should be restricted because of the potential for systemic toxicity from misapplication.[13] When used, the solutions should be washed off within 1 to 4 hours, and contact should not exceed more than 6 hours. Podophyllum ointment has been associated with severe toxicity.[13] There are several commercial preparations of podophyllum resin, generally as 25% solutions in tincture of benzoin for topical use.[10] There is also a purified topical product available for external genital warts, *Condylox* by Oclassen.[10]

A mixture of semisynthetic lignan glycosides termed CPH82 has been found to be more effective than placebo when given to patients with rheumatoid arthritis in ameliorating clinical and immunological variables. [14]

TOXICOLOGY: The ripe fruit pulp of the mayapple is edible, often being made into marmalades or jellies. [5] Podophyllin is potentially lethal when ingested. Great care must be taken in its external use. Chronic use of podophyllum resin as a cathartic has resulted in hypokalemia sometimes associated with metabolic alkalosis. [15] At least 3 deaths have been attributed to either oral ingestion or topical application. [16,17] Podophyllum toxicity is multisystemic with characteristic neurologic manifestations. Clinical signs appear within 12 hours and include altered mental states, tachypnea, peripheral neuropathy, nausea, hypotension, vomiting, and fever. Rapidly progressive neurologic deficit varying from confusion to coma is always observed. Muscle paralysis with respiratory failure, renal failure, hallucinations, and seizures have been reported. Bone marrow suppression has been noted in acute intoxication and in chronic laxative abusers.

Seven cases of podophyllin toxicity have resulted in severe peripheral neuropathies, from topical or oral administration. The onset of the neuropathies generally occurred within hours of application or ingestion and the duration ranged from months up to four years with some neurologic deficit still present. Exact doses that were used, as well as how long they were left in contact with the treated area are often not given. [18,19,20,21,22,23,24]

Emesis may be useful during the initial phases of toxicity.[25] Topically administered resin should be removed with petroleum jelly. Podophyllum is lipid soluble; hemodialysis is ineffective, while charcoal hemoperfusion has reversed acute symptoms within hours. [18]

Podophyllum is teratogenic in animals and humans. Limb deformities and septal heart defects have been associated with its ingestion by pregnant women. [26] Preauricular skin tags and a simian crease were noted in an infant born to a woman treated with topical podophyllum resin from the 23rd to 29th week of pregnancy. Total contact with the drug was 4 hours.[27] An intrauterine death has been reported in a woman treated with podophyllum for vulvar warts during week 32 of her pregnancy.[24]

SUMMARY: Podophyllum and its extracts have been used internally as drastic cathartics and externally in the treatment of venereal warts. Semisynthetic plant derivatives are used to manage a variety of neoplastic disorders. The resin is a mitotic poison, and its misuse can lead to significant toxicity. It should not be administered to children, and use in pregnant women has been associated with congenital abnormalities and fetal death.

PATIENT INFORMATION— Podophyllum

Uses: Podophyllum has been used to treat refractory testicular tumors, small cancer cells of the lung, a variety of lymphomas and other neoplastic diseases, warts, genital warts, and rheumatoid arthritis.

Side Effects: Podophyllm has resulted in hypokalemia, altered mental states, tachypnea, peripheral neuropathy, nausea, hypotension, vomiting, fever, and muscle paralysis with respiratory failure.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PODOPHYLLUM

POINSETTIA

DATE OF ISSUE: AUG 1998

REPLACES MONOGRAPH DATED: NOV 1987

SCIENTIFIC NAME(S): Varieties of *Euphorbia pulcherrima* Wild. ex Klotzsch Family: Euphorbiaceae. This plant has also been referred to as *E. poinsettia* Buist and *Poinsettia pulcherrima* Grah

COMMON NAME(S): Poinsettia, Christmas flower, Easter flower, papagallo, Mexican flame leaf, lobster flower plant

BOTANY: The Euphorbiaceae (spurge family) is a large family of more than 1000 herbs, shrubs, and trees. All members of this family are characterized by the presence of a milky latex emulsion found in lactiferous vessels. When damaged, the plants secrete this latex. The poinsettia is a perennial ornamental found throughout the warmer climates of the US, including Hawaii, and Mexico. The flowers are small and yellow; it is the showy red leaf (bract) that has resulted in the decorative popularity of this plant.

HISTORY: The plant was introduced from Mexico into the US by J. R. Poinsett in the early 1800s. Many members of the genus *Euphorbia* have been used in folk medicine. *E. pulcherrima*sap has been used as a depilatory, and extracts of the plant have been used as an antipyretic and to stimulate the flow of breast milk. The plant may have once been used as an abortifacient.[1] Folk uses include remedies for skin, warts and toothache.[3]

CHEMISTRY: The stems and leaves may contain small amounts of alkaloids; however, there is conflicting data regarding the presence of these compounds. The latex contains from 7% to 15% caoutchouc.[2] Compounds found in the leaves and stems include germanicol, beta-amyrin, pseudotaraxasterol, pulcherrol, octaeicosanol, beta-sitosterol, rubber, caffeic acid and anthocyanin. [3] Epigermanicyl acetate, germanicyl acetate, germanicol, octacosanol and beta-sitosterol from poinsettia fruits have also been isolated. [4]

PHARMACOLOGY: Because this plant has often been associated with potential toxicity, a number of investigations have tried to establish the pharmacology of its components.

In rats fed 15 g/kg bracts or 5 g/kg leaf blades for 1 week, no change in behavior, body weight or adrenal weight was found. [5]

An increase in thyroid weight was observed among rats fed 15 g/kg of leaf material. No other pharmacologic activity was observed. Extracts of the plant have no antibiotic activity.[1]

The plant's latex has been used as a depilatory. Other reported uses include pain relief, antibacterial, and emetic. The latex contains 5% to 15% caoutchouc and some resin.[3]

TOXICOLOGY: Many published reports have warned of the toxicity of this plant; however, there appears to be little factual evidence for this claim. These reports seem to stem from a single case of death in a 2-year-old Hawaiian child after the ingestion of the leaves. [6] This poorly documented case remains the only known fatality and several authors have concluded that the report was based more on hearsay than fact. [1]

The results of an acute and a 1-week feeding study in rats found no changes in most parameters evaluated. [5] No deaths were found among 160 rats fed up to 22.5 g/kg of poinsettia, suggesting that the plant lacks oral toxicity. [7] Winek et al published the results of perhaps the most comprehensive evaluation of the toxicity of poinsettia. No rats died during an attempt to establish the oral LD-50; therefore, the LD-50 was considered to be greater than 25 g/kg body weight. Assuming no interspecies variation in toxicity, a 50 lb child would have to ingest about 1.25 lbs (500 to 600 leaves) to surpass the experimental LD-50. Vomiting would most likely preclude the ingestion of this amount of plant.[1]

Oral administration of poinsettia extracts in rats did not result in local toxicity (no erythema, edema, bleeding of the oral cavity) and instillation of the latex into the rabbit eye induced no corneal, iridal or conjunctival damage. No histologic abnormalities were found in rats fed high doses of the plant for 5 days. Repeated exposure to a water suspension of the plant induced mild skin irritation in albino rabbits, but this disappeared within 36 hours. Some photosensitivity was seen in albino rabbits.[7]

In mice, the intraperitoneal injection of 3 g of leaf extract per 100 g body weight resulted in one death in six animals tested; extracts of flowers and bracts, however, caused no deaths indicating a general lack of acute systemic toxicity. No alkaloids or glycosides were found in the plant. [8]

The National Clearinghouse for Poison Control Centers reported 228 cases of human ingestion of poinsettia in 1973; of these, only 14 cases had symptoms, the most serious being nausea and vomiting. A case report describes symptoms of local mucosa irritation and GI tract distress in an 8-month-old female who had chewed a poinsettia leaf.[9]

Some reports suggest that the milky latex of the poinsettia, like that of some other members of the Euphorbiaceae family (eg, pencil plant), may result in skin irritation in susceptible individuals,[10] or eye inflammation and temporary blindness.[3,11] However, animal studies and the lack of repeated documentation of topical irritation in humans indicates that this problem may not be widespread.

Suggested treatment of ingestion includes gastric lavage or emesis followed by symptomatic treatment, [12] in addition to demulcents, intestinal astringents and gastric sedatives. Give fluids to prevent dehydration. [11]

SUMMARY: The poinsettia is a popular ornamental most frequently seen around Christmas. Despite a legacy of severe toxicity, there is little published evidence to suggest that any part of the plant poses a great toxicologic danger. As a general precaution, this plant should be kept out of the reach of children and pets. If ingestion occurs, vomiting can be induced and the patient should be monitored. It is unlikely that a lethal or even pharmacologic dose could be ingested by a human. Topical irritation may occur in sensitive individuals, although the likelihood of this appears to be small.

PATIENT INFORMATION — Poinsettia

Uses: Poinsettias are used as Christmas ornamentation; their latex for a dipilatory; and for other uses such as pain relief, antibacterial and emetic. Folk uses include remedies for skin, warts, and toothache.

Side Effects: There is little published evidence to suggest that the plant poses a great toxicologic danger; however, the following side effects have occurred: Nausea, vomiting, local mucosa irritation, GI tract distress, skin irritation, eye inflammation, and temporary blindness.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POINSETTIA

POISON IVY

DATE OF ISSUE: MAR 1997

REPLACES MONOGRAPH DATED: SEP 1988

SCIENTIFIC NAME(S): *Tocicodendron diversilobum*(T & G); *T. quercifolium* (Michx.); *T. radicans* (L.) Kuntze; *T. vernix* (L.). Family: Anacardiaceae

COMMON NAME(S): Poison ivy; poison oak; poison sumac; markweed; poison elder; poison dogwood.

BOTANY: The contact sensitivities induced by poison ivy and several closely related species present a persistent public health problem. These dermatites affect from 50% to 70% of the general population.[1]

Poison ivy is a member of the sumac family (Anacardiaceae). Although originally classified as a member of the genus *Rhus*, it is now included in the genus *Toxicodendron*. Four related species are responsible for the majority of plant dermatites. These perennials are identified as:

T. diversilobum (T & G) Greene - Western poison oak

T. quercifolium (Michx.) Greene - Eastern poison oak

T. radicans (L.) Kuntze - Poison ivy, markweed, three-leaved ivy

T. vernix (L.) Kuntze - poison sumac, poison elder, poison dogwood

The nonpoisonous shrubby sumacs (*Rhus*spp.) also have long, pinnately divided leaves, but the flowers and fruits are in dense, terminal and erect clusters. [2]

T. diversilobum - The western poison oak is found along the Pacific coast from British Columbia to Mexico. It thrives in low places, thickets, and wooded slopes, usually below 5000 feet elevation. The 3-leaflet clusters are irregularly lobed and resemble oak leaves.

T. quercifolium - Eastern poison oak grows in the eastern and southern states from New Jersey to Missouri and North Florida. This erect, low, woody shrub is most frequently restricted to sandy soil, dry barrens and pine woods.

T. radicans - Poison ivy grows throughout the United States and Canada, with the exception of parts of the West Coast. The habit of this weed is extremely variable; it may grow as a nonclimbing woody shrub or as a vine along the ground, on low plants, or on high trees or poles. Only the presence of a cluster of 3 leaflets is a constant characteristic. The adage of "leaflets three, let it be; berries white, poison sight" remains a good rule of thumb. The plant is odorless but has an acrid, slightly astringent taste.[3] The leaflets vary in color from green in spring to yellow and red in autumn. The waxy white to yellowish fruits may remain on the plant throughout the winter.

T. vernix - Poison sumac is native to bogs of the north (as a shrub) and to swamps and river bottoms of the south (as a small tree). Its distribution is widespread but is predominantly east of the Mississippi river. The 7- to 13-leaflet clusters are arranged in alternate pairs, with a single leaflet at the end of the midrib.

A major factor in poison plant dermatitis is the failure to recognize the plant. In general, all of the plants discussed here have 3-leaflet clusters (with the exception of poison sumac). They also have U- or V-shaped leaf scars (the scar remaining at the point that the leaf breaks from the stem), and flowers and fruits arising in the axillary position (in the angle between the leaf and the branch). Another helpful finding is a black deposit often present when *Toxicodendron* has been injured. Following trauma, the oleoresin exudes, darkens on exposure to air, and hardens. One source suggests crushing a few leaves of a suspected plant on a piece of white paper, releasing the sap from the petioles; the resulting stain will darken markedly within 10 minutes if it is from *Toxicodendron*. Although the test is not conclusive, it provides supportive evidence in making a positive identification. [4]

Other members of the family anacardiaceae include the tropical cashew nut tree (*Anacardium occidentale*), the tropical mango tree (*Mangifera indica*), the Indian marking nut tree (*Semecarpus anacardium*) and Japanese lacquer tree (*Rhus vernicifera*). Because of their chemically similar allergens, these also may cause allergic contact dermatitis in sensitive individuals.[5] For example, cashew ingestion has been associated with mouth blistering and perianal itching, if the antigens (cardol and anacardic acid) have not been properly removed.[6] Contact dermatitis can also result from mango ingestion without first removing the fruit skin, or from lacquer tree sap (from *Rhus* spp.) in furniture.[5]

CHEMISTRY: An oily phenolic resin called toxicodendrol (lobinol) is present in all poisonous *Toxicodendron* species and contains a complex active principle known as urushiol. The name "urushiol" is derived from the Japanese term "sap."[5] It is a mixture of antigenic catechols.[7] These antigens are closely related to 3-n-pentadecylcatechol (3- PDC, hydrourushiol) but differ in the degree of unsaturation at the 3n-alkyl side chains, [3,8] and in their side chain lengths sumac has 13 carbons, poison ivy 15 carbons and oak 17 carbons.[5] In general, the more unsaturated or longer the side chain is, the more antigenically reactive the catechol. [9] Urushiol is carried by resin canals found in the bark, stem, leaflets, and certain flower parts. The relative percentages of 3-PDC and related catechols varies among the species and may also be related to environmental conditions. The danger of toxicity is greatest in spring and summer, when the sap is abundant, the urushiol content is high, and the plant is bruised easily.

Chromatographic procedures have been developed for use in separation and characterization of urushiol in poison ivy and poison oak. [10,11]

PHARMACOLOGY: Extracts of poison oak have been used in homeopathic medicine to treat conditions such as osteoarthritis. Controlled studies have failed to substantiate the efficacy of such treatments,[12] but the methodology of these studies has been questioned.[13,14]

Urushiols are haptens that must bind with skin proteins to form complete antigens. This is thought to occur on the surface of Langerhans cells, where the urushiols are irreversibly bound.[3,5] Sensitization appears to require bonding of quinones derived from urushiol components with nucleophilic groups on the proteins. [15] A later report suggests free radicals, and not quinones, to be the haptenic species derived from urushiol. [16] Blocking the C5-position on the catechol ring seems to suppress sensitivity.[15] Mouse data suggest that contact sensitivity to urushiol is mediated by serum factors. [17] In vitro studies with human lymphocytes, however, indicate that urushiol reacts initially with T cells. Interaction with a non-T accessory lymphocyte is necessary for reactivity. [18] A recent report describes processing or urushiol hapten by both endogenous and exogenous pathways for presentation to T-cells. [19] After the previously sensitized T-lymphocytes have been activated, the allergy cascade is locally initiated.[5]

Many more recent immunological studies continue, including: Isolation of urushiol triggered T-cells; [20] T-cell clone generation from blood;[20,21,22] enrichment and function of urushiol-specific T-lymphocytes;[23] role of keratinocytes in allergic contact dermatitis; [24,25] increased levels of telomerase activity in poison ivy dermatitis; [26] UL-8 enhanced expression;[27] and modulation;[28] and poison ivy analog sensitization. [29,30,31,32]

TOXICOLOGY: Toxicodendrol does not enter the blood. Minute quantities (0.001 mg) applied to the skin can cause dermatitis. The sensitivity may persist for years. Infants are not as readily sensitized as adults, and with intermittent exposure, the sensitivity decreases with age. After contact, the first symptoms of itching, burning and redness may appear in a few hours or may take up to 5 days, depending on the sensitivity of the individual. The rash is characterized by linear streaks of erythematous lesions where the plant has "brushed" the skin.[5] Urticarial plaques and bullae may develop, filled with fluid. Contrary to popular belief, this blister fluid does not contain urushiol, and therefore, cannot spread infection by fluid contact. Continued spreading of infection actually results from variation in time of onset of

clinical reaction ("delayed reaction"), antigen load and individual senstivity. [1] Secondary changes include the blisters oozing until a crust is formed. Intense itching may last for up to 7 days. Rare complications include hematologic changes, renal damage and psychological reactions. Barring complications, the dermatitis is self-limiting, lasting from 1 to 3 weeks. The skin usually recovers unblemished, because only the epidermal layer is involved; however, excessive scratching and infection may result in permanent scarring.[3]

Other means of exposure from the plant include inhaling resin droplets carried in smoke from burning poison ivy, which can cause fever, major lung infection and even death from the throat swelling shut.[32] Exposure to urushiol can also come about by contact through animal fur, contaminated clothing, garden tools and sports equipment. Urushiol is so long-lasting, (if not properly washed away), that dermatitis can occur years later if these still contaminated items are touched again. [3,32] Soaking contaminated clothing in a 1% solution of hypochlorite for 15 minutes, followed by laundering, should remove the resin (caution: may discolor clothing). Avoidance, however, remains the best approach to preventing *Toxicodendron* dermatitis.

If ingested, poison ivy can produce severe gastrointestinal effects. [3] Some individuals, however, can consume poison ivy without effect, apparently because of a lack of reactivity in the digestive mucosa.[33]

The choice of an appropriate treatment is dependent upon the severity of the episode. Treatment objectives include protecting the damaged skin until the acute reaction has subsided, preventing accumulation of epidermal debris, relieving the intense itching, and avoiding excoriation. Affected areas should be cleaned immediately with soapy water, however, oils from certain soaps may spread the sap. According to the American Academy of Dermatology in a recent report, water alone is best to use when contact with the plant is known. Urushiol is neutralized by water, and if the exposed area is washed with water within 5 to 10 minutes after contact, the reaction may be avoided.[34] Swabbing with alcohol may not halt the allergic reaction but may limit its spread. Wet compresses (Burow's solution, normal saline, potassium permanganate, 10% tannic solution), cornstarch, or oatmeal baths may provide symptomatic relief. Astringent soaks should not be used on the skin of the face or genitals. Other over-the-counter therapies include local anesthetics, antipruritics, antiseptics and counterirritants (eg, menthol). [5,35,36,37,38,39,40]

Calamine lotion has long been the drug of choice in poison ivy dermatitis. Its astringent action may also provide relief of itching, pain and discomfort of poison ivy.[41,42] Oral antihistamines can provide transient symptomatic improvement of pruritis (eg, hydroxyzine 10-25 mg 4 times/day as needed). [1,5] Topical antihistamines should be discouraged, because their use has been associated with skin sensitization; further, their use here is irrational, because these dermatites are not dependent on the release of histamine.[43] Two to three times per day application of topical corticosteroids such as betamethasone valerate 0.1% (*Valisone*), betamethasone dipropionate 0.05% (*Diprolene*), flucinolone acetonide 0.01%-0.25% (*Synelar*) and triamcinolone acetonide 0.1% (*Aristocort*, *Kenalog*) are all frequently prescribed and may slightly reduce erythema and pruritis, but they hardly alter the natural overall course of the lesions, unless applied early in the course.[1,44] Some systemic absorption may occur so application to the sensitive areas (eg, face), pregnant/nursing mothers, diabetics, etc, should be avoided. Occlusive dressings should not be placed over these creams because increased absorption will occur as well. [38] Low-dose otc topical steroids haven't been proven effective, except in the most mild cases.[1] In cases of extensive dermatitis, systemic steroids (for adult patients) are indicated. Oral prednisone 1 mg/kg/day tapered over 14 to 21 days is standard, and can dramatically improve the condition. [1] A common mistake is to taper the steroid dosages too quickly, resulting in rebound flares. Complications can result from prepackaged "dosepaks," because initial dosage here is approximately $^1/_2$ the recommended dosage. Other problems with this treatment include rapid tapering and too short a course of therapy. The manufacturer of this methylprednisolone dosepak does, however, include such a warning on its product.[1] A case report describes an example of this type of treatment failure and how it was resolved.[45]

Other treatment options include use of poultices prepared from narrow and broad leaf plantain to control the itching [46] and acupuncture, both with clinically unsubstantiated but variable results. A report of four cases has noted success with acupuncture in relieving the itching of the dermatites within a few hours to 2 days and promoting healing of skin lesions within 2 to 4 days.[47]

Desensitization by the administration of plant extracts is not regularly attained. In general, hyposensitization procedures require large doses and months of treatment, and the sensitivity is regained rapidly upon cessation of therapy. [48] Oral ingestion of antigens (bypassing Langerhans cells) may allow suppressor T-cell populations to develop, that can inhibit the response to skin contacting the plant. [1] Oral administration in inducing tolerance and desensitization to poison ivy dermatitis in Guinea pigs has been reported.[1,49] The three most widely used agents for hyposensitization are crude plant extract, alum-precipitated pyridine extracts, and synthetic 3-PDC. Commercial products vary in antigen content. The preparations are taken in gradually increasing daily doses for at least 4 weeks with maintenance doses several times a week during the growing season. Intramuscular preparations are usually given at weekly or biweekly intervals. [50] No well-controlled studies have established the efficacy of these preparations, although studies with a purified urushiol extract have demonstrated good hyposensitization compared with placebo. [51] A double-blind, placebo-controlled study of a 1:1 oral mixture of 3-PDC and heptadecylcatechol failed to demonstrate any decrease in sensitivity to poison ivy or poison oak in 44 subjects.[52] Animal studies, however, suggest that topical application of 5-methyl-3-n-pentadecylcathechol or a related compound could be effective in inducing tolerance to 3-PDC.[53] At best, hyposensitization reduces the duration and severity of the dermatitis, while inducing numerous side effects, including gastrointestinal disturbances, itching, and inflammation. There still remains no US Food and Drug Administration (FDA)-approved or reliable oral regimen for desensitization.[1]

Topical application may provide an alternative to systemic administration of agents to protect against poison-plant dermatitis. Clinical patch tests have identified several polyamide salts of a linoleic acid dimer that prevented dermatitis in 70% of subjects tested. The salts were particularly effective when both the preparation and the plant antigen were washed off the skin within 8 to 12 hours of antigen exposure. [54] The effectiveness of this, and other barrier preparations to prevent dermatitis has been evaluated in another report. The percent reductions in dermatitis severity per day in order of effectiveness were: *Stokogard* (Stockhausen, Greensboro, NC) which contains PPG-3 diamine dilinoleate; *Hollister Moisture Barrier* (Hollister, Inc., Libertyville, IL) containing a propylparaben, BHA mixture; *Hydropel* (C & M Pharmacal, Inc., Hazel Park, MI) with 30% silicone; *Ivy Shield* (Interpro, Inc., Haverhill, MA) a tea stearate mixture; *Shield Skin* (Mentor Corp., Minneapolis, MN) with plasticized ethyl cellulose; *Dermofilm* (Innovetec, Brussels, Belgium); and *Uniderm*(Smith & Nephew, Inc., Largo, FL) with lanolin, benzethonium chloride, quaternium-15 and others.[55]

Organoclay, an ingredient of antiperspirants, is the most recent, effective barrier cream studied thus far. This agent has reduced or totally prevented experimental dermatitis.[56] The oranoclay, quaternium-18 bentonite, has the ability to "bind" with urushiol. This product, recently approved by the FDA, contains 5% quaternium-18 bentonite in the form of a lotion, called *Ivyblock* (Enviroderm Pharmaceuticals, Inc.). When applied, the product lays down an active barrier on skin, blocking potential contact with the allergan, thus, offering protection from poison ivy, poison oak and poison sumac rash. [57] *Ivyblock* should be be available as of late 1996, and should be of great help in "high risk" individuals, including firefighters, utility and lumber workers, armed forces and certain medical professionals.

SUMMARY: The dermatites induced by poison ivy and closely related plant species remain a persistent problem for more than half of the US population. The oily resin, urushiol, causes the contact dermatitis. This binds with skin proteins, causing an allergic reaction. The rash is characterized by linear streaks of erythematous and pustular lesions, which may last several weeks. Treatment depends on the severity of the episodes, but systemic steroids have the most dramatic therapeutic effects. Desensitization by plant extracts is not reliable. New barrier creams are effective in preventing the dermatitis if applied before contact, especially products like *Ivyblock*. Avoidance remains the best approach to reducing the incidence of dermatitis.

PATIENT INFORMATION— Poison Ivy

Uses: There are **unsubstantiated** claims of usefulness in the treatment of conditions such as osteoarthritis.

Side Effects: Dermatitis in severity ranging from mild to fatal, depending upon point of contact and individual resistance.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POISON IVY

POKEWEED

DATE OF ISSUE: APR 1991

REPLACES MONOGRAPH DATED: SEP 1986

SCIENTIFIC NAME(S): Several species of *Phytolacca* are common throughout the United States, with the most common being *P. americana* L., *P. decandra* L. and *P. rigida*. Family: Phytolaccaceae

COMMON NAME(S): The plant goes by a long list of synonyms, some of which are American nightshade, cancer jalap, cancerroot, chongras, coakum, pokeberry, crowberry, garget, inkberry, pigeonberry, poke, red ink plant and scoke.

BOTANY: Pokeweed is an ubiquitous plant found in fields, along fences, in damp woods and in other undisturbed areas. Pokeweed is indigenous to eastern North America, California and Hawaii. This vigorous shrub-like perennial can grow to 12 feet. The reddish stem has large pointed leaves which taper at both ends. [1] The flowers are numerous, small and greenish-white which develop into juicy purple berries that mature from July to September.

HISTORY: The folk uses of pokeweed leaves have included the treatment of chronic rheumatisms and arthritis, and as an emetic and purgative. [2] The plant has also been used to treat edema,[3] skin cancers, rheumatism, catarrh, dysmenorrhea, mumps, ringworm, scabies, tonsillitis and syphilis. Poke greens, the young immature leaves, are commercially canned and sold under the name "poke salet." The juice of the berries has been employed as an ink, dye and coloring agent in wine. [4]

CHEMISTRY: The toxic components of the plant are triterpene saponins which include phytolaccigenin, jaligonic acid and phytolaccagenic acid (also called phytolaccinic acid),[5] esculenic acid and the minor component pokeberrygenin.[3] A tannin and resin are present in all portions of the plant. In addition, a toxic protein called pokeweed mitogen (PWM) has also been isolated. This mitogen has been shown to induce blood cell abnormalities. For this reason, protective gloves should be worn when handling the plant.[4]

PHARMACOLOGY: The pharmacologic activity of the plant has not been well defined. Small doses of all parts of the plant can cause adverse reactions (see Toxicology), but the mechanisms of these actions are generally unknown. Extracts of the plant that contain PWM can cause "transformation" of T and B lymphocytes, most likely through an immune-mediated mechanism.[6] PWM is used as a "cellular probe" in pharmacologic experiments. Several anti-inflammatory saponins have been isolated from the root;[7] the root, however, has no known medicinal value.

TOXICOLOGY: Pokeweed poisonings were common in eastern North America during the 19th century, especially from the use of tinctures as antirheumatic preparations, and from eating berries and roots collected in error for parsnip, Jerusalem artichoke or horseradish. [8]

All parts of pokeweed are toxic except the above-ground leaves that grow in the early spring. The poisonous principles are in highest concentration in the rootstock, less in the mature leaves and stems and least in the fruits. Young leaves collected before acquiring a red color are edible if boiled for 5 minutes, rinsed and reboiled. Berries are toxic when raw but are edible when cooked.

Ingestion of poisonous parts of the plant causes severe stomach cramping, nausea with persistent diarrhea and vomiting, slow and difficult breathing, weakness, spasms, hypotension, severe convulsions and death.[9] Less than 10 uncooked berries are generally harmless to adults. Several investigators have reported deaths in children following the ingestion of uncooked berries or pokeberry juice. [9,10]

Severe poisonings have been reported in adults who ingested mature pokeweed leaves [11] and following the ingestion of a cup of tea brewed from one-half teaspoonful of powdered pokeroot.[8]

In addition, a case of toxicity in campers who ingested properly cooked young shoots has been reported by the CDC. Sixteen of the 51 cases exhibited case-definitive symptoms (vomiting followed by any three of the following: Nausea, diarrhea, stomach cramps, dizziness, headache). These symptoms persisted for up to 48 hours (mean, 24 hr).[12]

Poisoning may also occur when the toxic components enter the circulatory system through cuts and abrasions in the skin.

Symptoms of mild poisoning generally last 24 hours. In severe cases, gastric lavage, emesis and symptomatic and supportive treatment have been suggested. [9]

In an attempt to curb potential poisonings from the use of this commercially available plant, the Herb Trade Association (HTA) formulated a policy stressing that the poke root is toxic and "should not be sold as an herbal beverage or food, or in any other form which could threaten the health of the uninformed consumer." Further, the HTA recommended that products containing pokeroot should be labeled clearly as to their toxicity. [13]

The FDA classifies pokeweed as an herb of undefined safety which has demonstrated narcotic effects.

SUMMARY: Pokeweed is a common plant found throughout parts of the United States. The young leaves may be eaten and the berries used for food, both only after being cooked properly. Mature leaves and all other parts of the plant are toxic (primarily gastrointestinal and central) if ingested.

PATIENT INFORMATION — Pokeweed

Uses: The young pokeweed leaves may be eaten and the berries used for food, both only after being cooked properly.

Side Effects: Ingestion of poisonous parts of the plant causes severe stomach cramping, nausea with persistent diarrhea and vomiting, slow and difficult breathing, weakness, spasms, hypotension, severe convulsions, and death.

Dosing: At doses of 1 g, dried pokeweed root is emetic and purgative. At lower doses of 60 to 100 mg/day, the root and berries have been used for rheumatism and for immune stimulation; however, there are no clinical trials that support these uses or doses. [8,14,15]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POKEWEED

POLICOSANOL

DATE OF ISSUE: SEP 2002

REPLACES MONOGRAPH DATED: N/A

COMMON NAME(S): Policosanol, polycosanol

SOURCE: Policosanol is a mixture of high molecular weight, primary aliphatic alcohols (waxy substances), of which octacosanol (1-octacosanol) is the main component (approximately 60%). This monograph reviews policosanol as the mixture. For information regarding the octacosanol component, refer to the individual monograph. Policosanol is isolated from sugar cane wax or beeswax. Beeswax may have different proportions of policosanol mixture than sugar cane wax. Octacosanol and related substances also are found in wheat germ oil, vegetable oils, alfalfa, and animal products. [1,2,3]

HISTORY: Policosanol and octacosanol are marketed as performance-enhancing dietary supplements. Products such as *Blackmores* (from the waxy coating of sugar cane)[4] and *Cholestin* (new formulation from honey bee wax as opposed to the old formulation of rice fermented in red yeast that was found to contain the prescription drug lovastatin)[5] are sold in the United States as agents to decrease cholesterol on various Web sites.

CHEMISTRY: Reports to determine constituents in policosanol from raw materials have been published. Eight aliphatic fatty alcohols in 1 study include 1-tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol, 1-nonacosanol, 1-triacontanol, 1-dotriacontanol, and 1-tetratriacontanol. [6,7] Three compounds isolated from Chinese beeswax were identified as dotriacontanol, triacontanol, and octacosanol in another report. [2]

PHARMACOLOGY: Numerous reports conclude that policosanol has beneficial effects in reducing cholesterol. A mechanism has been proposed as to how it modulates HMG-CoA reductase activity.[8] Studies in rabbits have shown the protective effects of policosanol against carotid artery thickening. [9] In rabbits and rats, policosanol demonstrated protective effects against atherosclerotic lesions. [10,11] A 54-week study in monkeys also confirmed reduction of spontaneous atherosclerotic lesions and long-term, persistent reduction in blood cholesterol levels. [12]

Human studies performed with policosanol confirm its positive effects. Several reports describe policosanol's effectiveness and tolerability. Numerous patient populations have been studied, all demonstrating the beneficial actions policosanol offers to improve lipid profiles. Some of these groups researched include patients with abnormal hepatic function,[13] the elderly,[14,15,16,17,18] postmenopausal women,[19,20] middle-aged patients,[21] hypertensive patients,[22] diabetics,[23,24] and patients with coronary risk factors.[25,26,27] One study performed in these high-risk patients found policosanol to lower total cholesterol, LDL cholesterol, and atherogenic indices and to raise HDL cholesterol.[28]

Policosanol also has been compared with HMG-CoA inhibitors and other lipid-lowering drugs. According to various reports, policosanol appears to have comparable efficacy and is better tolerated than some HMG-CoA inhibitors. Policosanol 10 mg/day had modest advantages compared with pravastatin 10 mg/day, with fewer adverse events reported.[29] Another report concluded that policosanol 10 mg/day has more favorable effects on lipid profile and platelet aggregation and fewer adverse reactions (eg, MI, jaundice) than pravastatin. [15] Policosanol improved HDL cholesterol and had a better safety profile than lovastatin [24] in 1 study, but showed similar effectiveness to lovastatin in another report. [30] Cholesterol-lowering effects of policosanol 10 mg/day administration for 8 weeks were slightly better than fluvastatin 20 mg/day.[17] A 24% LDL cholesterol reduction was achieved with policosanol vs a 22% decrease with lovastatin and a 15% decrease with simvastatin in a 6-week comparative study. Policosanol was the only drug to increase HDL cholesterol levels. [31] Policosanol was more effective and better tolerated than acipimox (Mexico).[32] Coadministration of policosanol and benzafibrate (Argentina) provided additional benefit on lipid profiles. [33] Another report comparing besafibrate (Russia) with policosanol concludes that policosanol 10 mg had superior hypolipidemic effects. [34]

Policosanol 10 mg vs 20 mg is similar in effectiveness.[35] Policosanol at a dose of 40 mg/day offers no significant additional cholesterol-lowering efficacy over a 20 mg/day dose.[36]

Long-term evaluations of policosanol also have proven benefits. Both a 12- and a 14-month study showed the effectiveness of policosanol in lowering total cholesterol and LDL levels, as well as improvement in coronary heart disease (CHD). [18,21] Policosanol lowered cholesterol 20% in patients taking it for 5 years and 17% in those receiving it for 3 years.[37]

In human studies, policosanol as a hypolipidemic antioxidant has been reported and found to be beneficial. [38,39]

Policosanol also has been studied for its effects on platelet aggregation. A 20 mg/day dose was found to be as effective as aspirin 100 mg/day. [40] Other reports demonstrate that policosanol inhibits platelet aggregation as well. [41,42,43] However, low-dose policosanol (5 mg/day) was ineffective.[44]

Policosanol may be beneficial to patients with intermittent claudication, as determined by a reduction in lower limb symptoms and an improvement in walking distance.[45,46]

Other areas of study involving policosanol include brain activity, [47] and aerobic functional capacity improvement in CHD patients.[48]

INTERACTIONS: Policosanol may increase the hypotensive effects of beta-blockers (as seen in rats). [49] Policosanol markedly increased nitroprusside-induced hypotensive effects in rats as well.[50]

TOXICOLOGY: Most of the animal studies performed demonstrate the safety of policosanol. Administration of the drug in rats proved to be safe with regards to reproductive performance and fetal development.[51] It also was found to be nonteratogenic in rats and rabbits.[52] No evidence of carcinogenicity was observed in mice[53] or rats.[54]

Numerous studies regarding human toxicity from policosanol are available, which find little or no adverse events from the drug. Results of postmarketing surveillance in 27,879 patients found only mild adverse reactions in 0.31% of patients, primarily including weight loss, excess urination, and insomnia. [55] A pharmacoepidemiological study including 6611 patients confirmed tolerability to policosanol in routine clinical use. [56] Almost all of the single studies researched found policosanol to be safe, effective, and well-tolerated, with no (or very mild) adverse events. [13,14,15,16,17,19,20,22,23,24,25,26,27,28,29,30,32,33,35,39,42,44,45,46] Policosanol had fewer serious vascular events and fewer hospitalizations vs placebo in another study. [18] In addition, no drug-related adverse events were observed in a 3-year follow-up study.[39]

SUMMARY: Policosanol is a waxy mixture obtained primarily from sugar cane wax. Numerous reports conclude that it has beneficial effects in reducing cholesterol. According to various reports, policosanol has comparable efficacy and is better tolerated than some statins. Research also has demonstrated its positive benefits in platelet aggregation and intermittent claudication. Toxicology research in animals and humans finds few or no adverse events from policosanol.

PATIENT INFORMATION — Policosanol

Uses: Policosanol has cholesterol-lowering effects and is beneficial in platelet aggregation and intermittent claudication. BR>

Interactions: In rats, policosanol markedly increased nitroprusside-induced hypotensive effects and also may increase the hypotensive effects of beta-blockers.

Side Effects: Animal and human studies have demonstrated few or no adverse events from policosanol. Postmarketing surveillance found only mild adverse reactions in 0.31% of patients, including weight loss, excess urination, and insomnia.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POLICOSANOL

POPPY

DATE OF ISSUE: JUN 2003

REPLACES MONOGRAPH DATED: DEC 1990

SCIENTIFIC NAME(S): *P. somniferum* L. and *P. bracteatum* Lindl. are important commercially and medicinally.[1] Family: Papaveraceae

COMMON NAME(S): *P. somniferum*: Opium poppy, poppyseed poppy. *P. bracteatum*: Thebaine poppy, great scarlet poppy.

BOTANY: The opium poppy is a small annual. The bright showy flowers of the genus *Papaver* range in color from white to deep reds and purples. The seeds of the plants vary in color from light cream to blue-black.

HISTORY: The earliest accounts of the use of poppy derivatives date to the Sumerians in Mesopotamia, where the plant was used medicinally and was known as *hul gil* (the plant of joy).[2] The medicinal uses of poppy were described by the ancient Greeks, and opium, as an addictive agent, was described by the Arabs more than 900 years ago. Because of the wide distribution of the opium poppy, its use has been recognized by most major cultures. Opium was used in the US during the Civil War. Morphine was isolated from crude opium in 1803, and in 1874, morphine was reacted with acetic anhydride to yield diacetylmorphine (heroin). This compound was developed by Bayer and Company for cough, chest pain, and pneumonia. It was later recognized as having a high addiction potential. Derivatives of opium continue to play a major role as antitussives, antidiarrheals, and analgesics. Their abuse potential remains high and efforts to curtail the illicit cultivation of the opium poppy have met with only limited success. Poppy seeds are used in the preparation of confections and breads.

CHEMISTRY: The chemistry of *Papaver* is well known. Upon scoring the unripened seed capsule, a milky latex exudes.[3] The dried latex is known as opium, which contains more than 30 alkaloids. Purification of opium results in the isolation of more than 30 alkaloids. [4] The most important of these alkaloids are morphine (20%), codeine (2%), papaverine (2%), noscapine (5%, once called narcotine), and thebaine (1%). Codeine is the most widely used opium alkaloid and is obtained from natural sources or through the methylation of morphine or modification of thebaine. About 90% of morphine isolated from opium is converted synthetically to codeine.

Because of the medicinal importance of morphine derivatives, efforts have been made to identify a species of *Papaver* that contains high levels of a suitable starting compound for the commercial synthesis of codeine, yet which contains low levels of abusable morphine (which can be readily converted illicitly to heroin). In some varieties of *P. bracteatum*, thebaine constitutes 98% of the total alkaloid content. [5] Commercially, thebaine may be readily converted to codeine, oxycodone, hydrocodone, or dihydrocodeine. Its conversion to morphine, and subsequently to heroin, requires advanced chemical skills and equipment, which makes such procedures less likely to be performed illicitly. [6] Consequently, *P. bracteatum* may become the species of choice as a legal source of alkaloid precursors.

PHARMACOLOGY: The pharmacologic effects of the morphine alkaloids differ widely. Codeine and morphine are sedative analgesics and can relax smooth muscle tone, making them useful in the treatment of diarrhea and abdominal cramping. Codeine and its derivatives are antitussives. Papaverine relaxes involuntary smooth muscle and increases cerebral blood flow. These drugs exert their pharmacological action preferentially through the activation of the u-opioid receptor. Chemical modifications of the morphinan derivatives allow the biological activity to be shifted from the activation of the u to that of the d-opioid receptor. [7]

Although large doses of thebaine can induce convulsions, no case of human thebaine abuse has been reported. [6] The addictive characteristics of the opium alkaloids have been recognized for millenia.

The oral intake of poppy seed is a simple and readily available method for diagnosing vesico-enteris fistula. The diagnosis is usually based on radiography. However, in up to 50% of patients this method is not accurate. In a study of 26 patients, 17 were given 250 g of poppy seeds orally, with 11 excreting poppy seeds in the urine. The diagnosis was confirmed by conventional radiography. However in 2 patients the poppy seed test was the only preoperative diagnostic procedure that proved the existence of the fistula.[8]

TOXICOLOGY: The abuse potential of opium has had an enormous impact on many societies. Deaths caused by respiratory depression have been described and heroin-induced deaths are reported commonly. As little as 300 mg of opium can be fatal to humans, although addicts may tolerate doses as high as 2000 mg over 4 hours. Death from circulatory and respiratory collapse is accompanied by cold, clammy skin, pulmonary edema, cyanosis, and pupillary constriction. Thebaine has an LD50 of 20 mg/kg in mice.[4]

Careful attention has been focused on the fact that morphine and codeine can be detected in significant amounts in urine following the ingestion of foods prepared with poppy seeds. After the ingestion of 3 poppyseed bagels, urinary codeine and morphine levels were 214 ng/mL and 2797 ng/mL, respectively, after 3 hours. Analysis of poppy seeds indicated that an individual consuming a single poppyseed bagel could ingest up to 1.5 mg of morphine and 0.1 mg of codeine. [9] Opiates have been detected in urine more than 48 hours after the ingestion of culinary poppy seeds. [10] Morphine is also excreted in the urine when morphine, codeine, or heroin is used. These results confirm that a positive finding of morphine or codeine in urine may not always be caused by the ingestion of drugs of abuse. [11] However, the detection of urinary narcotine, papverine, or thebaine may be utilized to differentiate poppy seed consumption from illicit codeine, morphine, or heroin use. [12,13]

Furthermore, case reports have noted dependence on poppy seeds. Cases of excessive poppy seed consumption associated with feelings of elation are becoming more prevalent, especially in Eastern Europe.[14]

As well as dependence, poppy seeds in food can induce immediate-type allergic reactions ranging from mild local symptoms to severe anaphylactic reactions. They are known to cross-react with other plant-derived allergens, such as nuts, cereals, and sesame. In a small study of patients with GI complaints or systemic reactions caused by poppy seed ingestion, an association with sensitization to pollen was shown. It was proposed that pollen and poppy seeds must exert effects by a similar mechanism of action.[15]

The Mexican poppy (*Argemone mexicana* L.) has been associated with poisoning, resulting in symptoms of sedation, sluggishness, and abdominal contractions in rats fed its seeds.[16]

Icelandic poppies (*Papaver nudicaule*) have been associated with allergic contact dermatitis. In a case report, an elderly woman developed acute eczema of her palms and perioral skin after gardening. It appears that a small number of plant families cause 95% of all reported cases of plant dermatitis confirmed by patch testing. There have also been reports of contact dermatitis from opium and morphine.[17] A 20-year-old atopic man presented with contact urticaria and facial edema after contact with poppy flowers.[18] Poppyseed allergy has been demonstrated after ingestion of poppy cake, causing epigastric pain, angioedema, and respiratory distress. Reports of reactions to poppy seed are rare, affecting mainly atopic patients. [19] A single case report exists of anaphylaxis. [20]

SUMMARY: The opium poppy continues to represent one of the most commercially important plants worldwide. Its use in medicine dates to antiquity as do its addictive effects. Although an important commercial source of morphine, *P. somniferum* may be supplanted by *P. bracteatum*, a related plant high in thebaine, a compound which can be readily converted commercially to codeine, but only with extreme difficulty to morphine and heroin.

PATIENT INFORMATION — Poppy

Uses: Poppy has been used to relax smooth muscle tone, making it useful in the treatment of diarrhea and abdominal cramping, and used as a sedative analgesic and antitussive.

Side Effects: Poppy is known for its highly addictive qualities and has been associated with poisoning and symptoms of sedation and sluggishness, and abdominal contractions.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POPPY

PORIA

DATE OF ISSUE: SEP 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Poria cocos* (schw.) wolf (*P. cocos* was formerly known as *Sclerotium cocus*) Family: Polyporaceae

COMMON NAME(S): Poria, fu-ling(Mandarin/Chinese), tuckahoe, Indian bread, hoelen

BOTANY: Poria is a large potato-shaped formation known as sclerotium that grows on pine tree roots. The sclerotium can get as large as 30 cm long and 1 kg in mass. Poria is a type of brown rot fungus that can attack and destroy timber. The texture is soft and elastic and the flavor is sweet and bland. Poria flowers are rough with either white or pink interiors. The fungus is harvested and then dried in the shade. [1,2]

HISTORY: Poria has a history in Asian medicine of "draining dampness," for insomnia, to balance electrolytes, and "invigorate" the spleen. Poria has been known as the "medicine of immortality." A legend about Bok-Ryung, the Korean name for poria, tells of an upper class daughter, Ki-Ryung, falling in love with a servant, Ki-Bok, which at the time was strictly forbidden. They decided to run away together, but Ki-Ryung became ill. In Ki-Bok's search for medicinal herbs, he shot a rabbit, followed it, and eventually found the arrow stuck in a hole in the ground near a pine tree. Here, Ki-Bok discovered a mushroom, which he believed was a blessing from God to cure his love. He prepared an infusion of this mushroom, Ki-Ryung drank it, and was cured. This mushroom was named "Bok-Ryung" from their names. [2]

CHEMISTRY: Poria contains several monosaccharides including the *D*- forms of glucose, xylose, mannose, galactose, fucose, and rhamnose.[3,4] Several studies report beta-d-glucan structured polysaccharides being present as well, discussing behaviorial characteristics and antitumor potential. [5,6,7,8,9] The glucan pachyman, specifically, has been evaluated. [10,11,12] Compounds O-acetylpachymic acid, methyl-O-acetylpachymate and Me pachymate have also been isolated from poria. [13,14]

Several reports list triterpene derivatives present in poria. [15,16,17,18] Many include lanostane triterpenes.[19,20,21,22,23] Examples include polyporenic acid C, pachymaic acid,[24] pachymic acid, tumulosic acid, a carboxylic acid,[25] and dehydropachymic acid.[26,27]

Poria also contains 15 amino acids, including primarily aspartic acid, serine, and valine. [28] Enzymes carboxyl proteinase (aspartic proteinase),[2,29,30] beta-pachymanase, protease, and ergosterol and choline have also been found in poria. [1]

PHARMACOLOGY: Several reports can be found on the immunological effects of poria. In vitro testing demonstrates poria extract as being a suppressor of cytokine secretion.[31,32] In mice at doses of 250 and 500 mg/kg, poria appeared to be a promising and potent candidate for modulation of the brain-endocrine-immune axis.[33] Poria monosaccharides, including mannose, galactose, glucose, and others were effective in humoral, cellular, or nonspecific immunities in another report. [34] A review concludes that a decoction including poria has potential importance to strengthen energy in cancer immunotherapy and to detoxify anticancer drugs. [35]

A number of articles report antitumor effects of poria, some of which include the following: Polysaccharides from plants including ascomycetes, basidiomycetes, and fungi imperfecti have well-known anti-tumor effects.[36] Several reports confirm these actions and prove how beta-d-glycans (ie, beta-pachymans) and several new or modified polysaccharides possess anticancer activities in vitro or in mouse tumor against sarcoma 180 and Ehrlich ascites carcinoma. [5,6,7,8,10,13,37,38,39,40] Similarly, later studies report immunostimulation of T-cells and other modulations [28,41] and synergism between certain fungal polysaccharides in a mixture containing poria. [41]

Triterpene fractions of poria possess antitumor effects as well. Lanostane-type triterpenes, including pachymic acid, 3-O-acetyl-16-alpha-hydroxytrametenolic acid, dehydropachymic acid, dehydroeburiconic acid, and poricoic acid, demonstrated antitumor activity in sarcoma 180 and skin tumor formation in mice. [42,43,44,45] Certain triterpenoid fractions from poria showed high inhibitory activity on growth of lung, ovary, skin, central nerve, and rectal cancers and possessed antimicrobial actions. [18] A clinical trial evaluated a Chinese herbal remedy containing a 5-component mixture including poria, studied human uterine myomas. In 110 premenopausal patients with this condition, symptoms of hyper- and dysmenorrhea were improved in > 90% of cases and shrinkage of uterine myomas occurred in ˜ 60% of the cases. [46]

Anti-inflammatory effects of poria have been reported. Triterpene carboxylic acids and derivatives in poria extract inhibit induced mouse ear edema, paw edema, other edemas, chronic inflammation, and dermatitis in mice.[17,45,47,48,49] Pachymic and dehydrotumulosic acids were found to inhibit phospholipase A2 in snake venom, showing potential as natural anti-inflammatory agents. [22]

Reports of poria or formulas containing poria include blood flow analysis, [50] improvement of cerebral blood flow in rats with cerebral ischemia,[51] promotion of hippocampal long-term potentiation in vivo,[52] memory improvement from the effect on neurotransmitters,[53] and antidepressant effects similar to *Prozac*(fluoxetine HCl).[54]

Poria may possess antiemetic actions as well. Triterpene fractions inhibited induced emesis in frogs. [55] A patent for poria lanostane triterpenes as antiemetics has been applied for in Japan and includes doseforms such as tablets, granules, injections, and suppositories. [56] A mixture of 7 herbs including poria studied in > 400 children was effective in 96.4%, with a cure rate of 90% vs controls for acute and chronic diarrhea and noninfective and infective diarrhea. [57]

Poria extract has been studied to measure melanocyte proliferation as a possible application in vitiligo treatment. [58]

TOXICOLOGY: Toxicity of poria polysaccharides has been reported as low during IP administration of 100 mg/kg killing none of the mice in 1 report. [36] Glucans and modified derivatives from poria were suggested to be less toxic than 5-fluorouracil in cancer studies. [40]

SUMMARY: Poria is part of a certain fungus that prefers pine tree roots. Several animal reports confirm its immunological and antitumor actions. One human study finds poria to be beneficial in uterine myomas. Anti-inflammatory actions of poria are proven in animal studies, as are CNS studies in memory improvement or antidepressive effects. Various other effects include antiemetic, antidiarrheal, and vitiligo treatment. No studies have directly linked poria to any severe toxicities. Supportive clinical studies are needed.

PATIENT INFORMATION— Poria

Uses: Poria has been used for its immunological, antitumor, diuretic, anti-inflammatory, anti-emetic, and CNS effects, primarily in animal studies.

Side Effects: No studies have directly linked poria to any severe toxicities.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
      PORIA

POTATO

DATE OF ISSUE: MAR 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Solanum tuberosum* L.

COMMON NAME(S): Potato, white potato

BOTANY: The potato is a weedy plant recognized for its tuberous growth and valued as a commercial foodstuff. Potatoes are propagated vegetatively from the underground runners of the plant from the "eyes" of the potato.[1]

HISTORY: Potatoes have been cultivated since 500 BC; the Central and South American Indians were probably among the first to select hardy cultivators of the potato as a food staple.[1,2] Despite the Spaniard introduction of the plant into Europe in the late 1500s, the tubers did not become a popular food source until the 17th century because of church and mythological concerns about the toxicity of the plant. Once accepted, potatoes were widely disseminated to Germany, other parts of Europe and Russia.

By the 17th and 18th centuries, potatoes formed such a significant part of the Irish diet that intake for adults exceeded 8 lbs/day. However, the potato blight destroyed more than 80% of the crop, resulting in the starvation of more than 3 million Irish.[2]

Traditional uses of the potato include: Using raw potato poultices for arthritis, infections, boils, burns and sore eyes; brewing potato peel tea to soothe edema or bodily swelling; and drinking raw potato juice to soothe gastritis or stomach disorders.[3] (No clinical data exist to support these uses.)

Today, the potato remains an important food with over 200 metric tons being harvested annually worldwide; surpassed only by wheat.[2] Potatoes are also used as a source of starch[4] and alcohol.

CHEMISTRY: Potatoes are a poor source of protein, with only about 5% of the composition being protein. They are, however, reasonable sources of iron, riboflavin and vitamin C,[1] which are found primarily in the thick periderm of the skin.[2] The potato contains a variety of steroidal alkaloids chemically related to the cholestane ring structure. Examples of these compounds include solasodine and solanidine.[5] Potatoes are rich in starch, and potato maltodextrin may be used in the preparation of commercial foods.[6]

PHARMACOLOGY: Over 2000 species of *Solanum* are potentially toxic; *S. tuberosum* is one of only six of these species that produces a tuber.[2] Crop residues from the potato are often implicated in animal/livestock toxicoses.

TOXICOLOGY: The toxicity is related to the presence of the steroidal solanum alkaloids. The solanum glycosides, such as solanine, produce gastrointestinal disturbances including nausea, vomiting, diarrhea and hemolytic and hemorrhagic damage to the gastrointestinal tract.[5] Solanine may also cause an exanthemous syndrome which, together with gastrointestinal and neurological symptoms, may be severe enough to be fatal.[7] Solanine is not destroyed in the cooking process.[8] Ingested solanine is relatively less toxic than that administered parenterally.[7] The biological half-life of solanine is 11 hours.[9]

Even though human fatalities due to the consumption of green potatoes have been reported periodically, proof that solanine was the causal agent has not been firmly established.[8] Concentrations of 38 to 45 mg/100 g solanine have been found in potatoes implicated in human fatalities, compared to 3 to 66 mg/100 g in fresh, healthy potatoes.[8] A level of 20 mg/100 g is generally considered the upper limit of safety.[8]

Solanine has been specifically implicated in the development of fetal malformation in livestock.[5] Solasodine is teratogenic in hamsters when given orally; in some experiments in which pregnant hamsters were fed potato extracts, more than one-quarter of the pups exhibited malformations.[5] Other studies have found that neural tube defects in hamsters may be caused by the solanidine triglycosides, alpha-chaconine and high-dose solanine.[10]

The association between the ingestion of blighted potatoes by pregnant women and subsequent fetal deformities in offspring has not been well established, but remains a growing concern. Anencephaly may have been associated with the ingestion of potatoes infected with Phytophora infestans in women in the Congo.[11]

Potatoes also contain contain a variety of compounds that may potentially interfere with biological systems. These include cholinesterase inhibitors, invertase inhibitors and protease inhibitors;[8] all may have evolved as part of a defense mechanism toward invading microbes.

Because potatoes may be high in bacteria and fungi counts, persons exposed to potato dust have demonstrated a high incidence of work-related respiratory and general symptoms;[12,13] in one survey, 46% of those assessed had respiratory symptoms secondary to exposure to potato dust.[12]

Potatoes may affect glycemic control[14] and insulin levels; therefore, diabetic persons may eat the vegetables as appropriate starch equivalents.

SUMMARY: The potato remains an economically and socially important food product. While its ingestion is safe, persons should refrain from eating damaged or green potatoes which may have elevated levels of solanum alkaloids that have been associated with a variety of types of toxicity.

PATIENT INFORMATION — Potato

Uses: Potatoes are rich in starch and may affect glycemic control and insulin levels of diabetic persons.

Side Effects: Ingestion of damaged or green potatoes can result in GI and neurological disturbances. Exposure to potato dust has demonstrated a high incidence of work-related respiratory and general symptoms.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    POTATO

PRECATORY BEAN

DATE OF ISSUE: FEB 2004

REPLACES MONOGRAPH DATED: JUN 1991

SCIENTIFIC NAME(S): *Abrus precatorius* L. Family: Fabaceae (beans)

COMMON NAME(S): Precatory bean, love bean, rosary pea, Buddhist rosary bead, crab's eye, jequirity seed, bead vine, black-eyed Susan, prayer beads, weather plant, lucky bean, and numerous other locally used common names.[1,2]

BOTANY: The *A. precatorius* plant is native to southeast Asia and is now found in other tropical and subtropical regions. It is found commonly in Florida and Hawaii where it grows as a slender vine generally supported by other plants or a fence. The plant has clusters of pink flowers, and its compound leaves are sensitive to light, drooping at night and on cloudy days. The fruit splits open as it dries to reveal 3 to 5 hard-coated, brilliant scarlet or (rarely) white seeds with a small black spot at the point of attachment. This spot helps identify the seeds, which are sometimes confused with *Rhynchosia*, in which the black and red colors are reversed. Seeds of *A. precatorius* may also be confused with those of *Ormosia*, also a toxic member of the Leguminosae.[1,3]

HISTORY: The precatory bean has found widespread use as an art object and ornament. The colorful, hard beans have been used as pendants, rosaries, rattles, necklaces, and in toys such as noise shakers.[2]

All parts of the plant have been used in traditional medicine. Dilute infusions have been used in South American and African folk medicine for the treatment of ophthalmic inflammations such as conjunctivitis. Precatory beans have been used medicinally to hasten labor, stimulate abortion, and also have found some use as an oral contraceptive in traditional medicine. The seeds also have been used to treat fever in Chinese medicine. The leaves and roots of the plant have been used in Ayurvedic medicine for treatment of asthma, bronchitis, and other respiratory conditions. [1,4]

Because of the great potential for toxicity, the use of this plant is not be recommended.

CHEMISTRY: Several indole alkaloids (eg, abrin, hyaphorine, precatorine), triterpenoids, and a new glycoside have been isolated from the plant. [4,5,6]

The protein abrin has been isolated from the seed and is responsible for its toxic effects. It has been described as a single glycoprotein of molecular weight 60,000 to 65,000.[7] Two proteins of differing amino acid composition have been purified from precatory beans, designated abrin A and C. Abrin C exhibits more potent hemagglutination activity than abrin A.[8] Both abrin A and C may be subdivided into smaller units of molecular weight of about 30,000.

Another lectin, abrus agglutinin, which is nontoxic to animal cells and exhibits potent agglutinating activity toward erythrocytes, has been described. [9] *Abrus* seeds also contain a potent proteinase inhibitor. [10]

PHARMACOLOGY: Abrin is a type 2 ribosome inactivating protein. The toxin is composed of 2 chains (A and B) with distinct functions. The B chain (the haptomere) binds to galactose units of cell surface carbohydrates. [11]

The A chain (effectomere) is responsible for the toxic activity. Once inside the cell, the A chain migrates to the 60S unit of the ribosome, acting to inhibit further protein synthesis. Abrin has a strong inhibitory effect on protein synthesis, moderate inhibitory effect on DNA synthesis, and little effect on RNA synthesis. [12]

Abrin has been used as a "molecular probe" to investigate cellular function. It has also been evaluated in the treatment of experimental cancers. Although effective when given intraperitoneally (IP) to mice pretreated with L1210 leukemia, no increase in lifespan was noted when the compound was administered IV. [13] In another study in mice, abrin injected IP at a dose of 7.5 mcg/kg every other day for 10 days was effective in reducing solid tumor mass. [14] Abrin has been used with some clinical success as an analgesic in terminally ill patients. [15]

Ethanolic extracts of the leaves of *Abrus* possess d-tubocurarine-like neuromuscular blocking activity.[16]

TOXICOLOGY: The seeds, roots, and leaves of *A. precatorius* are all poisonous. The toxin is released when the hard outer covering is pierced (thus allowing absorption into the intestinal secretions) by chewing or drilling holes in the seeds (eg, beadwork, ornaments, jewelry). [2] Necklaces made of the pierced seeds have been reported to induce dermatitis.[17] Intact seeds remain impervious to gastric fluid and pose less of a toxicologic potential. [18] Fatal poisoning in children has been reported after the thorough chewing of as little as half of 1 seed. [1,2]

The onset of toxicity usually occurs in 1 to 3 days; symptoms may persist for longer than 10 days. Because of the irritant effects of abrin on the GI mucosa, ingestion of precatory beans causes severe stomach cramping accompanied by nausea, vomiting, severe diarrhea, cold sweat, and fast pulse. Coma, circulatory collapse, acute renal failure, and hepatotoxicity have also been reported. [2,10]

Treatment is supportive and symptomatic. Because of the necrotizing action of abrin, gastric lavage or induced emesis should be used cautiously. [2] Measures to maintain circulation include the correction of hypovolemia and electrolyte disturbances. [2,3] Alkalinization of the urine to control uremia and enhance toxin excretion has been recommended.[2,19]

A radioimmunoassay has been developed for abrin.[20]

The LD 50 of abrin given IP to mice is 0.04 mcg;[8] 5 mg of the alkaloid abrin is reported to be toxic to humans.[17] In goats, ground seeds administered at a dose of 1 and 2 g/kg/day caused death in 2 to 5 days.[21]

SUMMARY: Phytotoxin poisoning from *Abrus* represents a rare but extremely dangerous and potentially fatal hazard, especially to the young. Because of the necrotizing action of abrin, gastric lavage or induced emesis should be used cautiously. Treatment is supportive and symptomatic. While precatory beans generally have little exposure in American culture, health professionals should remain aware of their potential danger.

PATIENT INFORMATION — Precatory Bean

Uses: The precatory bean has experienced some success as an analgesic in terminally ill patients.

Side Effects: Precatory bean is highly toxic. Because of the irritant effects of abrin on the GI mucosa, ingestion of precatory beans causes severe stomach cramping accompanied by nausea, vomiting, severe diarrhea, cold sweat, and fast pulse. Coma, circulatory collapse, acute renal failure, and hepatotoxicity also have been reported.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PRECATORY BEAN

PRICKLY PEAR

DATE OF ISSUE: AUG 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Opuntia tuna mill* (tuna) and *Opuntia ficus-indica* (barbary fig, Indian fig). Other species include: *Opuntia fragilis* (brittle prickly pear), *Opuntia streptacantha*.

COMMON NAME(S): Prickly pear, Nopal

BOTANY: Prickly pear is a perennial cactus native to tropical America and Mexico, preferring a dry habitat and rocky soil. It can grow to approximately 3 m high. The round stems (pads) have a thorny skin covered in spines. Prickly pear flowers are yellow. The oval, pear-shaped, purplish fruit has prickly outer skin with a sweet inner pulp.[1,2,3,4]

HISTORY: Prickly pear has been used as a food source (conserves) and for alcoholic drinks in Mexico for hundreds of years. Native Americans have applied the pads to wounds and bruises.[2,5]

CHEMISTRY: Older studies concerning certain enzyme studies from *Opuntia* species are available.[6,7,8,9] Constituents of *O. fragilis* have been identified.[10] Later studies discuss the chemistry of various *Opuntia* species, including isolation of albumin from *O. ficus-indica*,[11] amino acid composition (including taurine) in *O. ficus-indica* fruits,[12] and fatty acid evaluation in 3 varieties from *O. ficus-indica* seeds.[13] Prickly pear fruit is high in nutritional value. Analysis of pulp, skin, and seeds reveals high amounts of calcium, potassium, and carbohydrates.[14] Other reported nutrients include vitamin C, iron, and phosphorus.[4,15] Mucilage, sugars, and other fruit acids are also found in the fruit.[2] Flavonoids, isorhamnetin-glucoside, kaempferol, luteolin, penduletin, piscidic acids, quercetrin, rutin, and beta-sitosterol have been found in *O. ficus-indica* flowers.[3]

PHARMACOLOGY

Nutrition: Prickly pear fruit is nutritious.[2,14] The cactus pads are used in a variety of cooking preparations, including soups and salads. The taste has been compared with green beans or asparagus, with the sticky mucilage similar to okra.[5] Prickly pear fruit liquid has been studied as a natural sweetener.[16]

Dermatologic effects: Prickly pear cactus flowers have been used as an astringent for wounds and for their healing effects on the skin.[3] The cactus pads have been used for medicinal purposes (mainly by Indian tribes in Mexico and the southwestern US) as a poultice for rash, sunburn, burns, insect bites, minor wounds, hemorrhoids, earaches, and asthmatic symptoms.[17]

GI effects: The pectins and mucilage from the plant are beneficial to the digestive system. The flowers are used for GI problems such as diarrhea, colitis, and irritable bowel syndrome.[2] *Opuntia* has been studied as a dietary fiber source.[18] *O. ficus-indica* species extracts exhibit protective effects on gastric mucosa and exert an anti-inflammatory action.[19] Anti-inflammatory actions have also been demonstrated in species *O. dillenii* in induced rat paw edema.[20]

Lipid effects: Raw *O. ficus-indica* plant had potentially beneficial effects in hypercholesterolemic parameters in rats.[21] A pectin isolate from *Opuntia* decreased LDL metabolism in guinea pigs.[22,23,24] However, *Opuntia* in capsule form in a human trial had only a marginal beneficial effect on cholesterol and glucose levels.[25]

Hypoglycemic effects: *Opuntia* species have been studied for these effects.[26,27,28] Several reports demonstrate specifically species *O. streptacantha* as having hypoglycemic actions in animal and human studies.[29,30,31,32] *O. fuliginosa* extract has controlled induced diabetes in rats.[33] *O. megacantha* has reduced blood glucose levels in rats but was also shown to be nephrotoxic.[34]

Antiviral actions: One study reports *O. streptacantha* as having antiviral actions in animals and humans.[35]

TOXICOLOGY: Dermatitis from the plant was the most common toxicity found in current literature searches on prickly pear. A case report of cactus dermatitis in a 2-year-old child was described after contact with *O. microdasys*.[36] Two other patients were affected by this same species, both experiencing dermatitis, and one developing severe keratoconjunctivitis in the right eye.[37] A case of cactus granuloma in a 24-year-old male is described from contact with *O. bieglovii* thorns.[38] Granuloma formation has also been seen from *O. acanthocarpa* spines embedded in the dermis with onset occurring within several days and lasting several months. Treatment with topical corticosteroids has been recommended.[39]

Side effects may include exacerbation of hypoglycemia if combined with oral hypoglycemic agents.

Other toxicities include the following: *O. streptacantha* is nontoxic in mice, horses, and humans in oral and IV preparations;[35] *O. megacantha* is nephrotoxic, as described in 1 report in rats.[34]

SUMMARY: Prickly pear is a cactus native to tropical America and Mexico. It has been a source of food and drink for hundreds of years by Native Americans. The fruit is high in nutritional value. The flowers have been used to treat wounds, as have the cactus pads. Application of the pads to rashes, burns, and other wounds appears to be beneficial. Certain *Opuntia* species may also be of use in GI disorders and to lower cholesterol and glucose levels. Dermatitis is the most common toxicity associated with the plant and its spines.

PATIENT INFORMATION — Prickly Pear

Uses: Prickly pear has been used to treat wounds, GI complaints, lipid disorders, and diabetes.

Side Effects: Dermatitis may be the most common side effect from prickly pear. *O. megacantha* has been shown to be nephrotoxic in rat studies. Side effects may include exacerbation of hypoglycemia if combined with oral hypoglycemic agents.

Dosing: Used primarily as a food, prickly pear was given as a treatment for diabetes in a single published clinical trial, with 30 capsules/day reported to be an unrealistic level for good compliance.[25]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PRICKLY PEAR

PROPOLIS

DATE OF ISSUE: FEB 1996

REPLACES MONOGRAPH DATED: FEB 1992

SCIENTIFIC NAME(S): *Propolis balsam*, *propolis resin*, *propolis wax*

COMMON NAME(S): Propolis, bee glue, hive dross

BOTANY: Propolis is a natural resinous product collected from the buds of conifers and used by honeybees to fill cracks in their hives. [1] It is a sticky mass that is greenish brown in color with a slight aromatic odor and is important in the defense of the hive. [2]

HISTORY: Propolis displays strong antimicrobial activity and has been used as a chemotherapeutic agent since ancient times. [3] Its use was found in folk medicine as early as 300 B.C. for medical and cosmetic purposes, as well as an anti-inflammatory drug and wound healing agent. [4,5,6] More recently, it has been reported to possess versatile biologic activity as an antibacterial, antiviral, fungicidal, local anesthetic, anti-ulcer, anti-inflammatory, immunostimulant, hypotensive and cytostatic properties in vitro. [7,8] Proponents of the use of propolis suggest that it stimulates the immune system, thereby raising the body's natural resistance to infection. [1] It has been advocated for both internal and external use.

CHEMISTRY: The composition of propolis continues to be elucidated and appears to vary with its vegetation source. The alcohol extract of the resin is called propolis wax; the residue is called propolis resin. Extraction of the resin with hot petroleum ether is called propolis balsam. Propolis contains 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen and 5% other substances (minerals). [9] Several flavonoids have been isolated and may be responsible for its antibacterial and fungicidal effects. [8] The flavonoids pinocembrin, galangin and pinobanksin, in addition to p-coumaric acid benzyl ester and caffeic acid phenethyl ester (CAPE), demonstrate antimicrobial activity. [1] The extract contains amino acids, flavonoids, terpenes and cinnamic acid derivatives. [10] The water extract also contains lectin. [11] Propolis balsam is described as having a hyacinth-like odor due to its cinnamyl alcohol content.

PHARMACOLOGY: Romanian and other Eastern European researchers have published numerous reports of successful clinical trials in which propolis was given to aid wound healing and to treat tuberculosis, fungal and bacterial infections. [12] More recently, Western researchers have investigated the antibacterial properties of this material. Propolis was active in vitro against some gram-positive bacterial and tubercle bacillus; it also demonstrated limited activity against gram-negative bacilli. Some propolis flavonoids have demonstrated antiviral activity in vitro. [13] Propolis inhibits bacterial growth of *Streptococcus agalactiae* by preventing cell division as well as disorganizing the cytoplasm, cytoplamsic membrane and the cell wall. It also causes a partial bacteriolysis and inhibits protein synthesis. [14] None of the chemical constituents, however, are as effective as anti-infective agents in vitro as streptomycin, chloramphenicol, oxytetracycline, nystatin and griseofulvin. [15,16] No antibacterial activity was observed in the urine of three volunteers who ingested propolis 500 mg 3 times a day for 3 days. [16]

Ethanolic and aqueous extracts of propolis indicate anti-inflammatory and antibiotic activities in vitro and in vivo. The exact mechanism for these effects is not clear. An aqueous extract of propolis has been shown to inhibit the enzyme dihydrofolate reductase. This activity may be partially due to the content of caffeic acid in propolis. This may explain some of the protective functions of propolis, similar to those shown for several nonsteroidal anti-inflammatory drugs (NSAIDs). [17]

A 13% aqueous extract of propolis was tested orally in three doses (1, 5 and 10 ml/kg) on the carrageenan rat paw edema model and on adjuvant-induced arthritis in rats. The extract showed potent dose-related anti-inflammatory activity comparable to diclofenac (as the reference standard). [10] Diethyl ether extracts of propolis were shown to possess cytostatic activity against cultured human KB (nasopharynx carcinoma) and HeLa (carcinoma cervicis uteri) cells in vitro. [7] Ethanolic extracts resulted in a 55% survival rate for mice bearing Ehrlich carcinoma and compared well with a 40% survival rate after bleomycin therapy. The investigators noted; however, an interaction between the agents that resulted in a reduction in survival rate when used as a combination therapy. [18] The ethanolic extracts have also been shown to accerlerate bone formation, regenerate tissue and induce some enzyme systems in vitro. [1]

The effect of the active component of propolis, caffeic acid phenethyl ester (CAPE), was studied on the growth and antigenic phenotype of a human melanoma cell line (HO-1) and a human glioblastoma multiforme cell line (GBM-18). The growth of both cell lines was suppressed by CAPE in a dose-dependent way, with HO-1 cells being more sensitive than GBM-1 cells. The results suggest a potential role for CAPE as an antitumor agent. [19]

Another study explored whether CAPE inhibits the tumor promoter processes associated with carcinogenesis. The treatment of SENCAR mice with very low doses of CAPE (0.1 to 6.5 nmol/topical treatment) strongly inhibits the oxidative processes that are essential for tumor promotion. The findings show CAPE as a potent chemopreventive agent, which may be useful in combating diseases with strong inflammatory or oxidative stress components. [6]

Propolis extracts also possess weak free radical scavenging characteristics. [20] This activity has been associated with an extended longevity among mice that had been pretreated with propolis and exposed to high doses of radiation. [21]

Propolis was studied in albino rats of various ages with toxic liver damage of various duration. The drug was found to have moderate antioxidative properties (30% to 60%) and showed improvements in the hepatic secretion of bile, cholic acids and cholesterol. However, the membrane-stabilizing effect of the drug was not exerted in all models. [22]

Ethanolic extracts of two propolis types showed a similar scavenging action against the different species of generated oxygen radicals. The antioxidative properties of propolis may be attributed to their free radical scavenging activity against alkoxy radicals. [23]

Activity tests prove the high antioxidative and inhibitory capacities of propolis in vitro. Experiments documented the photodynamic quenching properties of propolis extracts. [4] Topical application of propolis extract to dental sockets have been shown to enhance epithelial growth. [24] Propolis decreases dental caries of rats infected with *Streptococcus sobrinus* 6715. [2] Propolis prepared as a mouth rinse aids repair of intra-buccal surgical wounds and exerts a small pain-killing and anti-inflammatory effect on patients who underwent sulcoplasty. [25]

TOXICOLOGY: While reports of toxicity are rare, propolis has long been recognized by apiary workers as being a potent skin sensitizer. Several cases of propolis-induced dermatitis have been reported. These have occurred after the topical use of cosmetics containing propolis and, in one case, after the application of a 10% alcoholic propolis solution for the treatment of genital herpes. [26] Acute oral mucositis with ulceration following the use of propolis-containing lozenges has also been reported. [27]

SUMMARY: Propolis is employed in a variety of topical and systemic preparations. Claims range from the treatment of wounds to improvement of the immune response. A number of in vitro investigations have found a variety of activities to be associated with propolis. Significant studies have shown the anti-inflammatory, antitumor and antioxidant effects of propolis. These three capacities of the drug may contribute significantly to the medical field in the future. However, more studies are needed to confirm these effects.

PATIENT INFORMATION— Propolis

Uses: Studies have shown that propolis has anti-inflammatory, antitumor, and antioxidant effects.

Side Effects: Propolis has been reported to cause propolis-induced dermatitis and acute oral mucositis with ulceration.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PROPOLIS

PULSATILLA

DATE OF ISSUE: MAY 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Pulsatilla vulgaris* Mill. (*Anemone pulsatilla* L.), *P. pratensis* L., *P. patens*(L.) Mill. (*A. patens* L.) Ranunculaceae (buttercup family)

COMMON NAME(S): Pasque flower, meadow anemone, pulsatilla, wind flower, Easter flower

BOTANY: Several closely related species of pulsatilla have found medicinal use in Europe and North America. They are perennial herbs that grow in well-drained, sandy or rocky soil, blooming early in spring soon after snow has melted. The single large flower is characterized by the large, colored bracts, which have the appearance of petals. The whole plant is covered with silky hairs that give the ripe fruit the appearance of a mop head. All parts of the fresh plant have an acrid taste. Molecular research has defined the relationships between different species of pulsatilla and related genera, and has suggested that the genera Pulsatilla, Hepatica, and Knowltonia should be merged into the single genus Anemone.[1]

HISTORY: The dried whole plant of pulsatilla has been used in Europe for a variety of medicinal purposes, including dysmenorrhea and other gynecological disorders, skin diseases, asthma, and eye infections, and as a diuretic and expectorant.[2] It is widely used in homeopathic preparations, once being considered specific for measles, and also used for toothache, earache, and indigestion. A large number of Asian species of pulsatilla (eg, *P. cernua Spreng*., Japanese name "Hakutoo," *P. chinensis* (Bunge) Regel. and others, Chinese name "Bai Tou Weng") have also been used medicinally.[3,4]

CHEMISTRY: The most notable compounds in pulsatilla and many other Ranunculaceae are ranunculin, protoanemonin, and anemonin. Ranunculin is a glycoside that is enzymatically hydrolyzed when the tissues are crushed to the volatile unsaturated lactone protoanemonin, which then dimerizes to anemonin on exposure to air. Protoanemonin is extremely volatile and vesicant. Anemonin was first isolated in 1792,[5] and protoanemonin was elucidated in 1920.[6] Ranunculin was characterized in 1951, and the gross structure of anemonin was proposed.[7] The complete stereostructure of anemonin was determined by x-ray crystallography in 1965.[8]

Triterpene saponins are found in various species of pulsatilla,[3,4,9,10,11,12] while flavonoids also have been isolated.[13] A novel bicyclic quinone was recently reported from *P. koreana*.[14]

PHARMACOLOGY: Protoanemonin has been reported to have antibacterial,[15,16,17,18] antimalarial,[17] and antifungal[19,20] activity, and has been found to be cytotoxic as well.[21] These properties may be due to the ability of protoanemonin to alkylate reactive moieties on proteins and other biomolecules. In animals, protoanemonin and anemonin have a sedating effect, while anemonin was antipyretic,[22] effects also seen in screening of the extract of *P. alpina*.[23] A uterotonic effect of the extract has also been documented.[24]

The saponins of pulsatilla species have been reported to have cytotoxic,[25] antifungal, molluscicidal,[26] and sucrase inhibitory properties.[27] The lignan beta-peltatin, isolated from *P. chinensis*, was strongly cytotoxic.[25] Antibacterial properties were reported for pulsaquinone, the quinone isolated from *P. koreana*.[14]

TOXICOLOGY: Fresh plant material of pulsatilla is extremely toxic and should not be ingested or applied to the skin. Blistering of the skin is due to protoanemonin, which, since it is volatile and reactive, both evaporates or is converted to anemonin on drying of the plant.[7] Paradoxically, protoanemonin is antimutagenic in the Ames test.[28] Sheep and other animals have been killed by overgrazing on protoanemonin-containing plants, and abortions and teratogenic effects have been observed.[29]

SUMMARY: Pulsatilla is monographed in the *British Herbal Pharmacopoeia* and is listed in the Commission E monographs as unapproved. It was official in the US Pharmacopeia from 1882 to 1905, and in the National Formulary from 1916 to 1947.

Pulsatilla has confirmed antibiotic and uterotonic activity; however, the main active principle, protoanemonin, is clearly toxic. It cannot be recommended for human use.

PATIENT INFORMATION — Pulsatilla

Uses: Pulsatilla has confirmed antibiotic and uterotonic activity; however, it is not recommended for human use.

Side Effects: Pulsatilla is extremely toxic and should not be ingested or applied to the skin.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PULSATILLA

PURSLANE

DATE OF ISSUE: JAN 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Portulaca oleracea* L. Family: Portulacaceae

COMMON NAME(S): Purslane, garden (common) purslane, pigweed, ma chi xian (Chinese), munyeroo, portulaca, "pusley"

BOTANY: The purslane family includes several fleshy plants. *P. oleracea* is a herbaceous, succulent annual, cosmopolitan weed. Some consider it a weed because of its growth patterns. Purslane grows 10 to 30 cm tall and has reddish-brown stems, alternate wedge-shaped leaves, and clusters of yellow flowers containing 4 to 6 petals that bloom in summer. Its numerous seeds are black, shiny, and rough. The plant prefers sandy soil. The herb, juice, and seeds are mainly used. Golden purslane (*P. sativa*) is a similar, related species to purslane, with yellow leaves, but is a larger plant and is not weedy. [1,2,3,4,5,6,7]

HISTORY: In ancient times, purslane was considered one of the anti-magic herbs used to protect against evil spirits. [6] Purslane's use as a medicinal herb dates back at least 2000 years, but it was used as food well before this period. Ancient Romans used purslane to treat dysentery, intestinal worms, headache, and stomachache.[2,3,6] The Zulu used the plant as an emetic.[6] Purslane was part of the Australian aborigines' diet as a salad green. The Chinese, French, Italians, and English also used purslane in salads. A folk use of purslane includes reducing fever. [5]

CHEMISTRY: Purslane is a rich source of omega-3 fatty acids, which are beneficial in congenital heart disease (CHD) and certain cancers. [3] One report states that in spite of its genetic diversity, purslane remains one of the most abundant vegetable sources of omega-3 fatty acids. [8] Other reports confirm the high fatty acid content in the plant.[9,10] Purslane contained 8.5 mg fatty acid per gram (wet weight) in another study.[11] Several other articles and reviews confirm purslane's high omega-3 fatty acid content.[12,13,14,15] Fatty acids in purslane seeds (eg, linoleic acid, palmitic acid) have also been evaluated. [16] One report concludes that the omega-3 fatty acid concentration found in purslane is dependent on nitrogen source. [17]

Purslane also contains carbohydrates, lipids, glycosides, alkaloids, sterols, triterpenes, and flavonoids. [18] Phenolic constituents of the plant include scopoletin, bergapten, isopimpinellin, lonchocarpic acid, robustin, genistein, and others. [19] Plant acids present include citric, malic, ascorbic, succinic, fumaric, and acetic acids. [20] The volatile oil of *P. oleracea*has also been studied and contains mainly linalool and 3,7,11,15-tetramethyl-2-hexadecen-1-ol. [21]

Purslane is a rich source of vitamins, with vitamins A, B, C, and E contained in the plant. [2] Purslane is high in carotenoid content, including beta-carotene. [9,10] Calcium, magnesium, potassium, folate, and lithium are also present.[2,6] Amino acids in the leaves of Portulaca species include phenylalanine, alanine, tyrosine, and aspartate.[22] Antioxidants including glutathione and alpha-tocopherol are also found in purslane. [15] The plant's constituents include mucilage as well.[2] A gum has been found in purslane, which may be considered a food emulsifier.[23] A review is available, comparing various plant gums, including purslane. [24] The enzyme phosphoenolpyruvate carboxylase from purslane leaves has been described. [25] Chemical composition of *P. oleracea* at different growth stages has been evaluated.[26]

PHARMACOLOGY: Purslane is a versatile herb and has several culinary uses including "cooked greens" much like spinach or collards. [5] Its nutritive quality, especially the rich source of omega-3 fatty acids purslane provides, has a beneficial effect on cholesterol and triglyceride levels, in heart disease, and in strengthening the immune system.[3,4] Purslane is also high in vitamin and mineral content.[3] The plant possesses marked antioxidant activity.[27]

Purslane has long been considered of value in the treatment of urinary and digestive problems. The juice has diuretic effects. [2] Purslane is also considered to be a "cooling aid" and cleansing stimulant of the kidneys, helpful in the bladder for urinary tract infection. [3,6]

The plant's mucilagenous properties make it useful in GI problems. [2] Purslane, placed in animal feed, prevents diarrhea as well as provides immunostimulation in 1 report.[28] Other sources mention purslane as effective in treating hookworms and amoebic dysentery. [2,4] Besides having vermicidal properties, purslane has been reported to possess antifungal effects, with marked activity against the genus Trichophyton. [29] The phenolic constituents of the plant exhibit antimicrobial effects. [19] Purslane in a combination mouthwash also demonstrated antimicrobial as well as anti-inflammatory effects.[30] Skin conditions such as acne, psoriasis, or sunburn may benefit from purslane.[2] Other uses of the plant include the following: A poultice for backache/dysmenorrhea; [1] neuropharmacological actions;[31] and in cosmetics as a gamma-linolenic acid (GLA) source.[5]

TOXICOLOGY: Purslane is said to be safe, even in high dosages, as it is eaten as a vegetable. [4] Individuals with a history of kidney stones should use purslane with caution as it may increase kidney filtration, urine production, and possibly cause a stone to move. [6] Purslane injection induces powerful contractions of the uterus, but oral purslane is said to weaken uterine contractions. Avoid use during pregnancy. [2]

SUMMARY: Purslane is an herbaceous plant prevalent in China, Japan, and North America. Its use as a medicinal herb dates back at least 2000 years; it was used as a food source long before this time. Purslane is a rich source of omega-3 fatty acids, which are beneficial in heart disease and strengthening the immune system. It is also high in vitamins and minerals. Purslane has been reported as beneficial in urinary and digestive problems, especially as a mucosal demulcent. It also has antifungal and antimicrobial effects. Purslane should not be given to pregnant women.

PATIENT INFORMATION — Purslane

Uses: Purslane is beneficial in urinary and digestive problems. It has antifungal and antimicrobial effects. It is high in vitamins and minerals and has been used as a food source. It possesses marked antioxidant activity. These potential uses have not been verified by clinical studies.

Side Effects: Avoid use during pregnancy. Purslane is said to be safe, even in high dosages; however, individuals with a history of kidney stones should use purslane with caution.

Dosing: No dosing information is available on purslane. The leaves have been used widely as a potherb and, therefore, are known to be safe.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PURSLANE

PYCNOGENOL

DATE OF ISSUE: APR 2001

REPLACES MONOGRAPH DATED: FEB 1991

SOURCE: The name "pycnogenol" is, in itself, a source of confusion. In product literature, this term is a trademark of a British company for a proprietary mixture of water-soluble bioflavonoids, derived from the bark of the European coastal pine, *Pinus maritima* (also known as *P. nigra* var. maritima, a widely planted variety of pine in Europe).

However, the term "pycnogenol" also has been assigned to a group of flavonoids termed the flavan-3-ol derivatives. [1] Numerous plants have been found to be sources for the class of compounds generally termed the flavonoids, and the chemical condensation of flavonoid precursors results in the formation of compounds known as condensed tannins. The broader term, bioflavonoid, has been used to designate those flavonoids with biologic activity.

HISTORY: Pycnogenol is available commercially *otc* in the US in health food stores and pharmacies. Product literature indicates that pycnogenol, when taken as a dietary supplement, is a powerful free radical scavenger. The compound may improve circulation, reduce inflammation, and protect collagen from natural degradation. Pycnogenol has been available in Europe for some time, where it is taken as a supplement or incorporated into topical "anti-aging" creams.

CHEMISTRY: Pycnogenol is a mixture of bioflavonoids designated proanthocyanidins. In some studies, pycnogenol-related compounds are designated procyanidol oligomers (PCOs).[2]

PHARMACOLOGY: A US patent for this material describes a mixture of proanthocyanidins that are effective in combating the deleterious effects of free radicals. The compound is said to assist in the treatment of hypoxia following atherosclerosis, cardiac or cerebral infarction, and to reduce tumor promotion, inflammation, ischemia, alterations of synovial fluid, and collagen degradation. [3]

An important property of flavonoid-containing mixtures in the modulation of nitric oxide (NO) metabolism is inflammation action, which may help explain the biological activity of pycnogenol in human conditions associated either with oxidative stress or dysfunction of NO production. [4,5] Neuropathological features of Alzheimer disease include intracellular neurofibrillary tangles and an amino acid residue peptide identified as amyloid ß-protein. A study using an in vitro model of cellular injury induced by amyloid ß-protein demonstrated the protective effects of pycnogenol on biomembranes. [6]

Several studies have been conducted to evaluate the pharmacologic activity of pycnogenol. In 1 study, daily oral doses of pycnogenol were given for 30 days to patients with a variety of peripheral circulatory disorders. Pain, limb heaviness, and feeling of swelling decreased during therapy in most patients. [7] Similar results have been reported by other investigators. [8]

PCOs have been shown to bind to skin elastic fibers when injected intradermally to young rabbits. As a result, these connective fibers became highly resistant to degradation by elastases injected into the same tissue. These preliminary data suggest that some connective tissues may be protected from enzymatic degradation by PCOs.[2]

Results of a study comparing the response of human breast cancer cells (MCF-7) and normal human mammary cells (MCF-10) to apoptosis in the presence of pycnogenol suggest that pycnogenol selectively induced death in MCF-7 and not in MCF-10 cells. Further research is needed to access the therapeutic value of pycnogenol as a chemoprotective agent.[9]

In a study with rats, intragastrically administered pycnogenol was inhibitory toward tobacco-specific nitrosamine (NNK) activation in lung microsomes suggesting possible chemoprotection toward NNK-induced lung tumorigenesis.[10]

Another US patent for pycnogenol describes a method of inhibiting platelet aggregation with an agent that is able to normalize and enhance platelet reactivity without adversely affecting the bleeding time.[11] This was based on a study conducted in a group of smokers who were given a single dose of 100 to 120 mg pycnogenol or 500 mg aspirin. In this study, pycnogenol rapidly reduced smoking-induced platelet aggregation without increased bleeding. [12]

Another US patent was issued for a regimen and composition for treating attention deficit hyperactivity disorder (ADHD) by the use of proanthocyanidin with and without a heterocyclic antidepressant and a citrus bioflavonoid. [13] A letter to the editor describes the treatment of over 100 patients with ADHD, using nutritional supplements similar to pycnogenol.[14] The author found that the most important improvements noted by patients were in the areas relating to sustained attention and distractibility.[14] A case report showed that a 10-year-old patient with ADHD demonstrated improvement when treated with pycnogenol. [15] In most cases of children with ADHD, the common practice is to combine pycnogenol with dextroamphetamine (eg, *Dexedrine*).[16]

TOXICOLOGY: No significant reports of adverse effects from pycnogenol have been published. Some children treated for ADHD with pycnogenol became irritable and showed decreased energy.[14]

SUMMARY: Pycnogenol is a mixture of water-soluble bioflavonoids derived from a European species of pine. Preliminary animal and clinical data suggest that the oral ingestion of pycnogenol may be beneficial in the management of peripheral vascular diseases and inflammatory collagen diseases. Clinical trials are needed to further assess pycnogenol chemoprotective actions and use for Alzheimer disease and ADHD.

PATIENT INFORMATION — Pycnogenol

Uses: Pycnogenol may provide chemoprotective actions and protect against Alzheimer disease. Pycnogenol is said to help with the treatment of ADHD. Because the effectiveness, safety, and toxicity of pycnogenol for these disorders have not been tested adequately in clinical trials, contact your health care professional before discontinuing or adding to conventional ADHD medications. [17]

Side Effects: Some children taking pycnogenol for ADHD became irritable and showed decreased energy.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
    PYCNOGENOL

PYGEUM

DATE OF ISSUE: JAN 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Pygeum africanum* Hook. f., or *Prunus africana* (Hook. f.) Kalkm. (Rosaceae)

COMMON NAME(S): Pygeum, African plum tree

BOTANY: Pygeum is an evergreen tree native to African forest regions. It can grow to 150 feet in height. The thick leaves are oblong in shape; the flowers are small and white. Pygeum fruit is a red berry, resembling a cherry when ripe. The bark (red, brown or gray) is the part of the plant used for medicinal purposes. It has a "hydrocyanic acid"-like odor.[1,2,3]

HISTORY: The hard wood of pygeum is valued in Africa and is often used to make wagons.[1] Powdered pygeum bark is used by African natives to treat urinary problems.[1,3]

CHEMISTRY: The major bark components are fat soluble compounds. Triterpenes are present (14%), including ursolic, oleanolic and crataegolic acids. The lipid fraction contains fatty acids, which are 12 to 24 carbons in length. The ferulic acid esters are those bound to n-tetracosanol and n-docosanol.[3] N-docosanol has been used in some patent medicines.[4] Phytosterols present in pygeum include beta-sitosterol, beta-sitosterone and campesterol.[1,2,3,5] Tannins have also been found in the plant.[1]

PHARMACOLOGY: In France, *Pygeum africanum* extract (PAE) has become the primary course of treatment for enlarged prostate. In contrast, surgery is the main option in other Western countries.[1] Drugs used to alleviate symptoms of benign prostatic hypertrophy (BPH) (or hyperplasia) include anticholinergics, muscle relaxants, calcium antagonists, prostaglandin inhibitors, beta-agonists, tricyclic antidepressants and alpha blockers.[6] Pygeum clinical trials (mostly European), are encouraging, but more research is needed in the United States. Usual dosage of PAE is 100 mg/day in 6- to 8-week cycles.[2] The highest activity is found in the lipophilic extracts of the plant. Dosage of these extracts are standardized to contain 14% triterpenes and 0.5% n-docosanol.[3]

Most trial results report improvement of BPH symptoms. Reduction in gland size and other parameters occur, but are not as profound.[3] Pygeum is also therapeutic as an anti-inflammatory, to increase prostatic secretions and to decrease certain hormones in the glandular area, which reduces the hypertrophy. Other actions of pygeum include increase in bladder elasticity and histological modifications of glandular cells.[2]

PAE has had positive results in animal "hypophyseo-genito-adrenal axis" and prostatic adenoma.[7,8] Pretreatment of rabbits with pygeum reduces partial outlet obstruction in bladder dysfunction secondary to BPH.[9]

In human trials, symptomatic relief from BPH using PAE has been documented.[10,11,12,13,14,15,16,17] The extract, in combination with mepartricin, was successful in treating urinary symptomatology in 22 subjects with varying stages of prostatic adenoma.[12] In a 74-patient study, extracts of both pygeum and testosterone alleviated obstructive bladder symptoms caused by BPH.[13] Using PAE, nocturnal frequency, difficulty in initiation of urination and bladder fullness were three parameters improved over placebo in 60 patients.[14] In a placebo controlled, double-blind, multi-center evaluation, pygeum capsules (50 mg) were given twice daily for 60 days. Out of 263 patients in eight locations, 66% (vs 31% placebo) showed marked clinical improvement in micturitional disorders.[15] High dose PAE (200 mg/day) administered to 18 patients for 60 days improved both urinary symptoms and sexual behavior in another report.[16] PAE in combination with *Urtica dioica* in half doses was found to be as safe and effective as full doses (300 mg urtica and 25 mg PAE) in treating urine flow, residual urine and nycturia.[17]

Gland size reduction has also been reported for pygeum. PAE was found to be a potent inhibitor of rat prostatic fiberblast proliferation.[18] The extract also displays anti-inflammatory activity, which may affect gland size. It has been demonstrated that macrophages (inflammatory cells) produce chemotactic mediators that worsen BPH development. In one recent report, the proposed mechanism is that pygeum antagonizes 5-lipoxygenase metabolite production (in vitro), which decreases inflammation.[19]

Pygeum may help reverse sterility, which can be caused by insufficient prostatic secretions.[1] PAE has increased prostate secretions in both rats and humans.[20] It has also been shown to improve seminal fluid composition.[1] By improving an underlying problem, PAE may improve sexual function.[3,16]

When compared with saw palmetto in a double-blind trial, it was demonstrated that saw palmetto produced greater reduction of symptoms and was better tolerated; however, PAE may have greater effects on prostate secretion.[3]

The ferulic acid ester components are responsible for pygeum's endocrine system activity. N-docosanol reduces LH, testosterone and prolactin levels. This is important because accumulation of testosterone within the prostate (and subsequent conversion to the more potent form) is believed to be a major factor in prostatic hyperplasia. PAE's "phyto-estrogenic" action markedly reduces volume of prostatic hypertrophy.[21] Fat soluble components reduce cholesterol content within the prostate as well, decreasing accumulation of cholesterol metabolites.[3]

TOXICOLOGY: In human trials, a low incidence of toxicity has been demonstrated as well. No side effects were reported in 18 patients taking 200 mg/day of pygeum for 60 days.[16] Gastrointestinal irritation ranging from nausea to severe stomach pain has been documented but with only a small percentage discontinuing therapy.[3] In 263 patients, GI adverse effects occurred in five patients with only three patients having to stop treatment.[15] It is recommended that pygeum be taken only under professional supervision.[1]

SUMMARY: Pygeum bark has been used by African natives to treat urinary problems. In France, it is the main course of treatment for BPH. Most activity from the plant is found in the lipophilic extracts. Pygeum extract has decreased the incidence of many clinical symptoms of BPH including urine flow, difficulty in starting micturition and other bladder symptomatology. Pygeum may also play a role in anti-inflammation and cell proliferation inhibition in the gland area. Pygeum has increased prostate secretions and may improve sexual function. The extract also acts on the endocrine system, reducing certain hormones known to enlarge the gland. Pygeum has a low toxicity profile.

PATIENT INFORMATION — Pygeum

Uses: Pygeum has been used to improve symptoms of benign prostatic hypertrophy and to improve sexual function. Usual dosage is 100 mg/day in 6- to 8-week cycles.

Side Effects: GI irritation has been reported with the use of pygeum.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "P" MONOGRAPHS
      PYGEUM

"Q" MONOGRAPHS

QUASSIA

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Quassia is a collective term for two herbs: *Picrasma excelsa* and *Quassia amara* L. Family: Simaroubaceae.

COMMON NAME(S): Bitter wood, picrasma, Jamaican quassia (*Picrasma excelsa*), Surinam quassia, *Quassia amara*, Amara species, Amargo, Surinam wood, and ruda.

BOTANY: Surinam quassia is a 2 to 5 m tall shrub or small tree native to northern South America, specifically Guyana, Colombia, Panama, and Argentina. Jamaican quassia is a taller tree, reaching 25 meters, native to the Caribbean Islands, Jamaica, West Indies, and northern Venezuela. The pale yellow wood parts are used medicinally. Leaves are also used.[1,2,3]

HISTORY: Quassia has been used for malaria in the Amazon. It has also been used topically for measles, and orally or rectally for intestinal parasites, diarrhea, and fever. The plants at one time were also used as anthelmintics and insecticides. Central Americans have been known to build boxes to store clothing out of the quassia wood, which acts as a natural repellent.[1,3,4]

CHEMISTRY: Both quassia species have similar constituents. These include alkaloids (0.25%) such as canthin-6-one, 5-methoxycanthin-6-one, and carboline alkaloids. Terpenoids in one or both plants include isoquassin, mixtures of bitter principles (said to be 50 times more bitter than quinine), including quassin, neo-quassin, and 18-hydroxyquassin. Dihydronorneoquassin and simalikalactone D are also present. Other constituents include coumarins (*Q. amara*), thiamine (*P. excelsa*), B-sitosterol, and B-sitostenone.[1,2,3,4] From *Q. amara*, quassinoid quassimarin has been reported[5] and amarid 18-oxyquaxine has been isolated.[6] Nucleotide sequences of certain genes in *Q. amara* have been obtained.[7]

PHARMACOLOGY: Quassia has been used as an insecticide. Traditional use includes remedies for infestations of lice or worms, anorexia, and dyspepsia. [3] Certain tribes have used the plants for measles, fever, and as a mouthwash.[8,9,10]

Quassin demonstrates antilarval activity as well, being effective at concentrations of 6 ppm. [11] A mechanism of this larvicidal activity may be due to inhibition of cuticle development, as suggested in one report.[12] Quassia, as a tincture, has been used to successfully treat head lice in 454 patients. Canthin-6-one possesses antibacterial and antifungal activity. [3]

Quassimarin has been reported to have antileukemic properties when tested in animals. Antitumor activity in mice has been demonstrated, as has in vitro testing of quassin against human nasopharynx carcinoma.[3]

Quassin also displays antifertility effects, inhibiting testosterone secretion in rat Leydig cells. [13] Other changes include reduction in testis, epididymis, and seminal vesicle weight, reduction in sperm count, and decreased LH and FSH levels. [14]

The B-carboline alkaloids exhibit positive inotropic activity in animals. [3]

The extracts and purified mixtures of bitter principles ("quassin") have been used to give a bitter taste to various food products, especially alcoholic (eg, liqueurs and bitters) and nonalcoholic beverages, desserts, candy, baked goods, and puddings. [14]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Quassia is listed as generally regarded as safe (GRAS) by the FDA. No side effects were reported upon topical application of the scalp preparation in the 454 patients in the head lice study. [3] In doses of 250 to 1000 mg/kg, no signs of acute toxicity were observed in rats given quassia extract. [15] Large amounts, however, have been known to irritate the mucus membrane in the stomach and may lead to vomiting.[1] Excessive use may also interfere with existing cardiac and anticoagulant regimens. Due to the plant's cytotoxic and emetic properties, its use during pregnancy is best avoided. [3] Parenteral administration of quassin is toxic, leading to cardiac problems, tremors, and paralysis. [1]

SUMMARY: Quassia is a collective term for both *Picrasma excelsa* and *Quassia amara*. The plants have been used traditionally as anthelmintics, insecticides, and for malaria. They have been effective in treating head lice and also demonstrate antibacterial and antifungal actions. Quassia also possesses antifertility and antitumor actions. It is listed as a safe drug by the FDA, but in large doses may irritate the GI tract and cause vomiting. Use in pregnancy is not recommended. Low concentrations (about 0.007%) are used in bitter food and beverage formulations and sometimes as a flavoring substitute for quinine.

PATIENT INFORMATION — Quassia

Uses: Quassia has a variety of uses including treatment for measles, diarrhea, fever, and lice. Quassia has antibacterial, antifungal, antifertility, antitumor, antileukemic, and insecticidal actions as well.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Quassia is used in a number of food products and is considered to be safe by the FDA. If taken in large doses, this product can irritate the GI tract and cause vomiting. It is not recommended for women who are pregnant.

Dosing: Quassia wood has been used as a bitter tonic, with a typical oral dose of 500 mg of the wood. No recent studies have been performed to rationalize this dose. Several recent studies of topical quassia tincture for head lice have been reported.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Q" MONOGRAPHS
      QUASSIA

QUILLAIA

DATE OF ISSUE: MAR 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Quillaja saponaria* Molina. Family: Rosaceae

COMMON NAME(S): Quillaia, soapbark, soap tree, murillo bark, quillaja, Panama bark, China bark [1]

BOTANY: Quillaia is a large evergreen tree with shiny thick leaves. The generic name is derived from the Chilean word quillean, to wash, from the use made of the bark.[2] Although it is native to Chile and Peru, it is now widely cultivated in southern California. The inner bark is separated from the cork and collected for commercial use. It has an acrid, astringent taste.[2]

HISTORY: Quillaia has been used in traditional medicine to relieve cough and bronchitis, and topically to relieve scalp itchiness and dandruff. [1,3] The bark has been used by South Americans to aid in washing clothes.[3] Quillaia extracts are approved for food use and are used as foaming agents in some carbonated beverages and cocktail mixes. They are typically used in concentrations of about 0.01%. [1]

CHEMISTRY: Quillaia contains about 10% saponins.[2] These consist primarily of glycosides of quillaic acid (quillaja sapogenin, hydroxygypsogenin). [1,2] Quillaia saponin has been shown to be a mixture of acetylated triterpenoid oligoglycosides.[2] In addition, the bark contains tannin, calcium oxalate and numerous additional components.[1]

A highly purified saponin, designated QS-21, has been used as an adjuvant to enhance the activity of viral vaccines. [4] This saponin has been found to be a combination of two structural isomers.[5]

PHARMACOLOGY: The saponins derived from quillaia or its powdered bark can induce localized irritation and are also strong sneeze inducers. [1] Although the saponin is too irritating to the stomach and too strongly hemolytic to be ingested, it nevertheless has been shown to possess expectorant effects. The saponin depresses cardiac and respiratory activity.[1]

As noted above, a number of saponins have been derived from quillaia that serve as adjuvants when coadministered with certain vaccines. These saponins have been shown to boost antibody levels by 100-fold or more when used in the mouse.[6]

TOXICOLOGY: The effects of chronic low-low ingestion of quillaia are not well-defined. However, a short-term study in rats and long-term study in mice indicate that quillaia saponins are nontoxic.[1]

Quillaia saponin (sapotoxin) is reported to be highly toxic.[3] Severe toxic effects following the ingestion of large doses of the bark include liver damage, gastric pain, diarrhea, hemolysis, respiratory failure, convulsions and coma.[1] Digitalis may stabilize cardiac involvement.[3]

SUMMARY: Quillaia extracts are widely used to induce foaming in beverages. The saponins are responsible for this effect. However, quillaia saponins are generally considered to be highly toxic in high doses. Consequently, the traditional medical uses of quillaia have focused on its external application. Purified quillaia saponins have been shown to enhance the activity of certain vaccines in animals.

PATIENT INFORMATION — Quillaia

Uses: Reports show that quillaia can depress cardiac and respiratory activity and induce localized irritation and sneezing.

Side Effects: The ingestion of the quillaia bark results in liver damage, gastric pain, diarrhea, hemolysis, respiratory failure, convulsions, and coma.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "Q" MONOGRAPHS
  QUILLAIA

QUININE

DATE OF ISSUE: JAN 2003

REPLACES MONOGRAPH DATED: AUG 1993

SCIENTIFIC NAME(S): *Cinchona succirubra* Pav. ex Klotsch (red cinchona), *C. calisya* Wedd., and *C. ledgeriana* Moens ex Trim. (yellow cinchona). Family: Rubiaceae

COMMON NAME(S): Red bark, Peruvian bark, Jesuit's bark, China bark, cinchona bark, quina-quina, fever tree

BOTANY: The cinchonas are evergreen shrubs and trees that grow to heights of 15 to 31 m.[1] They are native to the mountainous areas of tropical Central and South America, including regions of Bolivia, Costa Rica, and Peru. The oblong seed capsule is about 3 cm long and, when ripe, splits open at the base. Each capsule contains 40 to 50 slender seeds that are so light that approximately 75,000 seeds equal 30 g.[2] In addition, these trees are found in Africa and Southeast Asia.[1,3] At least one other genus (*Remijia*) of the same family has been reported to contain quinidine.[4]

HISTORY: The dried ground bark of the cinchona plant has been used for centuries for the treatment of malaria, fever, indigestion, mouth and throat diseases, and cancer.[1,2,3] The name *cinchona* is said to be derived from the Countess of Chinchon, the wife of a viceroy of Peru, who it was long believed was cured in 1638 from a fever by the use of the bark;[4] however, the story has been widely disputed. Formal use of the bark to treat malaria was established in the mid-1800s when the British began the worldwide cultivation of the plant[2] in order to assure the continuing availability because the plant was in danger of extinction in some regions because of the harvesting of wild populations.[4]

Extracts of the bark have been used to treat hemorrhoids, to stimulate hair growth, and to manage varicose veins. Quinine has been used as an abortifacient.[2] Extracts of cinchona have a bitter, astringent taste and have been used as flavoring for foods and beverages. Although the use of quinine for the treatment of malaria has been largely supplanted by semisynthetic antimalarials, its use persists in some regions of the world.

CHEMISTRY: Typical cinchona bark contains about 16% of quinoline alkaloids consisting mainly of quinine, quinidine, cinchonine, and cinchonidine. The primary component of this mixture is quinine. Quinidine is the dextrorotatory isomer of quinine. Approximately 35 additional minor compounds related to quinine have been identified in the plant.[1,2] As a rule, the yellow cinchona has a higher alkaloid content than other varieties. Commercial formulations of quinine contain about 10% of dihydroquinine as an impurity.[5]

The cinchona alkaloids are extremely bitter tasting. Concentrations in the 100 to 300 ppm range are used to flavor beverages such as tonic water. Tonic water contains about 15 mg of quinine per bottle.[6] Quinine may have tumor necrosis factor (TNF)-suppressive activity as demonstrated in one small study.[7]

PHARMACOLOGY: Quinine is eliminated mainly by hepatic metabolism with very little excreted unchanged in the urine.[8,9,10] Cytochrome P450 3A4 has been shown to be important in the metabolism of quinine. Seven metabolites have been identified with 3-hydroxyquinine being the major metabolite.[5,8,9,11] In patients with acute renal failure who are infected with *Plasmodium falciparum*, up to 12% of antimalarial activity is due to the 3-hydroxyquinine metabolite.[11]

Antimalarial: Quinine is among the most potent of the cinchona alkaloids with respect to antimalarial activity.[1] Resistant strains of *Plasmodium* have been identified. A small, in vitro study showed potential of phenobarbital to partially reverse quinine resistance.[12] Calcium antagonists and other agents (eg, prochlorperazine) are being studied for reversing *P. falciparum* resistance to quinine.[13] Various antibiotics (ie, artemisinin, artemether, clindamycin, doxycycline, mefloquine) in combination with quinine are being tested and used to treat resistant strains of *P. falciparum*.[14,15,16,17,18,19] If the oral route is not available for administration of quinine in children, effective alternate routes (ie, IM, intrarectal, IV) can be used.[20,21,22,23] Close monitoring for adverse reactions is advised, especially in young children who are more susceptible to quinine toxicity.[21] The combination of quinine and clindamycin has been safely and effectively used in Thailand for the treatment of uncomplicated malaria.[24]

Antipyretic: Quinine has been thought to have antipyretic action.[25] Although quinine administered before acetaminophen produces a more rapid drop in temperature than administration after acetaminophen, quinine alone has no effect on fever.[26]

Leg cramps: Another common use of quinine has been for the treatment of leg cramps caused by vascular spasm. For more than 50 years, quinine, quinidine, and hydroquinine have been used to prevent muscle cramps.[27] Various crossover, randomized trials, and 2 meta-analyses have confirmed that quinine is effective in the prevention of nocturnal leg cramps.[27,28,29,30] However, because 157 adverse drug reactions attributed to quinine were reported from 1969 to 1992, the Food and Drug Administration (FDA) concluded that quinine was not safe for use in this condition.[31] In 1994, the FDA prohibited the marketing of quinine for nocturnal leg cramps and discontinued its availability and the labeling of products for this use in prescription and nonprescription form.[31,32] However, a quick search of the Internet found a multitude of quinine preparations available and advertised for leg cramps.[33]

Other uses: Quinine is bacteriostatic, highly active in vitro against protozoa, and inhibits the fermentation of yeast.[2]

Quinine and quinidine have cardiodepressant activity. The latter compound is used for its antiarrhythmic activity.

A mixture of quinine and urea hydrochloride is injected as a sclerosing agent in the treatment of internal hemorrhoids, varicose veins, and pleural cavities after thoracoplasty.[2]

Quinine has been used to reverse multidrug resistance in patients with acute leukemias who express a higher incidence of P glycoprotein expression in blast cells. A high cure rate and better survival were shown in patients treated with combined quinine and chemotherapy when compared with chemotherapy alone. Although a higher incidence of side effects occurred, this combination has potential in treating acute leukemias.[34,35]

INTERACTIONS

Increased elimination of quinine: Cigarette smoking and rifamycins (eg, rifampin) cause a marked increase in elimination of quinine.[5,8,9,36,37]

Decreased elimination of quinine: Cimetidine[5,36] and ketoconazole decrease the clearance of quinine.[8,36]

Effects of quinine on other drugs: Serum levels of amantadine, carbamazepine, digoxin, phenobarbital, and warfarin may be elevated by quinine.[5,11,36,38] Quinine may enhance the effects of nondepolarizing muscle relaxants and succinylcholine. Close monitoring of neuromuscular function is required.[36]

Dosage adjustment may be necessary. For additional information please refer to the "Evidence-Based Herb-Drug Interactions" appendix.

TOXICOLOGY

Pregnancy: Quinine has been previously listed as being contraindicated during pregnancy because of fetal and abortifacient effects. [25] A review of the safety of antimalarial drugs in pregnancy state that standard (antimalarial) doses of quinine showed no evidence of increased risk of abortion or preterm delivery. Quinine has been shown to be secreted into breast milk, but insignificant amounts are ingested by the infant. However, high doses of quinine can cause uterine stimulation in pregnant women and deafness and optic nerve hypoplasia in children. [39]

Adverse effects: Quinine exhibits considerable inter- and intraindividual variations in metabolism and elimination, with differences also seen in healthy compared with malaria-infected patients. Adverse effects are dose-related. [40]

Cardiac events: Because quinine is related to quinidine, ventricular fibrillation, prolongation of the QT_c interval, and other adverse cardiac events can occur. [13] Administration of IV quinine within 72 hours of mefloquine may cause QT_c prolongation. [17] Closely monitor patients with a cardiac history if quinine is given.

Cinchonism: The ingestion of these alkaloids can result in the clinical syndrome known as *cinchonism*. People who are hypersensitive to these alkaloids also may develop the syndrome, which is characterized by severe headache, abdominal pain, convulsions, visual disturbances and blindness, auditory disturbances such as ringing in the ears, paralysis, and collapse. [1]

Hematologic disorders: Therapeutic doses of quinine have resulted in acute hemolytic anemia, [3] a limitation for its use in patients who are glucose-6-phosphate dehydrogenase deficient. [5] Quinine also has been associated with other serious hematologic disorders such as agranulocytosis, disseminated intravascular coagulation, [41,42] hemolytic uremic syndrome (HUS), [11,41,43,44,45,46] neutropenia (leukopenia), [47] pancytopenia with coagulopathy, [48,49] and thrombocytopenia (the most common hematologic adverse effect). [47,50,51,52] Patients may present with one or several concomitant hematologic adverse events. Two deaths have been attributed to quinine-induced thrombocytopenia. [50,52]

Hypersensitivity reactions: Ground cinchona bark and quinine have been reported to cause urticaria, contact dermatitis, and other hypersensitivity reactions. These reactions also may occur with the use of topical preparations containing cinchona extracts or quinine. [2]

Systemic hypersensitivity reactions can present as HUS, with acute renal failure and simulating sepsis. [11,46]

Hypoglycemia: Children with severe malaria often present with hypoglycemia. [53] Quinine has been shown to increase insulin secretion. [54,55] Quinine-induced hypoglycemia has been documented in patients with and without malaria. [56,57] Quinine-stimulated insulin release may be amplified in pregnancy, aggravating hypoglycemia. [39] Monitor plasma glucose levels.

OVERDOSAGE: Quinine and related alkaloids are rapidly absorbed from the GI tract; a single 2 to 8 g oral dose of quinine may be fatal to an adult. [1,2,5] Treatment of an overdose is generally supportive. Urinary acidification can be employed if necessary. [25] Quinine is not eliminated by hemofiltration or hemodialysis. [10]

SUMMARY: Quinine and its related alkaloids have been used for more than 100 years for the treatment of malaria and associated febrile states. Quinidine possesses antiarrhythmic activity. Chronic ingestion may lead to cinchonism. Hypersensitivity reactions have been observed, along with hematologic adverse events.

PATIENT INFORMATION — Quinine

Uses: Quinine has been used for the treatment of malaria and associated febrile states, leg cramps caused by vascular spasm (not approved by the FDA), internal hemorrhoids, varicose veins, and pleural cavities after thoracoplasty.

Interactions: Rifamycins and cigarette smoking increase the elimination of quinine. [5,8,9,35,36] Cimetidine [5,35] and ketoconazole [8,35] decrease the clearance of quinine. Serum levels of amantadine, carbamazepine, digoxin, phenobarbital, and warfarin may be elevated by quinine. [5,7,35,37] Quinine may enhance the effects of nondepolarizing muscle relaxants and succinylcholine. Close monitoring of neuromuscular function is required. [35] Dosage adjustment may be necessary. For additional information please refer to the "Evidence-Based Herb-Drug Interactions" appendix.

Side Effects: Quinine can cause cinchonism, hypoglycemia, serious hematologic disorders, urticaria, contact dermatitis, and other hypersensitivity reactions.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Q" MONOGRAPHS
    QUININE

"R" MONOGRAPHS

RASPBERRY

DATE OF ISSUE: JUN 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Rubus idaeus* L. and *Rubus strigosus* Michx. Family: Rosaceae (roses)

COMMON NAME(S): Red raspberry

BOTANY: The cultivated red raspberries *Rubus idaeus* (Eurasian) or *R. strigosus* (North American, also known as *R. idaeus* var. *strigosus*) are two of many *Rubus* species worldwide. While the berries are cultivated as food items, it is the leaves that have been used medicinally. Raspberries grow as brambles with thorny canes bearing three-toothed leaflets and stalked white flowers with five petals. The red berries detach easily from their cores when ripe. While some species of *Rubus* primarily reproduce clonally and commercial red raspberries are propagated as clones, DNA fingerprinting has indicated that wild *R. idaeus* populations exhibit substantial genetic diversity.[1]

HISTORY: The leaves of red raspberry were used for their astringent properties to treat diarrhea in the 19th century. A strong tea of raspberry leaves was used in painful or profuse menstruation and to regulate labor pains in childbirth.[2] The Eclectics used a decoction of the leaves to suppress nausea and vomiting. A gargle of raspberry leaf infusion has been used for sore throats and mouths and to wash wounds and ulcers.[3]

CHEMISTRY: While substantial effort has been devoted to the chemistry of raspberry fruit as a food item, relatively less has been published on the chemistry of the leaves. The principal compounds isolated from red raspberry leaves are hydrolyzable tannins. Simple compounds such as 1,2,6-tri- *O*-galloyl-glucose and penta-*O*-galloyl glucose[4] are oxidatively coupled through galloyl groups to form more complex compounds such as casuarictin, pedunculagin, sanguin H-6,[5] and lambertianin A,[6] with as many as 15 galloyl groups coupled to 3 glucose units.[7]

Common flavonoids have also been isolated from the leaves of raspberry. Rutin was isolated,[8] as were kaempferol, quercitin, quijaverin, and kaempferol-3-*O*-ß-D-glucuronopyranoside.[9] Major leaf volatiles studied by GC-MS include the monoterpenes geraniol and linalool as well as 1-octane-3-ol and decanal.[10] Phenolic acids common to the Rosaceae family have also been identified.[11]

PHARMACOLOGY: The tannin components of the leaves have a definite astringent action,[12] which may be helpful in diarrhea or as a mouthwash; however, there is little pharmacologic evidence at present to support the use of raspberry leaf tea in pregnancy, menstruation, or childbirth. A preliminary study found fractions of raspberry leaf extract that stimulated and relaxed uterine muscle in pregnant rats, but this must be confirmed.[13] Blackberry (*R. strigosus*) leaves, which have similar chemistry to raspberry leaves, have been found to have a slight hypoglycemic activity in rabbit models; however, the chemistry responsible for this effect was not elucidated.[14],[15]

TOXICOLOGY: There is no evidence that raspberry leaf tea is toxic.

A raspberry leaf monograph is included in the *British Herbal Pharmacopeia*, vol. 2.[16] It is listed as unapproved in the *German Commission E Monographs*.[17]

SUMMARY: Raspberry leaf tea is a source of hydrolyzable tannins, which have an astringent action. There is little pharmacology to support its wide use in pregnancy; however, it appears to be safe under normal conditions of use.

PATIENT INFORMATION — Raspberry

Uses: Raspberry leaves may be helpful for diarrhea or as a mouthwash because of their astringent action. They have been used historically in painful or profuse menstruation and to regulate labor pains in childbirth, but there is little evidence to support this use.

Side Effects: There is no evidence that raspberry leaf tea is toxic.

Dosing: Typical doses of raspberry leaf as a tea are 1.5 to 2.4 g/day. A clinical trial has been conducted to define its safety in labor.[18]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
      RASPBERRY

RED BUSH TEA

DATE OF ISSUE: MAY 1997

REPLACES MONOGRAPH DATED: AUG 1990

SCIENTIFIC NAME(S): *Aspalathus linearis* (Burm. f.) R. Dahlgr. This plant is also referred to as *Borbonia pinifolia* Marloth or *Aspalathus contaminata* (Thunb.) Druce. Family: Leguminosae

COMMON NAME(S): Red bush tea, rooibos tea

BOTANY: Red bush grows as a low bush, attaining a height of 4 to 5 feet. It has long, needle-like leaves and small colorful flowers. The plant is native to South Africa and is cultivated extensively for its commercial value as a substitute for common tea. The leaves and twigs are collected, washed, bruised, fermented, dried, cut and packaged for use in preparing teas. During this procedure, the leaves change from green to brick red due to the release of a red pigment found in the leaves and stems.[1]

HISTORY: "Bush teas" are common throughout Africa and are frequently used as substitutes for common tea. Red bush tea has been popular in South Africa for decades, and commercial preparations are sometimes found in Europe and the US. One reason for the popularity of this tea is its almost total lack of physiologically active compounds. Consequently, red bush tea is selected as a fragrant, nonstimulating beverage. [2]

CHEMISTRY: Red bush tea is devoid of significantly active compounds. It contains no caffeine and is low in tannins (less than 5%). It contains a relatively high level of vitamin C (approximately 9.4%).[1,3]

PHARMACOLOGY: Red bush tea and its protective and suppressive effects have been studied. Suppression of mutagenic activity of "certain potent mutagens" has been performed in mice.[4] Oncogenic transformation of mouse cells induced by x-rays was suppressed in the presence of the tea extract. Suppression variability was dependent upon extract concentration and length of treatment time.[5] Prevention of age-related accumulation of lipid peroxides in rat brain has also been reported. Red bush tea's protective effects against CNS damage in certain brain areas have been additionally demonstrated. [6] Flavonoids contained in the tea show antioxidative qualities both in vitro and in vivo. Red bush tea's radioprotective effects may be due to a "free radical scavenging" mechanism. [7,8]

TOXICOLOGY: No reports have been identified regarding toxicity with this plant or its teas. A single article reports salmonella contamination from rooibos tea, possibly from lizard origin.[9]

SUMMARY: Red bush tea is a native African beverage that is also sold in Europe and the United States. It was found to have both protective and suppressive effects in animal studies. The mechanism may be due to the plant's ability to scavenge free radicals. More research is needed to further prove red bush tea's antimutagenic and CNS-protective effects. The plant appears to have a low toxicity profile, and the tea is a good option for those who wish to drink a mild, nonstimulating or sedating tea.

PATIENT INFORMATION — Red Bush Tea

Uses: Although no significantly active compounds exist in the leaves, red bush tea has a high vitamin C content. It is being investigated as an anti-cancer drug and as a prevention for brain damage caused by aging.

Side Effects: No reports have been identified regarding toxicity with red bush tea. There is one report of salmonella contamination from rooibos tea, possibly from lizard origin.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "R" MONOGRAPHS
  RED BUSH TEA

RED CLOVER

DATE OF ISSUE: NOV 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Trifolium pratense*, Family: Leguminosae

COMMON NAME(S): Cow clover, meadow clover, purple clover, trefoil

BOTANY: The plant's medicinal value is found in its red and purple fragrant blossoms, dried for utilization. It is a perennial that flowers for a short duration. Several hairy-looking stems grow 0.3 to 0.6 m high from a single base. The leaves are ovate, nearly smooth, and end in a long point; the center is usually lighter in color. It is found most commonly in meadows of a light sandy nature in Britain and throughout Europe and Asia from the Mediterranean to the Arctic Circle. Also, it has been found in the mountains. Red clover is now naturalized in North America and Australia for hay and as a nitrogen-fixing crop. [1]

HISTORY: The flowers possess antispasmodic, estrogenic, and expectorant properties. Chinese medicine has used red clover in teas as an expectorant. Russians recommend the herb for bronchial asthma. Traditionally, the herb has been used in treating breast cancer. [2] Topically it is used to accelerate wound healing and to treat psoriasis.[3] Research has indicated increased compliance of arterial vessels. In Australia, *Promensil* has been marketed for hormone replacement and *Trinivin* for benign prostatic hyperplasia.[4]

CHEMISTRY: The main chemical classes contained in red clover include carbohydrates, isoflavonoids, flavonoids, and saponins. Other constituents are coumaric acid, fats, minerals, and vitamins. Isoflavones are comprised of biochanin A, formononetin, daidzein, and genistein. These phytoestrogens comprise 0.17% of the herb. A volatile oil including methyl salicylate is distilled from the flowers. [5]

PHARMACOLOGY

Hormone replacement: Isoflavones mimic estrogen effects in the body.[6] If an estrogen supplement is given, it binds to intracellular receptors and acts as an agonist to natural estrogen. Through negative feedback, production of GnRH, FSH, and LH is stopped, resulting in cessation of the production of estrogen. Studies have shown that cattle grazing on red clover displayed fertility problems.

Arterial compliance: In a placebo-controlled study of 17 women, arterial compliance, an index of elasticity of large arteries (eg, thoracic aorta) in which compliance diminishes with age and menopause, increased by 23% when 40 mg of red clover was given for five weeks followed by 80 mg for 5 more weeks. The hormonal effects of the isoflavonoids aid in arterial compliance, because arterial compliance decreases in post-menopausal women. [7]

Chemoprotective: Biochanin A has been reported to inhibit carcinogenic activity in cell cultures. [5]

INTERACTIONS: Isoflavonoids may interfere with hormonal therapies. Red clover should probably not be taken with oral contraceptives, estrogen, or progesterone compounds. Its coumarin effects may enhance anticoagulation. If possible, avoid red clover in patients receiving an anticoagulant or aspirin. If concurrent therapy is unavoidable, closely monitor prothrombin time or the International Normalized Ratio (INR).

TOXICOLOGY: Grazing animals have shown infertility and growth disorders because red clover acts as a natural estrogen agonist. Doses greater than 40 to 80 mg daily should be avoided. It should not be taken during pregnancy or lactation. Coumarin activity may also be problematic at high doses. [4]

"Clover disease," related to the consumption of red clover by sheep, has lead to infertility, abnormal lactation, dystonia, and prolapsed uterus.

Use should be avoided in patients with a history of breast cancer.

SUMMARY: Red clover has not proven efficacious for all listed uses. Limited evidence-based studies have been conducted. The chemistry of the herb is well documented and grazing cattle have shown isoflavone effects. Red clover has been used in hormone replacement therapy and arterial compliance, and as a chemoprotective and expectorant.

PATIENT INFORMATION — Red Clover

Uses: Red clover has been used in hormone replacement therapy and arterial compliance and as a chemoprotective.

Interactions: Isoflavonoid properties may interfere with hormonal therapies. Red clover should not be taken with oral contraceptives, estrogen, progesterone compounds, anticoagulants, or aspirin.

Side Effects: Do not take during pregnancy, lactation, or in patients with a history of breast cancer. Avoid large doses. Coumarin activity may be problematic at high doses.[4] "Clover disease," related to the consumption of red clover by sheep, has lead to infertility, abnormal lactation, dystonia, and prolapsed uterus.

Dosing: Formerly used as a sedative at doses of 4 g of blossoms, red clover is now used primarily as a source of estrogenic and antioxidant isoflavones. Extracts standardized on isoflavone content (*Menoflavon*, *Rimostil*) have been given to perimenopausal women in several clinical studies at daily doses of 25 to 90 mg of isoflavones.[8,9,10]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    RED CLOVER

REISHI MUSHROOM

DATE OF ISSUE: JUL 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Ganoderma lucidum* (Leysser ex Fr.) Karst. Family: Polyporaceae

COMMON NAME(S): Reishi, ling chih, ling zhi, "spirit plant"

BOTANY: The reishi mushroom is a purplish-brown fungus with a long stalk and fan-shaped cap. It has a shiny, "varnish"-coated appearance, with spores resembling brown powder that can sometimes be seen. The reishi grows on decaying wood or tree stumps. It prefers the Japanese plum tree but also grows on oak. The fruiting body is the part of the plant used for medicinal purposes. This mushroom grows in China, Japan, and North America and is cultivated throughout other Asian countries. Cultivation of reishi is a long, complicated process. The reishi grows in 6 colors, each having its own characteristics: *Aoshiba* (blue reishi), *Akashiba* (red reishi), *Kishiba* (yellow reishi), *Shiroshiba* (white reishi), *Kuroshiba* (black reishi), and *Murasakishiba* (purple reishi).[1]

HISTORY: Reishi has been used in traditional Chinese medicine for over 4000 years for treating problems such as fatigue, asthma, cough, and liver ailments, and to promote longevity.[1] The Chinese name ling zhi means "herb of spiritual potency."[1] A Japanese name for the reishi is mannentake, meaning "10,000-year-old mushroom." Reishi's use is documented in what is said to be the oldest Chinese medical text, which is over 2000 years old. This book contains information on about 400 medicines but lists the reishi as the most superior.[2] Cultivation of reishi began in the 1980s.[3]

CHEMISTRY: The reishi mushroom is known to be high in polysaccharide content, including beta-d-glucan and GL-1.[1,4] Triterpene constituents of the plant also have been analyzed.[5] Triterpene antioxidants including ganoderic acids (A, B, C, and D), lucidenic acid B, and ganodermanontriol have been found in reishi.[1,6] Terpenoids 1, 2, and 3, and terpenes lucidenic acid O and lucidenic lactone also exist in the plant.[7] One report discusses peptidoglycan from reishi containing ˜ 7% protein and 76% carbohydrate.[8] Certain enzymes from reishi have also been reported.[9] The reishi mushroom contains minerals including calcium, magnesium, and potassium. Germanium, lanostan, coumarins, ergosterol, and cerevisterol are also found in reishi.[1,7]

PHARMACOLOGY

Anticancer immunostimulant effects: Older texts make mention of reishi's immunostimulatory and anticancer effects.[2] Modern research confirms these indications, attributing the polysaccharide components to be responsible for these properties. Polysaccharides beta-d-glucan and GL-1 have been found to inhibit sarcoma.[4] Reishi has been shown to be of benefit in myeloblastic leukemia and nasopharyngeal carcinoma in combination with other chemotherapeutic agents, demonstrating tumor shrinkage, significant changes in hemoglobin counts, and overall quality-of-life markers.[3] In vitro studies find reishi (and other plant) polysaccharides to be antigenotoxic and antitumor promoting.[10] Extract of reishi shows radioprotective ability and protective ability against hydroxyl radical-induced DNA strand breaks in another report.[11] Reishi has demonstrated positive effects on cytokine release from human macrophages and T-lymphocytes, confirming its role in immunopotentiation.[12] Reishi's anticancer properties are almost certainly "host-mediated" through stimulation of the immune system.

Hepatitis: The reishi mushroom also has been beneficial in the treatment of hepatitis.[12] One report describes how it minimized experimental liver damage when studied in rats.[13] Another report shows improvement in 92% of 355 hepatitis patients taking reishi.[14]

Cardiovascular effects: Positive effects on the cardiovascular system also have been demonstrated by reishi. Decreases in high blood pressure have been affected by the ganoderic acids.[1,3] ACE-inhibiting triterpenes from reishi have also been discussed.[15] The risk of coronary artery disease may also be decreased by reishi, which was found to decrease platelet adhesion.[1] In one report, ganodermic acid was found to exert inhibitory effects on platelets, leading to decreased thromboxane formation.[16] Reduction of cholesterol from reishi has been addressed, including decreases in triglycerides and LDL.[1]

Antiviral effects: Certain polysaccharides isolated from reishi have been proven effective against herpes simplex virus types 1 and 2.[17] Certain reishi isolates also have been tested against other viral strains including influenza A and demonstrated effectiveness against their growth.[18]

Other effects: There are numerous claims for reishi (some unconfirmed) including the following: Decrease in blood glucose levels in mice, treatment of diabetic ulcers,[3] altitude sickness,[1] and headaches.[3]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY

Side Effects: Side effects from reishi may include dizziness, dry mouth, stomach upset, nose bleed, sore bones, irritated skin, diarrhea, or constipation from initial use, which may disappear with continued use or may develop from use over 3 to 6 months.[1] Because reishi may increase bleeding time, it is not recommended for use with anticoagulants. Pregnant or lactating women should consider these issues and consult a doctor before taking reishi.[1]

SUMMARY: The reishi mushroom has been used in traditional Chinese medicine for over 4000 years. It is high in polysaccharide content, which is mainly responsible for anticancer and immunostimulatory effects. It has liver protectant actions, beneficial effects on the cardiovascular system, antiviral actions, and other effects. Side effects are mild and may include dizziness, GI upset, or irritated skin. The use of reishi with anticoagulants or in pregnant or lactating women is not recommended.

PATIENT INFORMATION — Reishi Mushroom

Uses: Reishi is high in polysaccharide content, which is mainly responsible for possible anticancer and immunostimulatory effects. It also may have liver protectant actions, beneficial effects on the cardiovascular system, antiviral actions, and other effects.

Interactions: Do not take with anticoagulants.

Side Effects: Side effects are mild and may include dizziness, GI upset, or irritated skin. Do not use reishi with pregnant or lactating women.

Dosing: The effective dose for reishi has not been well established by human clinical trials, although a wide variety of animal studies have been carried out. A dose of 6 to 12 g/day of powdered fungus has been recommended.[19]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    REISHI MUSHROOM

RHODIOLA

DATE OF ISSUE: FEB 2004

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Rhodiola rosea* L. Family: Crassulaceae (stonecrops)

COMMON NAME(S): Golden root, roseroot, arctic root

BOTANY: *Rhodiola rosea* is a perennial plant with a thick rhizome and yellow, fragrant flowers. It grows in sandy soil at high altitudes in the arctic areas of Europe and Asia, including eastern Siberia. The plant reaches a height of 30 to 76 cm. Unique compounds set *R. rosea* apart from the other *Rhodiola* species.[1]

HISTORY: The Greek physician Dioscorides first recorded this plant in *De Materia Medica*, renaming it from *Rodia riza* to *Rhodiola rosea*, referring to the rose-like aroma of the freshly cut root. Linnaeus documented use of *R. rosea* as an astringent to treat hernia, leucorrhea, hysteria, and headache. For centuries, the plant has been used in Russia and Scandinavia, where the bulk of the research has been published. [1]

CHEMISTRY: Three cinnamyl alcohol vicianosides (eg, rosavin, rosin, rosarin) have been found to be specific to *R. rosea*.[2] Another report confirms these 3 substances along with rosiridin and salidroside to be the 5 marker compounds present to reliably identify *R. rosea*.[3] *R. rosea* extracts used in most clinical trials were standardized to a minimum of 3% rosavins and 0.8% to 1% salidroside because of this naturally occurring ratio in the plant. [1] The phenylethanol derivatives salidroside (rhodioloside) and tyrosol have been found in the underground part of the plants. [4] Flavonoids in *R. rosea* include rodiolin, rodinin, rodiosin, acetylrodalgin, tricin, and other catechins and proanthocyanidins. [1,5] Monoterpenes present include rosiridol and rosaridin. Triterpenes include daucosterol and betasitosterol. [1] Terpenes and volatile compounds have been isolated from *R. rosea* as well and include the essential oil components of monoterpene hydrocarbons, monoterpene alcohols and straight chain aliphatic alcohols, n-decanol, geraniol (responsible for the rose-like odor), linalool, nonanal, decanal, nerol, and cinnamyl alcohol. [6] Phenolic acids including chlorgenic, hydroxycinnamic, and gallic acids also are present. [1,5,7]

PHARMACOLOGY: Some traditional uses of *R. rosea* include the following: increasing physical strength and endurance, treating fatigue, depression, anemia, GI problems, infections, CNS disorders, fertility problems, cancers, aches, and pains. [1,8] *R. rosea* has been categorized as an adaptogen by Russian researchers, because of its ability to increase resistance to a variety of stressors. [5] Its use in Ayurvedic medicine for its marked adaptogenic properties has been studied. [9] *R. rosea* protected eggs of freshwater snail (*Lymnaea stacinalis*) against induced stressors, including heat shock and oxidative and heavy metal stress. For example, at least 90% of snail larvae preincubated with *R. rosea* survived vs 9% of control population.[10] Injections of the plant extract administered to rats prevented stress-induced elevations of beta-endorphins, ACTH, cortisol, insulin, thyroxin, and triiodothyronine. [11] Similarly, *R. rosea* given to rats increased swimming time up to 159% and improvement continued throughout the supplementation period.[12] Russian researchers conducted a double-blind, placebo-controlled study of the effects of *R. rosea* in foreign students during a stressful examination period. Improvement was seen in the treated group in the areas of physical fitness, mental fatigue, and neuromotor tests.[13] *Rhodaxon*, an adaptogen preparation based on *R. rosea* extract, was tested by the same authors in Russian high school students. It also demonstrated positive effects upon their physical and intellectual working capacity. [14] In a double-blind, crossover study of *R. rosea* extract administered to 56 young, healthy physicians experiencing fatigue during night duty, improvement was seen in overall levels of mental fatigue, including complex perceptive and cognitive cerebral functions.[15]

CNS activity of *R. rosea* has been reported. Earlier studies found the small and medium doses of the plant had stimulatory effects and larger doses had sedative effects.[1] In small and medium doses, it was confirmed by later studies that *R. rosea* stimulates norepinephrine, dopamine, serotonin, and nicotinic cholinergic effects in the CNS. It also enhances the effects of these neurotransmitters on the brain by increasing the permeability of the blood-brain barrier to precursors of dopamine and serotonin.[16,17,18] Improvement in learning and memory retention was observed in rats given certain doses of extract.[17,19] Closely related topics in the area of neurotransmitters include sleep studies. Improved sleep patterns were demonstrated under the area of "adaptogenic effects." [13,14,15] In addition, *Rhodiola* was effective in modulating sleep architecture and improving sleep quality in men living at high altitudes. [20] All of these studies collectively suggest *R. rosea's* usefulness in increasing energy and decreasing mental fatigue.

Other areas in the CNS where *R. rosea* may be of benefit include cerebral circulation [21] and psychoses. Psychostimulant effects of *R. rosea* were studied in 53 healthy patients and 412 with neuroses and asthenic syndromes. Fatigue, lack of appetite, irritability, and other symptoms responded favorably to *R. rosea* 50 mg doses 3 times/day.[22] In a 128-patient study, *R. rosea* alleviated fatigue, distractibility, headache, and other vegetative symptoms in 64% of cases. [23] In schizophrenic patients whose anticholinergic medications failed to relieve parkinsonian symptoms, *R. rosea* was found to be of benefit.[22,23]

The usefulness of *R. rosea* as an antioxidant and anticarcinogenic agent has been demonstrated in a number of studies. Several antioxidant compounds have been identified in the plant. These include p-tyrosol, organic acids, and flavonoids. Free-radical scavenging activity has been shown for alcohol and water extracts of *R. rosea*.[7] *Rhodiola* therapy may protect hypoxia-induced pancreatic injury by its antioxidant activity. [24] *R. rosea* as adjuvant therapy with cyclophosphamide potentiated antitumor and antimetastatic effects in mice with lung carcinoma.[25] A decrease in cyclophosphamide hepatotoxicity by *R. rosea* extract in mice tumor also was observed.[26] *R. rosea* inhibited tumor dissemination in mice in another report. [27] Several studies, also from the same authors, confirm the ability of *R. rosea* to exert anticarcinogenic actions and include the following: *R. rosea* inhibits growth rate of Ehrlich tumor and Pliss lymphosarcoma,[28] protects myelopoietic tissue from cyclophosphamide toxicity,[29] alters functional activity of murine bone marrow cells,[30] inhibits adenocarcinoma growth,[31] and demonstrates activity in cancer cells.[32] *R. rosea* extracts are antimutagens because of their ability to raise efficiency of intracellular repair mechanisms. [33] *R. rosea* extract administration improved certain parameters in superficial bladder carcinoma in a 12-patient study. [34]

Cardiac protection is another effect of *R. rosea*. One report found *R. rosea* to prevent stress-induced cardiac damage. It also prevented the decrease in adrenal catecholamines during stress. Several articles from the same authors investigated antiarrhythmic effects of *R. rosea* extract in animal models.[35,36,37,38,39,40] This effect may be due to an ability to induce opioid biosynthesis, [35] and may be related to stimulation of peripheral kappa-opioid receptors. [36,37] Rats pretreated with *R. rosea* did not experience a decrease in cardiac contractility leading to stability in contractility of heart tissue after cold stress was induced. [41]

Other effects of *R. rosea* include the following: increase in fertility maturation markers such as follicular growth and uterine lining proliferation in mice, [42] restoration of normal menses in 25 of 40 women suffering from amenorrhea,[42] improvement in 26 of 35 men with erectile dysfunction and/or premature ejaculation given *R. rosea* 150 to 200 mg/day for 3 months,[43,44] and efficacy of the plant to treat odontogenic inflammatory disease. [45]

TOXICOLOGY: *R. rosea* has a very low level of toxicity in rats. The LD_{50} was calculated to be approximately 3.4 g/kg (equal to 235 g in a 70 kg person). [46] Clinical doses are commonly 200 to 600 mg/day.[1] *R. rosea* was reported safe in acute and subacute toxicity studies. [9] No side effects were reported in a 56-patient study.[15] Data on safety and appropriateness of *R. rosea* in pregnancy and lactation are lacking.[5]

SUMMARY: *R. rosea's* name is derived from the rose-like aroma of the freshly cut roots. Traditionally, the plant has been used to increase physical strength and endurance. Modern studies have confirmed the plant's traditional uses, as it has the ability to increase resistance to a variety of stressors, thus, being categorized as an adaptogen. Several animal and human studies support its ability to improve stress-induced factors, including alleviation of fatigue, increase in physical and intellectual working capacity, and relief of irritability. *R. rosea* also has been shown to possess antioxidant and anticarcinogenic effects. Several animal studies are available confirming reduction in tumors, as well as protective effects seen in a variety of cancers. Cardioprotective and antiarrhythmic actions also have been

associated with *R. rosea*. Few or no side effects or toxicity have been reported from the plant.

PATIENT INFORMATION— Rhodiola

Uses: Limited clinical studies have confirmed *R. rosea's* ability to treat fatigue, depression, anemia, GI problems, infections, CNS disorders, fertility problems, cancers, aches, and pains. *R. rosea* also may possess antioxidant and anticarcinogenic effects.

Side Effects: Few or no side effects have been reported.

Dosing: Because the ingredients are not standardized, dosing recommendations cannot be made.

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Document Bibliographic Information:

- **Location In Book:**

- THE REVIEW OF NATURAL PRODUCTS (2004)
  "R" MONOGRAPHS
  RHODIOLA

RHUBARB

DATE OF ISSUE: JUN 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Rheum officiale* Baillon, *R. palmatum*, and *R. palamtum var. tanguticum* are the most commonly used *Rheum*species for medicinal purposes.[1] Family: Polygonaceae.

COMMON NAME(S): Rheum, rhaptonic, Chinese rhubarb,[1] da-huang, ta-huang,[2] radix et rhizoma rhei, Turkey rhubarb.[1]

BOTANY: Rhubarb is derived from the *Rheum*species. The perennial herb has a conical rootstock, which is fleshy and yellow inside and produces large, cordate, 7-lobed leaves 30 to 46 cm long.[2]

There are approximately 60 species of the Polygonaceae family recorded in the world and 40 Chinese *Rheum* species.[3] At least 18 species possess medicinal properties.[4]

Medicinal rhubarb consists of the dried rhizome and root of *R. officiale* Baillon or *R. palmatum*; of related species/hybrids grown in China (Chinese rhubarb); or of *R. emodi* or *R. webbianum*native to India, Pakistan, or Nepal (Indian rhubarb).[5] It is not common garden rhubarb, which is relatively inactive.

HISTORY: Rhubarb was first recorded and rated as one of the inferior category remedies in the oldest Chinese herbal books, 22 to 250 AD.[4] In the 1780s, the active constituents responsible for the root's cathartic action and astringency were still unknown. Initially, researchers learned that the medicinal root came from several varieties or species of rhubarb. By the end of the 19th century, it became clear that the particular medicinal characteristics of rhubarb were also affected by conditions under which the roots grew, such as soil composition and climate.[1]

Rhubarb has been used medicinally in Europe since the time of Marco Polo. The herb was brought via the eastern Mediterranean, by way of the Silk Route, from China across central Asia. The first reported sighting of the plant *in situ* was in the mountains of Bulgaria. In 1731, a Rhubarb Commission was set up at the Mongolian border to import the best possible root at a fixed price. At the same time, the British East India Company secured their positions in Chinese ports. Both companies supplied Europe.[1]

Rhubarb emerged as a "culinary delight," especially in Britain and the United States, in the 1830s and 1840s.[1]

CHEMISTRY: The *Rheum* species contains a number of anthraquinone derivatives. The free form anthraquinones —emodin, aloe-emodin, physcion, and chrysophamol—are present in nearly all species. Sennosides, responsible for the purgative action, are restricted to *R. palmatum*.[3,4]

Oxalic acid is present in the leaf blades.[2]

PHARMACOLOGY: Rhubarb was once widely used as a laxative; it is more potent than cascara or senna. However, use almost always causes intestinal grippe or colic. For this reason, it is seldom employed as a laxative today and cannot be considered the herb of choice.[2]

A number of additional properties have been reported in the literature. Unfortunately, most of the clinical trials are small and poorly designed. In some cases a number of different herbs are administered at the same time, making it difficult to determine which herb produced the outcome under investigation. Despite this, rhubarb has a strong role in traditional Chinese herbal therapy.

The anthraquinone derivatives of *R. emodi*and *R. palmatum* have been used as antifungal[6] and molluscicidal[7] agents, respectively. Rhein isolated from *R. officiale* has been reported to have significant antimicrobial activity against *Bacteroides fragilis*.[8] It also has been suggested that rhubarb has antiplatelet properties.[9] Some authors have claimed improvement of memory in senile patients.[10]

Initial experiments with rhubarb using rats have shown a reduction in inflammation and edema of injured lung tissue,[11] modulation of intestinal proglucagon expression, and possible glucose homeostasis.[12]

Renal effects: Use of *Rheum* in patients with elevated serum creatinine has been reported to prevent progression of chronic renal failure (CRF). Thirty patients were randomly allocated to receive 6 to 9 g/day of Rheum E (an oral extract of *Rheum*), 25 mg of captopril 3 times a day, or *Rheum*plus captopril. An additional 12 control patients received neither treatment. Allocation to either *Rheum* or captopril produced a slower progression to CRF when compared with controls.[13] A second study investigated the effects of rhubarb plus other herbs in 50 inpatients with CRF. Although the study was poorly designed, the authors claimed a beneficial outcome and proposed a mechanism for rhubarb's efficacy. After absorption from the GI tract, rhubarb's constituents inhibit protein decomposition, accelerate the reutilization of certain amino acids, and reduce the formation of free radicals.[14] Retention enemas also have been employed to deliver rhubarb. It is proposed that the strong purgative effect combined with increased peristalsis of the large intestine causes excretion of toxins. In a third clinical trial, 20 patients were treated with rhubarb, diluted to 600 to 800 mL and administered as a retention enema, once or twice a day. In those with only moderately increased serum creatinine, rhubarb reduced uremic symptoms and reduced blood urea nitrogen.[15] A number of studies have observed the effects of rhubarb in rats with CRF. Low molecular weight tannins purified from rhubarb produced an increase in glomerular filtration rate.[16] Additionally, rhubarb extract has been reported to diminish proteinuria.[17,18]

Lipid-lowering effects: Rhubarb appears to be a potential source of dietary fiber with a lipid-lowering effect. Giving mice a cholesterol-enriched diet for 4 weeks while feeding with rhubarb stalk fiber (*R. rhaponticum*) resulted in lower plasma concentrations of cholesterol and trigylcerides when compared with feeding with cellulose fiber.[19,20] Treating hypercholesterolemic men with the same regimen lowered serum total cholesterol (8%) and low-density lipoproteins (9%), while high-density lipoproteins remained unchanged.[21] It has been proposed that rhubarb (*rhei rhizoma*, *R. palmatum*) exerts its effects on cholesterol by inhibition of squalene epoxidase.[22] This enzyme is thought to catalyze the rate-limiting step in cholesterol biogenesis.

GI effects: Rhubarb is known to increase peristalsis of the colon without affecting the peristaltic movement of the stomach and duodenum. Thus, in cases of GI bleeds, it may be able to eliminate extravasated blood. Additionally, constriction of the blood vessels promotes hemostasis. One study investigated these effects of rhubarb on upper GI bleeding.[23] Rhubarb powder, administered at a dose of 3 g every 6 to 12 hours, was found to be effective in approximately 95% of cases (n = 400). The same investigators then compared rhubarb with "Western medicine" (eg, magnesium-aluminium compound orally, norepinephrine IM, PAMBA IV). Sixty patients were enrolled in the study; 30 were given rhubarb and 30 "Western medicine." In rhubarb recipients, the disappearance of occult blood occurred 5 days earlier than in those treated with "Western medicine."

Hypotensive effects: In a small study of 29 patients with persistent high blood pressure (more than 180/90 mmHg) a combined herbal preparation of *R. officinale*, *Coptis teeta*, and *Scutellaria baicalensis* was administered at a dose of 500 mg every 8 hours. The herbal combination was compared with placebo in a crossover trial. Systolic blood pressure was lowered 27 mmHg and diastolic 20 mmHg. However, it was not determined which of the ingredients in this formulation provided the antihypertensive effects.[24]

Neonatal jaundice: *R. officinale* has been used by the Chinese to treat neonatal jaundice. It has been suggested that the mechanism of action is an effect of laxative properties that interrupt the enterohepatic circulation of bilirubin. However, the main cathartic component of rhubarb is sennoside A, which must be converted to sennidine by the colonic bacteria for effect. Newborns have no gut flora during the first few days of life, so this hypothesis is questionable.[25]

INTERACTIONS: With long-term overuse, rhubarb can increase the toxic effects of the cardiac glycosides, and an effect on antiarrhythmics is possible because of the loss of potassium. Potassium deficiency can be increased by concurrent use of thiazide diuretics, corticosteroids, or licorice root. Additionally, deceased intestinal transit time may reduce the absorption time of orally administered drugs.[26]

TOXICOLOGY: The leaf blades (but not the stalks) of rhubarb contain enough oxalic acid to cause poisoning.[2] Localized oxalosis has been noted from a case report of 1 male patient. It appears that a small amount of rhubarb adhered to the wall of the tracheobronchial tree and produced a localized area of oxalosis with accompanying necrosis.[27]

SUMMARY: Rhubarb has been used as a laxative agent since the 1700s. However, since then this role has been superseded by other less aggressive agents such as senna. Rhubarb has been proposed to have other properties, including renal, GI, lipid-lowering, antibiotic, and antihypertensive effects. However, no conclusive evidence is available to support any of these claims. Despite this, rhubarb is widely used in traditional Chinese herbal therapies.

PATIENT INFORMATION — Rhubarb

Uses: Laxative agent.

Interactions: Interaction with cardiac glycosides (digoxin) and a reduction in the absorption of orally administered drugs when rhubarb is taken in large quantities.

Side Effects: Intestinal grippe and colic.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    RHUBARB

ROSE HIPS

DATE OF ISSUE: JAN 1999

REPLACES MONOGRAPH DATED: SEP 1991

SCIENTIFIC NAME(S): Commonly derived from *Rosa canina* L., *R. rugosa* Thunb., *R. acicularis* Lindl. or *R. cinnamomea*L. Numerous other species of rose have been used for the preparation of rose hips. Family: Rosaceae

COMMON NAME(S): Rose hips, "heps," dog rose (R. canina)

BOTANY: Rose hips grow from a perennial plant, which can grow 3 to 5 meters in height. Their thorny branches give way to pink and white flowers and scarlet fruits, called "hips."[1,2] These rose hips are the ripe ovaries or seeded fruit of roses forming on branches after the flower. [3] They are approximately 1 to 2 cm long by 0.5 to 1.5 cm thick; oval in shape; and fleshy, shrunken, and wrinkled. Inside the hips are 3 or more small (3 to 5 mm), angular, yellow-brown seeds. [2] *R. canina*is native to Europe, North Africa, and temperate areas of Asia. The fruits (hips) are picked in autumn and used for the "drug."

HISTORY: Once used as a folk remedy for chest ailments, *R. canina* hips were popular in the Middle Ages.[1] They are a natural source of vitamin C, which has led to their widespread use in natural vitamin supplements, teas, and various other preparations including soups and marmalades. [4] Although these products have been used historically as nutritional supplements, they have also been used as mild laxatives and diuretics. [5] Rose hip syrup was used as a nourishing drink for children. [1] It was also used to flavor teas and jams.[2]

CHEMISTRY: Fresh rose hips contain 0.5% to 1.7% vitamin C,[4] usually determined as a combination of l-dehydroascorbic acid and l-ascorbic acid. [6] However, the content of dried, commercially available rose hips products varies considerably. One report evaluates stability of vitamin C, using photometry and thin layer chromatography (TLC). Results showed that loss of vitamin C was dependent on "degree of coarseness" of rose hips. Fruits cut in half lost less than 50% vitamin C in 18 months storage, while ground drug lost 100% in 6 months.[7]

While some accounts suggest that rose hips are the richest natural source of vitamin C, a number of more concentrated sources have been identified. Citrus fruits contain approximately 50 mg vitamin C per 100 g; uncooked broccoli, kale, and kiwi fruit, approximately 100 mg; black currants, guavas, and some tropical vegetables, 200 to 300 mg; rose hips (*Rosa canina*), 1250 mg; acerola or Barbados cherry (*Malpighia punicifolia*), 1000 to 2330 mg; and *Terminalia ferdinandiana*, up to 3150 mg.[8]

Rose hips also contain vitamins A, B_1, B_2, B_3, and K. Other ingredients include pectin (11%), tannins (2% to 3%), malic and citric acids, flavonoids, red and yellow pigments, especially carotenoids, polyphenols, invert sugar, volatile oil, vanillin, and a variety of minor components.

PHARMACOLOGY: Vitamin C is used as a nutritional supplement for its antiscorbutic properties. Use of rose hips for their vitamin C content, in supportive therapy for cases of this vitamin deficiency is rational.[2] Because a significant amount of the natural vitamin C in rose hips may be destroyed during drying and processing, many "natural vitamin supplements" have some form of vitamin C added to them. One must read the label carefully to determine what proportion of the vitamin C is derived from rose hips vs other sources. Unfortunately, this information is not always available on the package label. However, when freshly consumed, rose hips have extremely high levels of vitamins in a form readily absorbed by the body.

A small pediatric population with osteogenesis imperfecta received ascorbic acid from rose hips, 250 to 600 mg/day for 10 to 42 months. Eight of 13 patients showed a decrease in number of fractures vs control, suggesting a positive outcome of vitamin C supplementation in this specific disease. [9]

Rose hips' effects have been evaluated on blood glucose levels in rabbits. No significant changes in levels were reported. [10]

The laxative activity of rose hips may be related to the presence of malic and citric acids, to purgative glycosides (multiflorin A and B), [11] or to pectin content in the plant.[2] Rose hips have also been used for diuretic actions, to reduce thirst, and to alleviate gastric inflammation. [1] Its diuretic action has been disputed.[2]

TOXICOLOGY: Rose hips ingestion is not generally associated with toxicity. More than 100 g of plant material would have to be ingested to obtain a 1200 mg dose of vitamin C, an impractical amount to ingest. Most people do not have any side effects from ingesting small quantities of the plant. Adverse effects associated with the long-term ingestion of multi-gram doses of vitamin C (ie, oxalate stone formation) have not been reported with rose hips. [12] *The German Commission E Monographs* lists risks of rose hips as "none known."[2] However, production workers exposed to rose hips dust have developed severe respiratory allergies, with mild-to-moderate anaphylaxis.[3] One report describes a German ground rose hips product sold as "itching powder" in novelty shops. The fibers of the plant seem to provoke itch and prickle sensations not by allergic means, but by mechanical irritation, similar to those of wool. [13]

SUMMARY: Rose hips are a pleasant-tasting source of natural vitamin C. Because the concentration of the vitamin is relatively low, one must ingest large amounts of the product to serve as a nutritional supplement. Many natural rose hips products are fortified with ascorbic acid. Rose hips also contain other vitamins and may be used as supplementation for deficiencies. Rose hips are not generally associated with toxicity.

PATIENT INFORMATION — Rose Hips

Uses: Rose hips provide vitamin C supplements. Rose hips have been used for diuretic actions, to reduce thirst, to alleviate gastric inflammation, and to flavor teas and jams.

Side Effects: There have been no reported side effects except in those exposed to rose hips dust who have developed severe respiratory allergies.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    ROSE HIPS

ROSEMARY

DATE OF ISSUE: MAY 2000

REPLACES MONOGRAPH DATED: FEB 1992

SCIENTIFIC NAME(S): *Rosmarinus officinalis* L. Family: Labiatae or Lamiaceae.

COMMON NAME(S): Rosemary, Old Man

BOTANY: Rosemary grows as a small evergreen shrub with thick aromatic leaves.[1] The plant has small pale-blue flowers that bloom in late winter and early spring. Although rosemary is native to the Mediterranean, it is now cultivated worldwide.[2,3] Other types of rosemary include bog rosemary (*Andromeda* species) and wild or marsh rosemary (*Ledum palustre* L.).

HISTORY: Rosemary is a widely used culinary spice. Tradition holds that rosemary will grow only in gardens of households where the "mistress" is truly the "master."[4] The plant has been used in traditional medicine for its astringent, tonic, carminative, antispasmodic, and diaphoretic properties. Extracts and the volatile oil have been used to promote menstrual flow and as abortifacients.[4,5] Rosemary extracts are commonly found as cosmetic ingredients and a lotion of the plant is said to stimulate hair growth and prevent baldness.[6]

Historical reports regarding the therapeutic use of rosemary as a medicinal plant are available.[7,8] Rosemary is one of the oldest known medicinal herbs, having been used centuries ago to enhance mental function and memory.[9]

CHEMISTRY: The leaves contain 0.5% to 2.5% of volatile oil. The major components of the oil include monoterpene hydrocarbons (alpha and beta-pinene), camphene, limonene, camphor (10% to 20%), borneol, cineole, linalool, and verbinol. Rosemary contains a wide variety of volatile and aromatic components. Flavonoids in the plant include diosmetin, diosmin, genkwanin, luteolin, hispidulin, and apigenin.[1,4,10] One analysis reports 3 new flavonoid glucuronides, also found in the leaves.[11] Other terpenoid constituents in rosemary include triterpenes oleanolic and ursolic acids and diterpene carnosol.[10] The concentration of phenolic diterpenes in certain commercial rosemary extracts has been determined by HPLC.[12] Phenols in rosemary include caffeic, chlorogenic, labiatic, neochlorogenic, and rosmarinic acids.[10] Rosemary contains high amounts of salicylates.[13]

PHARMACOLOGY: Rosemary is a known antimicrobial agent. The powdered leaves are used as an effective natural flea and tick repellent.[14] Rosemary oil possesses marked antibacterial, antifungal, antimold, and antiviral properties.[9,10] Activity against certain bacteria including *Staphylcoccus aureus*, *S. albus*, *Vibrio cholerae*, *Escherichia coli*, and *Corynebacteria* has been observed.[10] Rosemary oil was found to be most active against "meat spoiling" gram-negative (eg, *Pseudomonas*) and gram-positive (eg, *Lactobacillus*) bacteria in 1 report.[15] The effect of rosemary on *Candida albicans* has been described.[16] Another report discusses growth inhibition of *Aspergillus parasiticus* by rosemary oil.[17] However, a report on the use of rosemary to treat head lice found it to be ineffective.[18]

There are numerous reports available evaluating rosemary's anticancer effects. The extract contains properties that induce quinone reductase, an anticarcinogenic enzyme.[19] Other anticancer mechanisms include polyphenol constituents that inhibit metabolic activation of procarcinogens by Phase ? enzymes (P450), and induction of the detoxification pathway caused by Phase ?? enzymes (glutathione S-transferase).[20] Dietary supplementation of laboratory animals with 1% rosemary extract resulted in a 47% decrease in the incidence of experimentally-induced mammary tumors compared to controls.[21,22] This extract was found to enhance activities of enzymes that detoxify reactive substances in mouse liver and stomach.[23] Skin tumors in mice have been inhibited by application of rosemary extract to the area.[24] Rosemary increased detoxification of carcinogens in human bronchial epithelial cells as well.[25] Rosemary diterpene, carnosic acid, exhibited strong inhibitory effects against HIV-protease.[26]

Several reports exist concerning rosemary's antioxidative actions.[27,28,29,30,31] Carnosol and carnosic acid have been reported to account for more than 90% of the antioxidant properties of rosemary extract. Both are powerful inhibitors of lipid peroxidation and are good scavengers of peroxyl radicals.[32,33] Antioxidant activity depends directly on concentration of diterpenes such as these.[12] Rosemary antioxidants have less scavenging potential than green tea polyphenols but have more potential than vitamin E.[34]

Various reports involving other actions of rosemary include spasmolytic actions in smooth and cardiac muscle, alteration of complement activation,[10] liver effects,[35] immune effects,[36] aromatherapy for chronic pain treatment,[37] inhibition of adult respiratory distress syndrome in rabbits,[10] reduction of capillary permeability,[4] and antigonadotrophic activity in mice.[10] Rosemary may also reverse headaches, reduce stress, and aid in asthma and bronchitis treatment.[9] Rosemary inhibits uterotropic actions of estradiol and estrone by 35% to 50% vs controls.[38] Rosemary's pharmacology has been reviewed.[39]

TOXICOLOGY: Although the oil is used safely as a food flavoring and the whole leaves are used as a potherb and spice, ingestion of large quantities of the oil can be associated with toxicity.[40] Toxicity from the oil is characterized by stomach and intestinal irritation and kidney damage.[4] Although rosemary oil is irritating to rabbit skin, it is not generally considered to be a sensitizer for human skin. However, preparations containing the oil may cause erythema, and toiletries can cause dermatitis in sensitive individuals.[1,6,10] Allergic contact dermatitis from rosemary has been reported.[41] A case report discusses contact dermatitis in a 56-year-old man reacting to carnosol, the main constituent in a rosemary preparation.[42]

At least 3 case reports concerning toxic seizures associated with rosemary exist. The plant's monoterpene ketones are powerful convulsants with known epileptogenic properties.[43]

Certain molds may grow on rosemary.[44]

A case of occupational asthma caused by rosemary has been reported.[45]

Rosemary extract may possess an anti-implantation effect as seen in rat experimentation.[46] The plant is a reported abortifacient, and also affects the menstrual cycle.[10]

SUMMARY: Rosemary is a popular herb and widely used culinary spice. It has antimicrobial actions against a variety of bacteria, fungi, mold, and viruses. Its anticancer effects have been numerously reported and include inhibition of skin tumors, mammary tumors, and others. Rosemary has antioxidative actions. Certain constituents scavenge peroxyl radicals and detoxify harmful products. Other effects of rosemary include spasmolytic actions, liver and immune effects, and various actions from asthma treatment to aromatherapy. Allergic contact dermatitis has been associated with the plant, but rosemary is not generally considered to be a human skin sensitizer. Rosemary's constituents, monoterpene ketones, are convulsants, and have caused seizures in large doses. Rosemary is also an abortifacient.

PATIENT INFORMATION — Rosemary

Uses: Rosemary has been reported to decrease capillary permeability and fragility. Extracts have been used in insect repellents. The plant may have anticancer properties and has spasmolytic actions, liver and immune effects, and other various actions from asthma treatment to aromatherapy. It has antimicrobial actions against a variety of bacteria, fungi, mold, and viruses.

Side Effects: Ingestion of large quantities of rosemary can result in stomach and intestinal irritation and kidney damage. Allergic contact dermatitis has been associated with the plant, but rosemary is not generally considered to be a human skin sensitizer. Rosemary's constituents, monoterpene ketones, are convulsants, and have caused seizures in large doses. Rosemary is also an abortifacient.

Dosing: Rosemary leaf was approved for dyspepsia, high blood pressure, and rheumatism by the German Commission E at doses of 4 to 6 g/day. The essential oil has been used at doses of 0.1 to 1 mL.[47]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    ROSEMARY

ROYAL JELLY

DATE OF ISSUE: MAR 1992

REPLACES MONOGRAPH DATED: JUL 1986

SOURCE: Royal jelly is a milky-white secretion produced by worker bees of the species *Apis mellifers* L. to induce differentiated growth and the development of the queen bee. Queen bees are fed mostly royal jelly. Because of this specialized nutrition, queen bees differ from workers in several ways; the queens are about twice the size, they lay about 2000 eggs a day (female worker bees are infertile) and they live 5 to 8 years (about 40 times longer than worker bees).

HISTORY: These differences have led to the marketable assumption that ingestion of this product will do as much for humans as it does for bees; that is, increase size, improve fertility and enhance longevity. Royal jelly has also been sold as a skin tonic and hair growth stimulant. [1]

CHEMISTRY: Royal jelly is a complex mixture of proteins (12%), sugar (12%), fats (6%) and variable amounts of minerals, vitamins [2] and pheromones. About 15% of royal jelly is 10-hydroxy-trans-(2)-decanoic acid (HDA), [3] which is thought to play an important role in bee growth regulation. The product is rich in B vitamins, the most abundant of which is pantothenic acid. [1]

PHARMACOLOGY: The jelly has been found to possess antitumor activity in experimental mouse leukemias. [4] HDA has slight, pH-dependent antimicrobial activity; the compound is 25% less active than penicillin and 20% less active than chlortetracycline. [5]

There is no evidence that royal jelly has estrogenic activity or that it affects growth, longevity or fertility in animals. [6] In terms of revitalizing dried skin, the results from one 3-month study of 24 women noted that 10 showed improvement, 10 had no change and 4 showed symptoms of skin irritation. [1]

Despite these pharmacologic actions, there is little strong clinical evidence for any beneficial effects in man. [7]

TOXICOLOGY: Other than skin irritation, there are no reports of toxicity. Because some persons have reported allergic reactions to other bee products such as bee pollen, the potential for these events with royal jelly should be kept in mind. However, there have not been significant reports of allergic reactions with this product.

SUMMARY: Lyophilized royal jelly is sold in 100 mg capsules (50 capsules for more than $10) and is incorporated into topical creams and ointments. It is an adequate but expensive source of certain B vitamins. It does not possess recognizable preventive, therapeutic or rejuvenatory characteristics.

PATIENT INFORMATION— Royal Jelly

Uses: Royal jelly has been used in topical creams and ointments.

Side Effects: Royal jelly has caused some allergic reactions.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    ROYAL JELLY

RUE

DATE OF ISSUE: JUL 1997

REPLACES MONOGRAPH DATED: JUL 1989

SCIENTIFIC NAME(S): *Ruta graveolens* L., *R. montana* L. and *R. bracteosa*L. have also been reported to be used medicinally. Family: Rutaceae

COMMON NAME(S): Rue, common rue, garden rue, German rue. Not to be confused with meadow rue (*Thalictrum* spp.)

BOTANY: Rue is native to Europe but is now cultivated worldwide. It is often found growing along roadsides and in waste areas. It is an herbaceous evergreen half-shrub that grows to 2 or 3 feet tall. The leaves have three fleshy lobes and are "teardrop"-shaped. It blooms greenish-yellow flowers from June to August. The flowers have a characteristically disagreeable odor. The aerial parts, which are gathered in the summer, are used. The plant is both ornamental and medicinal. [1]

HISTORY: The leaves, other parts, and extracts of rue have been used for hundreds of years as insect repellents and, in folk medicine, as antispasmodics, sedatives and stimulants for the onset of menses. Depending on the local culture, rue extracts have been used as abortifacients. [2]

In New Mexico, rue is used traditionally as a tisane for ailments such as stiff neck, dizziness, headache, tightness in the stomach and inner ear problems. The oil has a strong bitter taste and was once used for the treatment of intestinal worms.

Roman naturalist Pliny the Elder (23 to 79 AD) mentions 84 remedies containing rue. [3] In ancient Greece and Egypt, aside from its use as an abortifacient, rue was also used to strengthen eyesight. [1]

CHEMISTRY: Rue has been studied extensively and has been found to contain a large number of chemical components. [4] Common rue contains a mixture of furoquinoline alkaloids in a concentration of approximately 1.5%, the most important of which appear to be arborine, arborinine and gamma fagarine. [5,6]

The acridone alkaloids (rutacridone epoxide, hydroxyrutacridone epoxide) are found in greatest concentration in the roots. [7] Other alkaloids include graveoline, graveolinine, kokusaginine, rutacridone and skimmianine. Flavonoid rutin is also present in the plant and is said to support and strengthen blood vessels, reducing pressure.[1,3]

A volatile oil is present in a concentration of approximately 0.1%. The oil is 90% methyl-nonylketone with the balance composed of related ketones, esters and phenols.[8]

The plant and its oil are rich in coumarin derivatives that appear to contribute significantly to the pharmacologic activity of the plant. These furocoumarins include bergapten, psoralen, xanthoxanthin, xanthotoxin, isopimpinellin and rutamarin. [1,3,9] Isolation of such furocoumarins has been performed using an improved extraction technique.[10] A new coumarin, "exo-dehydrochalepin" has been synthesized from rutamarin.[11] Other reports have described: Isolation of alkaloid isogravacridonchlorine from rue roots;[12] identification of dihydropyrano and dihydrofuro;[2,3,4,5,6] quinolinium alkaloids;[13] and purification of acridone synthase from rue cell cultures.[14]

PHARMACOLOGY: The rue plant and its extracts, in particular the tea and oil, have been reported to have antispasmodic effects on smooth muscles. This pharmacologic action has been attributed to the alkaloids arborine and arborinine and to the coumarins, in particular rutamarin. One study found the spasmolytic effect of arborinine on pig coronary muscle to be as potent as that of papaverine, while rutamarin was 20-fold more potent than papaverine. The antispasmodic effects of these compounds were reversible. While the pharmacologic half-life of arborinine was about the same as for papaverine, that of rutamarin was approximately 20 times longer. These spasmolytic effects were also observed in isolated gastrointestinal smooth muscle. [4]

A report studies *R. graveolens* extract as a potential potassium channel blocker on ionic currents in myelinated nerve cells. [15] Rue has been used to treat many ailments including epilepsy, eye strain, multiple sclerosis, Bell's palsy, heart conditions and as a uterine stimulant to encourage onset of menstruation. [1,3]

There are many references to the abortifacient effects of rue teas and oil. The abortifacient effect may be due to an anti-implantation action [2] or to a generalized state of systemic toxicity resulting in fetal death.[8] Antifertility action of *R. graveolens* has been reported in rats.[16,17] In one report, Chalepensin was found to be the active component, acting at early stages of pregnancy.[16]

More than 15 compounds have been identified that have significant in vitro antibacterial and antifungal activity. [6] The acridone alkaloids are the most potent antimicrobial compounds; the coumarins resulted in growth inhibition only at higher doses. The essential oil and flavonoids tested did not show significant activity. Other researchers have found that a number of components of rue interact directly with DNA replication, thereby preventing the propagation of some viruses. [18] The leaf of rue is said to alleviate cancer of the mouth, tumors and warts. In Chinese medicine, rue is used as a vermifuge and for insect bites. [1,3]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Because the antispasmodic effect of this plant occurs at relatively small doses, rue should only be taken with caution, if at all. The safety of the plant in pregnant women has not been established and most of the literature describing its potential abortifacient effects indicate that the plant should never be ingested by women of childbearing potential. [1,3]

Extracts of rue have been found to be mutagenic in experimental mutagenicity screens, but the clinical importance of these findings has not been established. [19,20]

The furocoumarins have been associated with photosensitization, resulting in skin blistering following contact and exposure to sunlight. This occurs in people who collect fresh rue and has been reported in those who rubbed fresh rue on themselves as an insect repellent. The toxicity of the dried leaves is most likely less than for fresh leaves because of the loss of volatile oil. [21,22] A tincture of *R. graveolens* L. exhibited marked photomutagenicity of varying degrees based on different alkaloid concentrations present in the compound.[23]

The volatile oil has an irritant quality and may result in kidney damage and hepatic degeneration if ingested. [8]

Large doses (more than 100 ml of the oil or about 120 g of the leaves in one dose) can cause violent gastric pain, vomiting and systemic complications including death. A single oral dose of 400 mg/kg given to guinea pigs has been reported to be fatal because of hemorrhages of the adrenal gland, liver and kidney. However, an oral daily dose of 30 mg given to human subjects for 3 months did not result in abnormal hepatic function. [24]

SUMMARY: Rue is an odiferous herb that has been used in traditional medicine and noted in folklore for hundreds of years. It has been used as an antispasmodic, and recent studies indicate that several of its components are similar to or more potent spasmolytics than papaverine in their effects on gastrointestinal and cardiac smooth muscle. The oil has been used as a folkloric abortifacient, and the plant should not be ingested, especially by pregnant women. Many compounds present in the plant possess antibacterial and antifungal properties. Rue has been used to treat intestinal worms and to repel insects. The furocoumarins contained in the plant are photosensitizers, and the topical application of the plant should be avoided. Although rue continues to be found in some herbal remedies, its use should be avoided.

PATIENT INFORMATION— Rue

Uses: Rue extract is useful as a potential potassium channel blocker. It has been used to treat many neuromuscular problems and to stimulate menstruation onset. Because rue has an antispasmodic effect at relatively small dose, take with caution, if at all.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side effects: Rue extracts are found to be mutagenic and furocoumains have been associated with photosensitization. If ingested, the rue oil may result in kidney damage and hepatic degeneration. Large doses can cause violent gastric pain, vomiting and systemic complications including death. Because of possible abortifacient effects, the plant should never be ingested by women of childbearing potential.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "R" MONOGRAPHS
    RUE

"S" MONOGRAPHS

SAFFLOWER

DATE OF ISSUE: JUL 2003

REPLACES MONOGRAPH DATED: NOV 1992

SCIENTIFIC NAME(S): *Carthamus tinctorius L.* Family: Compositae

COMMON NAME(S): Safflower, American saffron, zafran, bastard saffron, false saffron, dyer's-saffron

BOTANY: Safflower is native to the Middle East and is widely cultivated throughout Europe and the US. This annual reaches heights of about 1 meter with a single, smooth, upright stem. Its shiny oval, spiny-edged leaves alternate around the stem. The plant produces profuse flowers of yellow to deep red color. Seeds are produced in August and are enclosed in a mass of down.

HISTORY: Although safflower is recognized primarily as a source of a healthy edible oil, its traditional uses have not focused on the oil. Rather, safflower was originally valued for the yellow and red dyes yielded by its flowers. These dyes had been used for centuries to color cosmetics and fabrics. The use of safflower extract to dye the wrappings of mummies has been reported.[1] Safflower had been used as a replacement for saffron, but lost its popularity because of its lack of taste. Traditional uses of safflower tea included inducing sweating and reducing fever. The oil has been used as a solvent in paints.

CHEMISTRY: Safflower oil is characterized by the presence of a high proportion of unsaturated fatty acids. These fatty acids include linoleic (76% to 79%), oleic (13%), palmitic (6%), stearic (3%), and other minor straight-chained fatty acids. [2,3]

PHARMACOLOGY: There is evidence that diets high in unsaturated and polyunsaturated fatty acids can reduce cholesterol levels, particularly those fractions associated with the development of atherosclerosis and cardiovascular disease.

Safflower oil consumption has been reported to have variable effects on plasma lipids. In an 8-week study of dietary supplementation with safflower oil, a significant increase in platelet linoleic acid was associated with an acute change in thromboxane B_2 levels. However, another 6-week study in 12 people reported no statistically significant change.[4]

An 8-week study found that dietary modification with safflower oil reduced total serum cholesterol levels from baseline by 9% to 15%, low-density lipoprotein cholesterol by 12% to 20%, and apolipoprotein B levels by 21% to 24%. It has also been reported, in a study in 41 healthy subjects, that actual cholesterol synthesis is lower during diets rich in safflower oil compared with diets rich in butter. This might be associated with lower production rates of apo B-containing lipoproteins. [5] However, there were no reports of changes from baseline in serum triglyceride levels, high-density lipoprotein cholesterol levels, or apolipoprotein A-I levels. [6] Other studies have shown inconsistent results.[7]

There is evidence that endothelial dysfunction is an early event in the development of atherosclerotic disease. It has been suggested that meals rich in olive and safflower oil containing high levels of lipid oxidation products increase postprandial serum triglycerides without affecting endothelial function. The findings suggest that relatively short-term use of these vegetable oils for frying may not adversely affect postprandial endothelial function. This appears to be in line with widespread recommendations that saturated fats be replaced by polyunsaturated or monounsaturated fats in diets aimed at reducing the risk of coronary heart disease. [8]

There is some suggestion from animal studies that a moderate dietary intake of the essential fatty acids of the type found in safflower oil may be required to maintain the integrity of central nervous system function.[9]

Although safflower oil is a rich source of linoleic acid, it requires the activity of delta 6-desaturate for its conversion to dihomo-gamma-linolenic acid (DHGA) and arachidonic acid. By contrast, evening primrose oil appears to be a more bioavailable source of fatty acids for the production of DHGA than safflower oil. [7]

N-(p-coumaroyl)serotonin (CS) is a potent antioxidant compound present in safflower oil. An in vitro study demonstrated that this compound exerts unique growth-promoting activity for mouse fibroblasts and human fibroblasts. The authors propose that the growth-promoting effect of CS may result from its antioxidative activity, because antioxidative activity and an inhibitory effect of CS on proinflammatory cytokine production from human monocytes were observed at similar doses. [10]

Apart from its use in modifying lipid profiles, safflower has had limited medical uses, having been employed as a laxative and to treat fevers. [1]

TOXICOLOGY: No clinically important toxicity has been associated with the ingestion of safflower oil.

SUMMARY: Safflower had been widely recognized as a source of dye. However, more recently, the beneficial properties of the high unsaturated fat content of its oil has resulted in the worldwide consumption of the oil in place of saturated fats. Although the results of clinical studies generally indicate that dietary supplementation with this oil can reduce serum cholesterol levels, the changes in lipid profiles may not be as important as previously suggested in terms of reducing the risk of cardiovascular disease.

PATIENT INFORMATION — Safflower

Uses: Safflower has been used as a dietary supplement to modify lipid profiles, to treat fevers, and as a laxative. Clinical information is very limited.

Side Effects: There are no known side effects.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SAFFLOWER

SAFFRON

DATE OF ISSUE: APR 1993

REPLACES MONOGRAPH DATED: JUN 1986

SCIENTIFIC NAME(S): *Crocus sativus* L. Family: Iridaceae

COMMON NAME(S): Saffron

BOTANY: True saffron is native to Asia Minor and southern Europe. Its blue-violet, lily-shaped flowers contain the orange stigmas (part of the pistil), which are collected to produce the spice saffron. The plant is a bulbous perennial, growing 6 to 8 inches in height. Mature stigmas are collected by hand during a short blooming season. Over 200,000 dried stigmas, obtained from about 70,000 flowers, yield one pound of true saffron. [1] Saffron commands as much as $30 per ounce in the American market.

True saffron should not be confused with American saffron (safflower, Indian safflower) *Carthamus tinctorius*L. (family Compositae) that is produced from the tubular florets and is lighter red than true saffron. The two often are used for the same purposes, and less expensive American saffron is sometimes used to adulterate true saffron.

HISTORY: Saffron has been widely used for flavoring food and as a dye for cloth where it continues to find use in underdeveloped countries and among back-to-basics artisans. Folkloric uses of saffron have included its use as a sedative, expectorant, aphrodisiac and diaphoretic. Anecdotal reports from the tropical regions of Asia describe the use of a paste composed of sandalwood and saffron as a soothing balm for dry skin.

CHEMISTRY: The stigmas of *C. sativus* are rich in riboflavin, a yellow pigment and vitamins. In addition, saffron contains crocin, the major source of yellowish-red pigment. A hypothetical protocrocin of the fresh plant is decomposed on drying into one molecule of crocin (a colored glycoside) and two molecules of picrocrocin (a colorless bitter glycoside). [2] Crocin is a mixture of glycosides: crocetin, a dicarboxylic terpene lipid, and alpha-crocin, a digentiobiose ester of crocetin. In addition, cis- and trans- crocetin dimethylesters have been identified. Similar compounds have been isolated from other members of the Iridaceae. A compound named gardenidin, obtained from gardenias, has been shown to be identical with crocetin. The characteristic taste of the spice is attributed to the glycoside picrocrocin. Following hydrolysis, the compound yielded glucose and safranal, the main odiferous constituent. The essential oil derived from saffron is a complex mixture of more than 30 components, mainly terpenes and their derivatives. [2]

PHARMACOLOGY: United States patents have been issued for the proposed use of crocetin in the treatment of skin papillomas, spinal cord injuries, hypertension and cerebral edema in cats. It also has been used to increase fermentation yields. In vitro, a concentrated saffron extract has been shown to limit the growth of experimental tumor colony cells by inhibiting cellular nucleic acid synthesis. [3] Orally administered saffron (200 mg/kg) has been shown to increase the lifespan of mice with a variety of intraperitoneally transplanted and topical cancers, [4,5] suggesting that the product may have the potential to act as an anticancer agent.

A German patent has been granted for a preparation that contains a mixture of opium, quinine and saffron, which is used in the prevention of premature ejaculation. An aqueous extract of the corm (underground bulb) in combination with salicylic acid and vegetable oils is said to restore hair growth in baldness and has been granted an Australian patent.

Perhaps the most poorly understood of saffron's actions is its ability to increase oxygen diffusion. Atherosclerosis may be initiated by hypoxia at the vascular wall, and this hypoxia may be due to a decreased rate of oxygen diffusion from the red blood cells. [6] A way to counteract such diffusion decreases would be to use a drug that increases oxygen diffusion in plasma. Although few compounds appear to do this, crocetin has been found to bring about an 80% increase in the oxygen diffusivity of plasma. [7] A patent has been issued for the use of crocetin to increase oxygen diffusion into solutions such as plasma (US Patent No. 3,788,468 Jan. 29, 1974). Crocetin binds strongly to serum albumin. [8]

Injections of crocetin in rabbits fed 1% cholesterol diets for four to five months have been found to decrease cholesterol and triglyceride levels. [6,7] Serum cholesterol levels were 50% lower in the crocetin-treated animals than in the controls. The triglyceride level of the crocetin group remained in the normal range while the controls increased by 2000%. Vascular (aortic) damage was much less severe in the rabbits that received crocetin. The mechanism for these effects is poorly understood.

Epidemiologic evidence suggests that the low incidence of cardiovascular disease in parts of Spain may be related to the liberal, almost daily consumption of saffron. Algae in Japanese diets may have a similar protective effect. [9] Limited data make it difficult to correlate the effects observed following crocetin injections in animals with the oral consumption of saffron in humans.

TOXICOLOGY: There is no evidence to support saffron's reported emmenagogue (induces or increases menstruation) or abortifacient effects. Large doses of the stigmas have been reported to act as sedatives, [1] and Duke cites fatalities that have occurred from the use of saffron as an abortifacient. [10] The saponin-containing corm is toxic to young animals. Nevertheless, saffron is not generally associated with toxicity when ingested in culinary amounts.

SUMMARY: Saffron is a widely used spice. It is one of the few natural compounds that increases oxygen diffusion in vivo. An association between a reduced incidence of cardiovascular disease and chronic saffron injection has been suggested, but well-designed demographic studies must be conducted to confirm this relationship. Other data suggest that saffron may possess antineoplastic activity.

PATIENT INFORMATION— Saffron

Uses: Saffron increases oxygen diffusion in vivo and may possess antineoplastic activity.

Side Effects: Saffron is generally not associated with toxicity when ingested in culinary amounts.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SAFFRON

SAGE

DATE OF ISSUE: AUG 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Salvia officinalis* L. (Dalmatian sage), *S. lavandulaefolia* Vahl. (Spanish sage). Although a large number of other species of Salvia have been cultivated, these two represent the most commercially important species. Family: Labiatae or Lamiaceae

COMMON NAME(S): Garden sage, true sage, scarlet sage, meadow sage

BOTANY: Sage is a small, evergreen perennial plant with short woody stems that branches extensively and can attain heights of 2 to 3 feet. [1] Its violet-blue flowers bloom from June to September. The plant is native to the Mediterranean region and grows throughout much of the world. This plant should not be confused with red sage or the brush sage of the desert.

HISTORY: Dried sage leaf is used as a culinary spice and as a source of sage oil, which is obtained by steam distillation. Traditionally, sage and its oil have been used for the treatment of a wide range of illnesses; the name *Salvia* derives from the Latin word meaning "healthy" or "to heal." [2,3] Extracts and teas have been used to treat digestive disorders, as a tonic and antispasmodic. The plant has been employed topically as an antiseptic and astringent, and has been used to manage excessive sweating. [4] Sage has been used internally as a tea for the treatment of dysmenorrhea, diarrhea, gastritis and sore throat. The dried leaves have been smoked to treat asthma. Despite these varied uses, there is little evidence that the plant exerts any significant pharmacologic activity. The fragrance of the plant is said to suppress the odor of fish. Sage oil is used as a fragrance in soaps and perfumes. It is a widely used food flavoring, and sage oleoresin is also used in the culinary industry.

CHEMISTRY: *S. officinalis* contains 1% to 2.8% of a volatile oil. The highly aromatic plant contains a wide variety of minor chemical constituents including picrosalvin, carnosol, salvin and related ethers, flavonoids, phenolic acids and salviatannin (a tannin that undergoes degradation to phlobaphenes upon storage). Sage oil contains alpha- and beta-thujones, which account for about half of the composition of the oil. [1]

The composition of Spanish sage oil differs somewhat, with variable amounts of camphor, cineol, limonene, camphene and pinene. [1,4] Sage oil is often adulterated by the addition of thujone derived from the leaves of *Juniperus virginiana* (red cedar).

PHARMACOLOGY: Sage extracts have been shown to have strong antioxidative activities, with labiatic acid and carnosic acid reported to be the active compounds. [1]

The phenolic acid salvin and its monomethyl ether have antimicrobial activity, especially against *Staphylococcus aureus*. [1]

Sage oil has antispasmodic effects in laboratory animals and this is likely related to its effect as a gastrointestinal antispasmodic. There is some evidence that sage oil may exert a centrally mediated antisecretory action; the carminative effect is likely due to the irritating effects of the volatile oil. [5]

TOXICOLOGY: Although sage oil contains thujone, the oil does not have a reputation for toxicity. The oil has been found to be nonirritating and nonsensitizing when applied topically to human skin in diluted concentrations. Spanish sage oil was also nonphototoxic when applied to mice and pigs. [1]

Cheilitis and stomatitis, however, have been reported in some cases following the ingestion of sage tea. [4] Others have reported that ingestion of large amounts of the plant extract may cause dry mouth or local irritation.

SUMMARY: Sage is a widely used, popular spice and sage oil is used in a variety of culinary applications. Although the plant has a long history of use in traditional medicine, there is little evidence that it provides any unique effects beyond those typically associated with other volatile oils (ie, antispasmodic, carminative). Although the oil contains thujone, there is no evidence of direct toxicity.

PATIENT INFORMATION — Sage

Uses: Sage has no proven medical effects, but may be antispasmodic and carminative.

Side Effects: The only side effects reported with the ingestion of sage include cheilitis, stomatitis, dry mouth, or local irritation.

Dosing: Sage leaves, apart from their culinary uses, have been recommended for dyspepsia, excessive sweating, and as a gargle in coughs and colds. Typical dosage is 4 to 6 g/day of the leaf. [6]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
      SAGE

SAME

DATE OF ISSUE: OCT 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): S-adenosylmethionine, S-adenosyl-L-methionine, ademetionine, ademetionine 1,4-butanedisulfonate, ADE-SD4.

COMMON NAME(S): SAMe, SAM

HISTORY: SAMe was discovered in Italy in 1952. Since that time, numerous clinical studies have been performed on its efficacy. [3] SAMe has been used in Europe, where it has been available by prescription since 1975, to treat arthritis and depression. It is available in the US as a supplement by several companies (eg, Natural Made, Pharmavite, GNC).[2,3]

CHEMISTRY: SAMe is found in all living cells. It is a naturally occurring molecule produced by a reaction between the amino acid methionine and ATP. SAMe acts as a substrate in many biological reactions and is the precursor of certain essential amino acids. [1,2] The commercial product is not a botanical, but a supplement or biochemical compound produced in yeast cell cultures. One manufacturing process describes its preparation through fermentation of yeast *Saccharomyces cerevisiae*, enriched by the Schlenk method in the presence of methionine.[1]

SAMe is involved in a number of biochemical reactions involving enzymatic transmethylation. It is a precursor of certain compounds, including the amino acids cysteine, taurine, and glutathione. SAMe is an initiator of 3 metabolic pathways in the human body: Transmethylation, transsulfuration, and polyamine synthesis. Transmethylation involves methyl-group transfer to other molecules, enabling them to proceed to certain anabolic or catabolic reactions. Transsulfuration involves a pathway resulting in sulfates and reduced glutathione, an important antioxidant, which provides sulfhydryl groups to bind to and detoxify certain compounds. Eighty-five percent of all transmethylation reactions occur in the liver. SAMe, after donating the methyl group, is converted to cysteine, which is important for synthesis of glutathione and other sulfur-containing compounds.[1,4]

Determination of SAMe using high performance liquid chromatographic (HPLC) has been reported. [5]

PHARMACOLOGY: The properties of SAMe have been studied in a variety of areas including the CNS, osteoarthritis, fibromyalgia, liver disorders, and others.

CNS: SAMe's uses in depressive disorders were first seen in the early 1970s. Shortcomings from trials around this time (varied dosages of SAMe, small number of patients enrolled, severity of depression variation, etc) eventually led to improvement in consistency, specifically the Hamilton rating scale, grouping similar patients. [4]

Studies indicate the importance of the methylation process in the brain. SAMe is known to be an important methyl donor for a wide range of substrates (eg, proteins, lipids, hormones, nucleic acids). SAMe has shown some value in psychiatry, particularly in depressive disorders. A meta-analysis of all studies comparing SAMe with either placebo or standard tricyclic antidepressants has shown SAMe to have greater efficacy than placebo and efficacy comparable to that of tricyclics. [6] An adequate supply of SAMe must be attained for normal CNS function. Vitamin B_{12} or folate deficiency decreases the levels of SAMe, which lowers serotonin levels associated with depression.[7] Low SAMe levels in the cerebrospinal fluid (CSF) of patients with neurological and psychiatric disorders (eg, Alzheimer's disease, spinal cord degeneration, HIV-type neuropathies) suggest that supplementation with this compound may be beneficial in treating these disorders. [8,9] Similarly, increased plasma concentrations of SAMe were associated with mood improvement in depressed patients.[10] In another report, disruption of methylation by low SAMe levels was found to cause structural and functional abnormalities including myelopathy and depression. [11] Nerve regeneration requires the presence of SAMe.[12]

These findings support the hypothesis that in the CNS, SAMe has modulating effects on mood, with adequate amounts needed to maintain normal mood and remission of symptoms in patients with major depressive disorders. Dosage ranges for depression have been reported as 400 mg 3 to 4 times daily. If nausea and GI upset occur, the dosage can be tapered.[2]

Osteoarthritis: Animal studies have shown SAMe to prevent induced osteoarthritis in rabbits.[13] Higher chondrocyte counts and increased cartilage thickness were observed in rabbits administered SAMe vs placebo.[14]

SAMe appears to enhance native proteoglycan synthesis and secretion in human chondrocyte cultures in the cartilage of patients with osteoarthritis. [15] It possesses analgesic properties similar to NSAIDs but with no or minimal GI side effects.[16] SAMe has demonstrated gastric cytoprotective actions in animals.[17] Another problem with NSAID use involves in vitro suppression of articular cartilage proteoglycans synthesis which suggests that NSAIDs may even accelerate cartilage damage. [18]

Clinical trials involving a total of greater than 21,000 patients who received SAMe treatment, 458 patients who were given different NSAIDs (ibuprofen, indomethacin, naproxen, and piroxicam), and 279 who received placebo. The periods of treatment ranged from 3 weeks to 2 years. These controlled clinical trials demonstrated that SAMe improved both subjective and objective symptoms of osteoarthritis more than placebo and showed the same efficacy as the NSAIDs.[1,19,20] Maintenance dosage of SAMe for osteoarthritis is 200 mg twice daily.[2]

Fibromyalgia: Fibromyalgia is a disorder that is a common cause of chronic musculoskeletal pain and fatigue. At least 3 clinical trials found SAMe to be beneficial. Subjects given 200 mg SAMe per day parenterally demonstrated reductions in certain trigger points and painful areas, as well as mood improvements. The other reports confirmed SAMe's benefits in pain relief, morning stiffness, and mood enhancement.[2]

Liver disorders: Through methylation, SAMe regulates liver cell membrane lipid composition and fluidity, and by activation of the transsulfuration pathway, promotes endogenous detoxification processes in the liver. Further, it is the main source of glutathione, a major compound involved in several detoxification reactions in this organ.[21] SAMe restores normal hepatic function in conditions such as cirrhosis and cholestasis and aids in reversing hepatotoxicity. [4] Its liver-protectant actions are apparent in several studies, including actions against membrane alterations in rabbits fed high-cholesterol diets, [22] and in experimentation where high concentrations of SAMe were associated with reduced liver injury.[23,24,25,26,27] SAMe can be considered an important nutrient in alcoholic subjects.[28]

Others: Other beneficial effects of SAMe include treatment of migraine headaches (200 to 400 mg twice daily), [29] alteration of the aging process,[30,31,32] and sleep modulation.[33]

TOXICOLOGY: Other than occasional nausea and GI disturbances, no side effects, drug interactions, or disease contraindications have been found in recent literature reviews. Patients with bipolar disorder should not take SAMe, as it may lead to the manic phase. [2] In a field trial involving greater than 20,000 patients, the overall withdrawal rate caused by adverse effects was ˜ 5%, mainly during the first 2 weeks of treatment when the oral dose of SAMe was the highest (800 to 1200 mg daily).[4]

Toxicological studies of SAMe by parenteral and oral administration performed in different animal species recommended and commonly utilized in preclinical research labs included mutagenicity and carcinogenicity studies. They concluded that SAMe is completely safe even at the highest dosages. [1]

SUMMARY: SAMe is a naturally occurring molecule found in all living cells. It has been used in Europe, by prescription only, for depressive illness and arthritis since the mid-1970s. In the US, it is sold as a nutritional supplement. SAMe is useful in the treatment of depressive disorders, osteoarthritis, fibromyalgia, liver disorders, migraine headaches, and for sleep modulation. SAMe appears to have no significant side effects associated with its use.

PATIENT INFORMATION— SAMe

Uses: SAMe has been used in the treatment of depressive disorders, osteoarthritis, fibromyalgia, liver disorders, migraine headaches, and for sleep modulation.

Side Effects: Other than occasional nausea and GI disturbances, no side effects have been reported. Bipolar disorder patients should not use SAMe.

Dosing: SAMe has been studied in clinical trials for depression and Parkinsonism at oral doses of 800 to 3600 mg/day. It has been administered IV in a fibromyalgia trial at 600 mg/day.[34,35,36]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SAME

SANDALWOOD

DATE OF ISSUE: MAR 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Santalum album* L. Family: Santalaceae

COMMON NAME(S): Sandalwood, santal oil, white saunders oil, white or yellow sandalwood oil, East Indian sandalwood oil [1]

BOTANY: Indigenous to India, the Malay Archipelago, and Indonesia, the sandalwood is an evergreen tree that grows to 8 to 12 meters in height. [2] Australian sandalwood oil is prepared by distillation of the wood of *Eucarya spicata*, a small tree native to western Australia that contains sesquiterpene alcohols known as fusanols.[2] This oil is similar to the native Indian sandalwood oil in odor, although its topnotes are characteristically different. [1]

HISTORY: Sandalwood oil commonly is used as a fragrance in incense, cosmetics, perfumes and soaps. It also is used as a flavor for foods and beverages. [3] The wood has been valued in carving because of its dense character.

In traditional medicine, sandalwood oil has been used for a wide variety of conditions ranging from an antiseptic and astringent to the treatment of headache, stomach ache and urogenital disorders.

CHEMISTRY: Sandalwood oil is obtained from the heartwood of the plant. This volatile oil contains about 90% alpha- and beta-santalols with a variety of minor components including sesquiterpene hydrocarbons (about 6%). [3] The santalols are responsible for the pleasant odor of sandalwood although 2-furfuryl pyrrole also may contribute an effect.[3]

The seeds yield about 50% of a viscid, dark red, fixed oil. This oil contains stearolic acid and santalbic acid. Gas chromatography fingerprinting of sandalwood oils has been used successfully in light of the complex nature of the components of the oils. [4]

PHARMACOLOGY: Good clinical studies are lacking in support of the effects of sandalwood oil. The oil has been reported to have diuretic and urinary antiseptic properties.[1]

TOXICOLOGY: The oil has been found to be irritating in both mouse and rabbit skin test models. Santalol can cause dermatitis in sensitive persons [3] although it is generally considered to be nonirritating to human skin. [1] The santalols and related compounds have been identified in the blood of mice that inhaled sandalwood fumes under experimental conditions, indicating that systemic absorption of these compounds can occur. [5]

SUMMARY: Sandalwood is a fragrant wood from which an oil is derived for use in foods and cosmetics. The oil has been used widely in traditional Asian medicine and had been official in the United States at the turn of the century. Today, the oil finds little medicinal use but its widespread use as a popular fragrance continues.

PATIENT INFORMATION — Sandalwood

Uses: Sandalwood has been reported to have diuretic and urinary antiseptic properties, but mainly the oil extracted from the wood has been used as a fragrance enhancer.

Side Effects: Sandalwood can cause dermatitis in sensitive persons.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SANDALWOOD

SARSAPARILLA

DATE OF ISSUE: JUL 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Smilax* species including *Smilax aristolochiifolia* Mill. (Mexican sarsaparilla), *S. officinalis* Kunth (Honduras sarsaparilla), *Smilax regelii* Killip et Morton (Honduras, Jamaican sarsaparilla), *Smilax febrifuga* (Ecuadorian sarsaparilla), *Smilax sarsaparilla*, *Smilax ornata*. Family: Liliaceae.

COMMON NAME(S): Sarsaparilla, smilax, smilace, sarsa, khao yen

BOTANY: Sarsaparilla is a woody, trailing vine, which can grow to 50 meters in length. It is grown in the areas listed above. Many *Smilax* species are very similar in appearance regardless of origin. The part of the plant used for medicinal purposes is the root. Although this root has a pleasant fragrance and spicy sweet taste, and has been used as a natural flavoring agent in medicines, foods, and non-alcoholic beverages, it should not be confused with the sassafras tree, which has the distinctive flavoring of American root beer.[1,2]

HISTORY: The French physician Monardes described using sarsaparilla to treat syphilis in 1574. In 1812, Portuguese soldiers suffering from syphilis recovered faster if sarsaparilla was taken to treat the disease versus mercury, the standard treatment at the time.[3] Sarsaparilla has been used by many cultures for other ailments as well, including skin problems, arthritis, fever, digestive disorders, leprosy, and cancer.[1,3] Late 15th century accounts explaining the identification and the first descriptions of American drugs include sarsaparilla.[4] Sarsaparilla's role as a medicinal plant in American and European remedies in the 16th century is also evident.[5]

CHEMISTRY: Many *Smilax* species contain a number of steroidal saponins. *S. sarsaparilla* contains approximately 2% steroidal saponins, including sarsaponin, smilasaponin (smilacin), sarsaparilloside and its aglycones sarsasaponin (parillin), sarsasapogenin (parigenin), and smilagenin.[1,3] Other saponins include diosgenin, tigogenin, and asperagenin.[1] Phytosterols listed are sitosterol, stigmasterol, and pollinastanol.[1,2] One report lists three new steroidal saponins from *S. officinalis*.[6] Various saponins from other *Smilex* species exist as well, from *S. menispermoidea*,[7] *S. sieboldii*,[8,9] *S. lebrunii*,[10] *S. riparia*, and *S. china*.[11]

Other constiuents present in sarsaparilla include starch (50%), resin, cetyl alcohol, volatile oil,[1,2] caffeoylshikimic acid, shikimic acid, ferulic acid,[1] sarsapic acid,[12] kaempferol, and quercetin.[1] Minerals reported in the genus include aluminum, chromium, iron, magnesium, selenium, calcium, zinc, and others.[12] A related species, *S. glabra*, contains flavonol glycosides such as isoastilbin, isoengetitin, and astilbin.[13,14]

PHARMACOLOGY: Sarsaparilla has been used for treating **syphilis** and other sexually transmitted diseases (STDs) throughout the world for 40 years and was documented as an adjuvant for **leprosy** treatment in 1959.[15]

The ability of sarsaparilla to bind to endotoxins may be a probable mechanism of action as to how the plant exerts its effects. Problems associated with high endotoxin levels circulating in the blood stream such as liver disease, psoriasis, fevers, and inflammatory processes, all seem to improve with sarsaparilla.[3] Sarsaparilla has also displayed hepatoprotective properties in rats.[16]

Antibiotic actions of sarsaparilla are also seen but are probably secondary to its endotoxin-binding effects.[3] Antibiotic properties of the plant[1] are shown by its treatment of leprosy and its actions against leptosirosis, a rare disease transmitted by rats, as proven by Chinese studies.[12]

Other positive effects of sarsaparilla on the skin have been demonstrated. The endotoxin-binding sarsaponin from the plant has improved psoriasis in 62% of patients and has completely cleared the disease in 18%, as seen in a 1940s study.[17] Antidermatophyte activity from the species *S. regelii* has been demonstrated in a later report.[18] In addition, sarsaparilla has been used as an herbal or folk remedy for other skin conditions including eczema, pruritus, rashes, and wound care.[2,12]

Sarsaparilla's anti-inflammatory actions have made the plant useful for treating arthritis, rheumatism, and gout.[3,12] *S. sarsaparilla* inhibited carrageenan-induced paw inflammation in rats, as well as cotton pellet-induced exudation.[19]

The saponin sarsasapogenin can be synthetically transformed into testosterone in-vitro, for example, but it is unlikely that this can happen in-vivo. Some advertising claims of sarsaparilla being a "rich source of testosterone," are unsubstantiated as there is no testosterone present in the plant.[3] However, some sources state that sarsaparilla exhibits testosterogenic actions on the body, increasing muscle bulk and estrogenic actions as well to help alleviate female problems. In Mexico, the root is still used for its alleged aphrodisiac properties.[12] A recent review addresses smilax compounds (among others) present in bodybuilding supplements said to "enhance performance." Results of the study of over 600 commercially available supplements determined that there was no research to validate these claims.[20]

Other documented uses of sarsaparilla include the following: Improvement in appetite and digestion,[1] adaptogenic effects from *S. regelii*,[21] sarsaparilla in combination as an herbal remedy and mineral supplement,[22] and haemolytic activity of steroidic saponins from *S. officinalis*.[23] An overview of medicinal uses of sarsaparilla is available.[24] One report evaluating fracture healing finds sarsaparilla to have insignificant effects on tensile strength and collagen deposition.[25] Other species of smilax have been evaluated for antimutagenic actions (*S. china*),[26] GI disorders (*S. lundelii*),[27] and actions on hyperuricemic and hyperuricosuric rats (*S. macrophylla*).[28] The species *S. glabra* exhibits wormicidal effects,[29] improves hepatitis B in combination,[30] had marked therapeutic effects (in combination) in the treatment of intestinal metaplasia and atypical hyperplasia,[31] and hypoglycemic effects in mice,[32] and has hepatoprotective effects.[33]

TOXICOLOGY: No major contraindications, warnings, or toxicity data have been documented with sarsaparilla use. No known probelms have been seen regarding its use in pregnancy or lactation either; however, excessive ingestion should be avoided.[1] In unusually high doses, the saponins present in the plant could possibly be harmful, resulting in GI irriation.[2] The fact that sarsaparilla binds bacterial endotoxins in the gut, making them unabsorbable, greatly reduces stress on the liver and other organs.[3] Sarsaparilla has inhibited induced hepatocellular damage in rats, without any significant adverse reactions reported.[16]

One report describing occupational asthma caused by sarsaparilla root dust exists in the literature.[34]

SUMMARY: Sarsaparilla root has been used for many centuries and by many cultures for syphilis, inflammatory disorders, digestive problems, and skin diseases. The plant is rich in saponins, which may bind to endotoxins to exert its "blood purifying" and other related effects. The steroid structures present in sarsaparilla have been erroneously advertised as muscle bulk and performance enhancers, but no research thus far has validated these claims. Related species to sarsaparilla have their own documented effects as well. No major toxicity problems have been associated with the plant. Excessive dosing may cause gastric irritation.

PATIENT INFORMATION — Sarsaparilla

Uses: Sarsaparilla has been used for treating syphilis, leprosy, psoriasis, and other ailments.

Side Effects: No major contraindications, warnings or side effects have been documented; avoid excessive ingestion. In unusually high doses, the plant possibly could be harmful, including GI irritation.

Dosing: Typical doses of sarsaparilla for a variety of uses range from 0.3 to 2 g/day of the powdered root. [35,36]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SARSAPARILLA

SASSAFRAS

DATE OF ISSUE: JUN 1997

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Sassafras albidum* (Nuttal) Nees, synonymous with *S. officinale* Nees et Erbem. and *S. variifolium* Kuntze. Family: Lauraceae

COMMON NAME(S): Sassafras, saxifras, ague tree, cinnamon wood, saloop

BOTANY: Sassafras is the name applied to three species of trees, two native to eastern Asia and one native to eastern North America. Fossils show that sassafras was once widespread in Europe, North America and Greenland. The trees grow up to 100 feet in height and 6 feet in diameter, though they are usually smaller. Sassafras bears leaves 10 to 15 cm long that are oval on older branches but mitten-shaped or three-lobed on younger shoots and twigs. All parts of the tree are strongly aromatic. The drug is from the peeled root of the plant (root wood).[1]

HISTORY: Native Americans have used sassafras for centuries and told early settlers that it would cure a variety of ills. The settlers then exported it to Europe, where it was found to be ineffective.[2] A report on experiences of explorers and doctors finding, identifying and describing sassafras bark and other drugs during the late 15th century is available.[3]

Over the years the oil obtained from the roots and wood has been used as a scent in perfumes and soaps. The leaves and pith, when dried and powdered, have been used as a thickener in soups. The roots are often dried and steeped for tea, and sassafras was formerly used as a flavoring in root beer. Its use as a drug or food product has been banned by the US Food and Drug Administration (FDA) as carcinogenic; however, its use and sale persist throughout the United States. Medicinally, sassafras has been applied to insect bites and stings to relieve symptoms.[2]

CHEMISTRY: The pleasant-tasting oil of sassafras consists of approximately 2% of the roots and 6% to 9% of the root bark. The main constituent of the oil is safrole, which chemically is p-allyl-methylenedioxybenzene, which comprises up to 80% of the oil. Volatile oil also contains anethole, pinene apiole, camphor, eugenol and myristicin.[4,5]

The plant contains less than 0.2% total alkaloids (primarily boldine and its derivatives and reticuline) along with tanins, resins, mucilage and wax.[4,5,6] Six alkaloids, aporphine and benzylsoquinoline derivatives, have been found in root bark.[1] Two antimicrobial neolignans, magnolol and its related isomer (isomagnolol), from related species *S. randaiensis* have been isolated.[1] Analysis has also been performed on sassafras teas, using supercritical fluid extraction (SFE) with gas chromatographic-mass spectrometric (GC-MS) methods, commonly reporting 1% safrole levels.[8]

PHARMACOLOGY: Sassafras has been used as a sudorific agent,[9] a flavoring agent for dentifrices, root beers and tobaccos, and for treatment of eye inflammation.[4] Extracts of the roots and bark have been found to mimic insect juvenile hormone in *Oncopeltus fasciatus*.[10] The oil has been applied externally for relief of inset bites and stings and for pediculicides. Other external uses include treatment of rheumatism, gout, sprains, swelling and cutaneous eruptions.[4,5] A recent report compares safrole (the main constituent from sassafras oil), to indomethacin for anti-inflammatory activity and pain treatment in mice.[11]

The plant has been reported to have antineoplastic activity[12] and to induce cytochorme P-488 and P-450 enzymes.[5] Sassafras is said to be antagonistic to certain alcohol effects.[4] Alcohol extracts of the related *S. randaiense* Rehder exhibit antimicrobial and antifungal activity in vitro, and this activity appears to be due to the presence of magnolol and isomagnolol.[7]

TOXICOLOGY: Sassafras oil and safrole have been banned for use as flavors and food additives by the FDA because of their carcinogenic potential. Safrole and its metabolite, 1'-hydroxysafrole, act as nerve poisons and have caused malignant hepatic tumors in animals. Based on animal data and a margin-of-safety factor of 100, a dose of 0.66 mg safrole per kg body weight is considered hazardous for humans; the dose obtained from sassafras tea may be as high as 200 mg (3 mg/kg).[1,13] One study showed that even a safrole-free extract produced malignant mesenchymal tumors in more than 50% of black rats treated. These tumors corresponded to malignant fibrous histiocytomas in humans.[15]

Oil of sassafras is toxic in doses as small as 5 ml in adults.[16] Ingestion of 1 tsp (5 ml) produced shakes, vomiting, high blood pressure and pulse in a 47-year-old female.[17] Another case of a 1 tsp dose of sassafras oil in a young man also caused vomiting, along with dilated pupils, stupor and collapse.[4] There have been additional reports of the oil being fatal,[5] causing abortion[4] and causing liver cancer.[1,4,5] Safrole is a potent inhibitor of liver microsome hydroxylating enzymes; this effect may result in toxicity caused by altered drug metabolism.[13] Aqueous and alcoholic extracts of root bark can cause a range of effects in mice, inducing ataxia, ptosis, hypersensitivity to touch, CNS depression and hypothermia. Symptoms of sassafras oil poisoning in humans may include vomiting, stupor, lowering of body temperature, exhaustion, tachycardia, spasm, hallucinations, paralysis and collapse.[1,5]

Additionally, sassafras can cause diaphoresis[18] and contact dermatitis in certain individuals.[4] A case study reported oil of sassafras in combination as a teething preparation, which resulted in false positive blood tests for diphenylhydantoin, in a 4-month-old child.[19]

SUMMARY: Sassafras is an aromatic tree that has long served as a source for scents and flavorings. Considerable evidence indicates that sassafras, the principal component of oil of sassafras, and other components are carcinogenic in animals. Other toxic effects of sassafras include vomiting, stupor and hallucinations. It has also been associated with causing abortion, liver cancer, diaphoresis and dermatitis. Because there is no documented therapeutic benefit to ingesting sassafras or any of its extracts, the ingestion of this plant cannot be recommended.

PATIENT INFORMATION — Sassafras

Uses: Sassafras has been used historically for a variety of illnesses, and is now banned in the US, even for use as a flavoring or fragrance.

Side Effects: Besides being a cancer-causing agent, sassafras can induce vomiting, stupor and hallucinations. It can also cause abortion, diaphoresis and dermatitis.

Dosing: Sassafras root bark has been used as an aromatic and carminative at doses of 10 g; however, the carcinogenicity of its constituent safrole has limited its use.[14]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SASSAFRAS

SAVORY

DATE OF ISSUE: MAR 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Summer savory: *Satureja hortensis*L., syn. with *Calamintha hortensis* Hort. Winter savory: *Satureja montana* L., syn. with *S. obovata* Lag. and *Calamintha montana* Family: Labiatae

BOTANY: Summer savory is an annual herb that grows to about 2 feet in height featuring oblong leaves. Although it is native to Europe, it is now found throughout many parts of the world. Winter savory is a perennial shrub that grows to about the same height as summer savory, the leaves of which share some common characteristics with summer savory. Flowers of both species are pink to blue-white[1] and flower from June to September.[2]

HISTORY: The savories have been used for centuries as cooking herbs and have flavors reminiscent of oregano and thyme. [3] Because the flavor of the summer savory is somewhat sweeter than that of the winter savory, summer savory is used almost exclusively in commerce.[1] The green leaves and stems, both fresh and dried, along with extracts, are used as flavors in the baking and foods industries. Both summer and winter savory have a history of use in traditional medicine as tonics, carminatives, astringents and expectorants, and for the treatment of intestinal problems such as diarrhea and nausea. Summer savory is said to be an aphrodisiac[2] while winter savory has been said to decrease libido. [4]

CHEMISTRY: Dried summer savory contains approximately 1% of a volatile oil which is composed primarily of carvacrol, thymol and monoterpene hydrocarbons such as beta-pinene, p-cymene, limonene, camphene, etc.[1,5] The leaves contain a variety of minor components including minerals and vitamins. Winter savory contains about 1.6% of a volatile oil composed primarily of carvacrol (up to 65%), p-cymene and thymol. It also contains triterpenic acids including ursolic and oleanolic acids.[3,5] The relative composition of the volatile oil varies with location of cultivation, the species and the strain.

PHARMACOLOGY: The volatile oil of summer savory, as with many other volatile oils, possesses antifungal and antibacterial activity. [1,5] Summer savory has been reported to have a spasmolytic effect on isolated smooth muscle[5] and may have an antidiarrheal effect due to the phenolic compounds in the oil [1] and the tannins contained in the plant.[4]

The oil has been reported to possess an antidiuretic effect due to the carvacrol. [3] Teas of savory have been used traditionally in Europe to treat excessive thirst in diabetic patients, a use that may have some pharmacologic basis. [4]

TOXICOLOGY: Savory is generally recognized as safe for use as a condiment and flavor. When applied undiluted to the backs of hairless mice, summer savory oil was lethal to half of the animals within 48 hours. The oil is strongly irritating to other animal skin models, but is not phototoxic. [5] In diluted form the oil is not irritating to human skin.

SUMMARY: Summer and winter savory have been used for centuries as condiments. Their use in traditional medicine centers primarily on the antispasmodic and antibacterial effects of the volatile oil. Savory is not associated with significant toxicity and should be investigated for its antidiuretic properties.

PATIENT INFORMATION — Savory

Uses: Savory has antifungal, antibacterial, and antidiuretic effects, in addition to being widely used as a condiment.

Side Effects: Savory is not associated with any significant toxicity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SAVORY

SAW PALMETTO

DATE OF ISSUE: JUN 2000

REPLACES MONOGRAPH DATED: MAR 1994

SCIENTIFIC NAME(S): *Serenoa repens* (Bartram) Small. Also referred to as *Sabal serrulata*(Michx.) Nicholson or *Sabal serrulatum*Schult. Family: Palmae (Palms)

COMMON NAME(S): Saw palmetto, sabal, American dwarf palm tree, cabbage palm, fan palm, scrub palm

BOTANY: The saw palmetto is a low, scrubby palm that grows in the coastal plain of Florida and other southeastern states. Its fan-shaped leaves have sharp saw-toothed edges that give the plant its name. Dense clumps of saw palmetto can form an impenetrable thicket. The abundant 2 cm long berries are harvested from the wild in the fall and are dried for medicinal use. They also serve as a source of nutrition for deer, bears, and wild pigs. [1]

HISTORY: Native tribes of Florida relied on saw palmetto berries for food; however, Europeans often found the taste of the berries objectionable. [1] While native medicinal use of saw palmetto is not recorded, it was introduced into Western medical practice in the 1870s and was a favorite of Eclectic medical practitioners for prostate and other urologic conditions. Saw palmetto berries were official in the US Pharmacopeia in 1906 and 1916, and in the National Formulary from 1926 to 1950. While use in the US declined after that time, saw palmetto has long been a staple phytomedicine in Europe. Recent interest has been rekindled, and saw palmetto is currently ranked in the top 10 herbal products in the US. [2] It is primarily used for its activity in benign prostatic hyperplasia (BPH).

CHEMISTRY: Saw palmetto berries contain large quantities of beta-sitosterol and other plant sterols, [3] as well as free and esterified fatty acids. [4] Most standardized commercial preparations are "liposterolic" extracts containing nonpolar constituents such as fatty acids and sterols, produced either by conventional hexane extraction or by supercritical carbon dioxide extraction. The fatty acid components have been quantitated by gas chromatography [5] and supercritical fluid chromatography, [6] while the alcohols and sterols have been analyzed by TLC and electrospray mass spectrometry of ferrocenyl derivatives. [7] An acidic polysaccharide has been isolated from saw palmetto fruit that had anti-inflammatory activity. [8,9]

PHARMACOLOGY

BPH: Saw palmetto's mechanism of action in suppressing the symptoms of BPH is poorly understood. The leading hypothesis involves the inhibition of testosterone 5-alpha reductase, an enzyme that converts testosterone to 5-alpha-testosterone in the prostate. Hexane extracts of saw palmetto were found to inhibit the enzyme from human foreskin fibroblasts, while they had no direct effect on androgen receptor binding. [10] Investigators found various saw palmetto extracts to be much weaker 5-alpha reductase inhibitors in vitro than the synthetic drug finasteride. [11] Similarly, in humans, serum levels of dihydrotestosterone (DHT) were reduced markedly by finasteride, but not by saw palmetto. [12]

Further studies using both known 5-alpha reductase isozymes found that finasteride inhibited only type 1 reductase, while saw palmetto inhibited formation of all testosterone metabolites in both cultured prostate epithelial cells and fibroblasts. [13] A different saw palmetto extract, IDS 89, dose dependently inhibited 5-alpha reductase in both the stroma and epithelium of human BPH tissue. This inhibition was related to the free fatty acids present in the extract. [14] A tracer study found that radiolabeled oleic acid in saw palmetto extract was taken up preferentially by rat prostate compared with other tissues. [15] Studies in a coculture model of human prostate epithelial cells and fibroblasts found that saw palmetto inhibited both type 1 and type 2 isoforms of 5-alpha reductase without altering the secretion of prostate-specific antigen. [16] Other recent work has shown that saw palmetto extract inhibits trophic as well as androgenic effects of prolactin in a rat model of prostatic hyperplasia. [17] Structure-activity studies of pure fatty acid inhibition of steroid 5-alpha reductase have found gamma-linolenic acid to be the most potent and specific inhibitor of the enzyme. [18] It is possible that the C_{18} monounsaturated fatty oleic acid found in saw palmetto is partly responsible for the observed effects on 5-alpha reductase, though more extensive analysis of saw palmetto fatty acids is required.

There is less support for other hormonal mechanisms. One study found 5-alpha reductase inhibition and inhibition of DHT binding to androgen receptors, [19] and another study demonstrated inhibition of DHT and testosterone receptor binding. [20] Administration of saw palmetto extract over 30 days led to no changes in plasma levels of testosterone, follicle stimulating hormone, or luteinizing hormone. [21] Hormonal pathways were invoked to explain reduced prostate weights in castrated rats treated with estradiol, testosterone, and saw palmetto extract as opposed to estradiol and testosterone alone. [22] In the human prostate cancer line LNCaP, saw palmetto induced a mixed proliferative/differentiative effect that was not seen in the nonhormone-responsive PC3 human prostate cancer cell line. [23] Treatment of patients for 3 months with saw palmetto preceding prostatectomy caused a reduction in DHT levels in BPH tissue along with a corresponding rise in testosterone levels. A marked reduction in epidermal growth factor concentration was also observed in the periurethral region of the prostate. [24]

Although the mechanism of action of saw palmetto is not completely understood, clinical trials in BPH have shown convincing evidence of moderate efficacy. A 6-month, double-blind, head-to-head study vs finasteride in 1098 men found equivalent efficacy and a better side effect profile for saw palmetto. [29] Likewise, a 3-year study of IDS 89 in 435 BPH patients found clear superiority to placebo in reduction of BPH symptoms. [30] A 1-year study of 132 patients comparing 2 dose levels of saw palmetto demonstrated efficacy in symptom reduction but little difference between dose levels. [31] The general consensus has been that saw palmetto extracts reduce BPH symptoms without reducing prostate size, therefore delaying surgical intervention. [32] A meta-analysis that included a total of 18 clinical trials in BPH concluded that saw palmetto was better tolerated than finasteride and equivalent in efficacy. [33] A clinical trial in BPH of the saw palmetto constituent beta-sitosterol showed similar efficacy to that seen with saw palmetto itself. [34]

Other observations of saw palmetto extracts include a spasmolytic effect on rat uterus which was suggested to be because of effects on cyclic AMP and calcium mobilization, [25] an inhibition of smooth muscle contraction in rat deferens, guinea pig ileum, and bladder postulated as alpha-adrenoreceptor antagonistic, [26] shown by others to be noncompetitive in nature, [27] and interference with 5-lipoxygenase metabolites in neutrophils. [28]

INTERACTIONS: Because of well-documented antiandrogen and antiestrogenic activity, avoid taking with any hormone therapy including oral contraceptive and hormone replacement therapy. Saw palmetto also has shown immunostimulant and anti-inflammatory activity; hence, watch for patients taking drugs that may increase or decrease these effects. For reproducible effects, it is recommended that the fat-soluble saw palmetto extracts standardized to contain 85% to 95% fatty acids and sterols be taken at the recommended dosage of 160 mg twice daily. Effects occur in 4 to 6 weeks. There have been no demonstrated effect on serum prostate-specific antigen levels.

TOXICOLOGY: Saw palmetto products are generally well tolerated, with occasional reports of adverse GI effects. Its antiandrogenic activity suggests that it should not be used in pregnancy.

SUMMARY: Saw palmetto extracts are effective in the treatment of benign prostatic hyperplasia, reducing frequency of urination, increasing urinary flow, and decreasing nocturia. It is generally well-tolerated and may delay the need for prostate surgery.

Saw palmetto is approved by the German Commission E, and is monographed by WHO (vol 2), the British Herbal Pharmacopeia (vol 2), and in supplement 9 of the National Formulary. An American Herbal Pharmacopeia monograph is forthcoming.

PATIENT INFORMATION — Saw Palmetto

Uses: Saw palmetto is used to treat symptoms of benign prostatic hyperplasia, including reduction of urinary frequency, increase of urinary flow, and decrease of nocturia. Saw palmetto may delay the need for prostate surgery.

Side Effects: Saw palmetto is generally well tolerated, with occasional reports of adverse GI effects; do not use in pregnancy.

Dosing: The crude saw palmetto berries usually are administered at 1 to 2 g/day; however, lipophilic extracts standardized to 85% to 95% fatty acids in soft native extract or 25% fatty acids in a dry extract are more common. Some of the brand name products include *Permixon* (Pierre Fabre Medicament), *Prostaserene*(Indena) SCF extract, *Prostagutt*(WS 1473, Schwabe), *Remigeron*(Schaper & Brummer), *IDS 89*(Strathmann AG), *Quanterra Prostate*(Warner Lambert), and *LG 166/S* (Lab. Guidotti). Typical doses of standardized extracts range from 100 to 400 mg given twice daily for benign prostatic hypertrophy. [21,25,35,36,37,38]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SAW PALMETTO

SCHISANDRA

DATE OF ISSUE: OCT 1997

REPLACES MONOGRAPH DATED: JUN 1988

SCIENTIFIC NAME(S): *Schisandra chinensis*Baillon, *S. arisanensis*, *S. sphenanthera* Rehd, *S. rubriflora* franch. Family: Schizandraceae

COMMON NAME(S): Schisandra, schizandra; gomishi, hoku-gomishi, kita-gomishi (Japanese); *wu-wei-zu* (Chinese)

BOTANY: The family schizandraceae (schisandraceae) comprises two genera (*Schisandra* and *Kadsura*). *Schisandra* spp. are climbing, aromatic trees, with white, pink, yellow or reddish male or female flowers. The fruits are globular and red with several kidney-shaped seeds. The fruit is harvested in autumn when fully ripened. [1] *S. chinensis*is native to northeastern and north central China and is found in eastern Russia.

HISTORY: Schisandra is one of the many traditional Chinese materia medica that are recommended for coughs and various nonspecific pulmonary diseases. [2] It has been studied extensively in the Chinese and Japanese literature. Schisandra had been used for healing purposes for over 2,000 years. It is often used as an ethanolic tincture. The Chinese name for the plant, "wu-wei-zu," means "5-flavored herb," because of the flavor of the 5 main "elemental energies" of the plant. The fruit have a salty, sour taste.[1]

CHEMISTRY: This plant's chemistry has been studied extensively. The fruit contains reducing sugars and up to 10% organic acids (carboxylic, malic, citric, tartaric). The seeds contain reducing sugars, alkaloids and fatty esters. No flavones, glycosides or tannins are in the seeds or fruit. [3] About 2% of the fruit by weight is composed of lignins with a dibenzocyclooctane skeleton (eg, schizandrin, deoxyschizandrin and related compounds such as schizandrol, and schizanderer). In some specimens, the lignin content can approach 19% in the seeds and 10% in the stems. [4] More than 30 lignins have been identified in the seed, [2] including gomisins A, B, C, D, F and G;[5] tigloylgomisin P and angeloylgomisin.[6] Other plant constituents include phytosterols, volatile oil and vitamins C and E. [1] Determination methods have been performed for processing and standardization purposes. [7,8,9]

PHARMACOLOGY: Besides serving as a tonic and restorative, schisandra has other reported uses, such as liver protection, nervous system effects, respiratory treatment, GI therapy, adaptogenic properties and others.

Liver: The lignin components in schisandra possess pronounced liver protectant effects. The active principles appear to be the lignins such as wu-wei-zu C, shisantherin D, deoxygomisin A, gomisin N and gomisin C. The presence of one or two methylene dioxy groups appear to play an important role in hepatoprotection.[2,10] Animal studies on gomisin A offer convincing evidence of liver protection, including protective actions against: Halothane-induced hepatitis; [11] carbon tetrachloride; d-galactosamine and dl-ethionine toxicities; [12,13] hepatic failure induced by bacterium;[14] and preneoplastic hepatic lesions.[15,16,17,18] Gomisin A's mechanism for tumor inhibition may be a result of its ability to improve bile acid metabolism. [19] Gomisin A causes hepatic cell proliferation, improves liver regeneration, hepatic blood flow and liver function recovery in rats. [20] These effects are caused by protection of hepatocyte plasma membrane.[21] Ethanol extracts of schisandra have been found to increase liver weight in rats and mice. This action has been attributed to schizandrin B and schizandrol B. In a mouse study, extract added to a semipurified basal diet over a 14-day period increased the enzymatic metabolism of the mutagens benzo[a]pyrene (BaP) and aflatoxin B (AFB) and increased cytochrome P450 activity. Despite this increased level of metabolism, schisandra extract increased the in vitro mutagenicity of AFB. However, chemicals inducing similar patterns of enzymes have been found to reduce the in vivo binding of AFB to DNA. [22] It is also recognized that the schizandrins and about one-half dozen related compounds may temporarily inhibit or lower the activity of hepatic ALT. This has been observed in animals pretreated with hepatotoxins. [23,24,25]

Nervous System: Schisandra is a nervous system stimulant, increasing reflex responses and improving mental alertness. In China, the berries are used to treat mental illnesses such as depression. It is also used for irritability and memory loss. [1] Schisandra in combination with other herbs has improved memory retention disorder and facilitated memory retention deficit in animal testing. This suggests a possible use in treating age-related memory deficits in humans. [26] Schisandra, (also in combination with *Zizyphus spinosa* and *Angelica sinensis*) has accelerated neurocyte growth and may prevent atrophy of neurocyte process branches.[27]

Schisandra has been evaluated for its inhibitory effects on the CNS as well. In Chinese medicine, it is used as a sedative for insomnia. [1] This inhibition mechanism has been evaluated and may be related to the effects on dopaminergic receptors. [28] Gomisin A has also inhibited spontaneous and methamphetamine-induced motor activity in animals.[29]

Respiratory: Schisandra is used to treat respiratory ailments such as shortness of breath, wheezing and cough. [1] Gomisin A exerted antitussive effects when evaluated in guinea pigs.[29]

GI: In the rat intestine, schisandra extract reduces BaP metabolism, which is the opposite effect from that in the liver. Experiments show that it increases the activity of glutathione S-transferase. In the intestine, schisandra shifts BaP metabolism in favor of diols and 3-hydroxybenzo[a]pyrene and away from BaP- 4,5-epoxide and the mutagenic BaP quinones. Schisandra does not increase intestinal cytochrome P450 activity. [30] Schisandra has been used for treatment of diarrhea and dysentery.[1] One report found schisandra extract to have no significant effects on gastric secretory volume, gastric pH and acid output, [31] while another study found schisandra to have inhibitory effects on gastric contraction and stress-induced gastric ulceration when administered IV and orally in rats. [29] Metabolism of schisandra has been reported.[32,33,34] The plant helps the body "adapt" to stress. It has been used to balance fluid levels, improve sexual stamina, treat rash, stimulate uterine contractions and improve failing senses.[1] One report found antibacterial effects in alcohol and acetone extracts of the fruit. [3]

TOXICOLOGY: Schisandra has the capability to produce profound CNS depression. Because of its documented effects on hepatic and gastric enzyme activity, it is possible that schisandra may interfere with the metabolism of other concurrently administered drugs. The full spectrum of the clinical effects of the plant on the liver are not well-documented and the safety of the plant has not been established scientifically. However, research does not report any incidence of side effects.

SUMMARY: Schisandra is a traditional Chinese medicinal plant; the fruit is used most frequently in herbal medicine. The lignin content in the plant, the component responsible for pronounced hepatoprotectant effects, has been extensively studied. The plant may also help improve mental alertness, treat respiratory and GI problems, and help the body adapt to stress. Little information is available on side effects.

PATIENT INFORMATION— Schisandra

Uses: Schisandra has been used as a tonic and restorative, as well as for liver protection, nervous system effects, respiratory treatment, GI therapy and others.

Side Effects: Research indicates that side effects are infrequent, although schisandra has the ability to produce profound CNS depression and may interfere with the metabolism of other concurrently administered drugs.

Dosing: Schisandra fruit is used as an adaptogen at doses of 1.5 to 6 g/day. A standardized extract containing 3.45 schisandrin has been used in a clinical trial for improved athletic performance at 91 mg/day of extract.[35,36]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SCHISANDRA

SCULLCAP

DATE OF ISSUE: JAN 1993

REPLACES MONOGRAPH DATED: FEB 1990

SCIENTIFIC NAME(S): *Scutellaria laterifolia*L. Family: Labiatae

COMMON NAME(S): Scullcap, skullcap, helmetflower, hoodwort, mad-dog weed

BOTANY: Scullcap (*S. laterifolia*), a member of the mint family, is native to the United States where it grows in moist woods. Although it is widely distributed throughout large regions of North America, the plant has related species found as far away as China. Scullcap is an erect perennial that grows to 2 to 3 feet in height. Its bluish flowers bloom from July to September. Official compendia (eg, NF VI) recognized only the dried overground portion of the plant as useful; however, some herbal texts listed all parts as medicinal.[1] The aerial parts of the plant are collected during the flowering period, typically August and September. A number of species have been used medicinally, and the most common European variety has been *S. baicalensis* Georgii, a native of East Asia.

HISTORY: Scullcap appears to have been introduced into traditional American medicine toward the end of the 1700s, when it was promoted as an effective treatment for the management of hydrophobia (hence the derivation of one of its common names). It was later used as a tonic, particularly in proprietary remedies for "female weakness."[2] The plant had been reputed to be an herbal tranquilizer, particularly in combination with Valerian, but has fallen into disuse.

CHEMISTRY: The various species of *Scutellaria*contain several flavonoid glycoside pigments. These include scutellarein, wogonin, isoscutellarein and baicalin. A diterpenoid (scuterivulactone) has also been identified. [3]

PHARMACOLOGY: At the turn of the century, interest in scullcap grew and the pharmacologic properties of an extract were investigated. The extract was evaluated for its effect on the contractility of the guinea pig uterus in vitro and was found to have only a slight depressant effect in high doses and no effect in vivo when given in "normal" doses.[2]

Extracts of two other species also were found to be devoid of effects on the central nervous or circulatory systems in cats or rabbits. A more recent report using a tincture of the plant found a long-lasting decline in blood pressure in dogs.

Over the past 15 years, Japanese researchers have investigated the activity of the related plant *S. baicalensis*, which is more readily available in Japan. Animal studies indicate that extracts of the plant have a demonstrable anti-inflammatory effect. Although the mechanism of action is not well understood, it is believed that hot water extracts of *Scutellaria* and the active metabolites of the flavonoids baicalin and wogonin glucuronide (baicalein and wogonin, respectively) are potent inhibitors of the enzyme sialidase.[4] In another study, isoscutellarein-8-o-glucuronide from the leaf was found to be a potent inhibitor of the enzyme. [5]

Sialic acids are widely distributed in tissues where they occur as constituents of glycolipids and glycoproteins. They are present in mucus secretions and cell membranes where they are thought to be the sites at which viruses and other compounds attach and penetrate the cell wall. Serum sialic acid is known to increase in certain disease states (cancers, rheumatic diseases, infections, inflammations), and it has been postulated that an inhibitor of sialidase, such as scullcap extract, may have a therapeutic application.

A preliminary animal report suggests that the coadministration of scullcap with cyclophosphamide and 5-fluorouracil may decrease tumor cell viability and improve the tolerability of the cytostatic agents.[6]

Teas prepared from *Scutellaria* species have demonstrable in vitro antibacterial and antifungal activity. [7]

TOXICOLOGY: There is no evidence to indicate that *Scutellaria* is toxic when ingested at "normal" doses. According to the FDA, however, overdose of the tincture causes giddiness, stupor, confusion, twitching of the limbs, intermission of the pulse and other symptoms indicative of epilepsy. [8]

SUMMARY: *Scutellaria* has been employed in traditional American medicine for more than 200 years. It is generally recognized as being devoid of therapeutic activity although early claims suggested that the plant had potentially useful antibacterial and sedative effects. Recent studies indicate that it may possess anti-inflammatory activity related to its ability to inhibit the enzyme sialidase. The plant continues to be found in some herbal teas.

PATIENT INFORMATION— Scullcap

Uses: Scullcap is not recognized as having therapeutic activity, although recent studies suggest that it might have anti-inflammatory activity.

Side Effects: If taken in a normal dose, scullcap does not seem to exhibit any adverse effects.

Dosing: Scullcap traditionally has been used in doses of 1 to 2 g for hysteria, epilepsy, and as a bitter tonic and febrifuge; however, there are no clinical studies to support these uses or the dosage.[9]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SCULLCAP

SEAWEED

DATE OF ISSUE: FEB 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Over 9000 species exist, including *Ascophyllum*, *Chondrus*, *Ecklonia*, *Fucus*, *Gelidium*, *Gracilaria*, *Laminaria*, *Phaeophycota*, *Pterocladia*, and *Rhodophyceae*[1,2,3,4]

COMMON NAME(S): Brown seaweed, red seaweed, kelp, carrageenin, Irish moss[2,3]

BOTANY: Seaweeds are marine algae, saltwater-dwelling, simple organisms that fall into the general category of plants. Most of them are the red (6000), brown (2000), or green (1200) species and have root-like structures called holdfasts that serve an anchorage function. [4]

HISTORY: For centuries, seaweed has been of botanical, industrial, and pharmaceutical interest. Because of the high nutrient content, seaweed has been used as a food throughout Asia.[3]

Traditional Chinese medicine used hot water extracts of certain seaweeds in the treatment of cancer. Additionally, the Japanese and Chinese cultures have used seaweeds to treat goiter and other glandular problems since 300 BC. [5]

The Romans used seaweeds in the treatment of wounds, burns, and rashes.[3] The Celts noted that ordinary seaweed contracted as it dried and then expanded with moisture. In Scotland during the 18th century, physicians used dried seaweed stem to successfully drain abdominal wall abscesses. They also inserted seaweed into the cervix in an attempt to treat dysmenorrhea. Many reports outline the use of seaweed to induce abortion. Seaweed was employed intravaginally for vaginal atresia and was used urethrally and rectally for strictures.[1]

CHEMISTRY: The major chemical extracts of seaweed are alginates, agars, and carrageenans. Alginates are cell wall constituents of brown seaweeds. They are chain-forming heteropolysaccharides composed of blocks of mannuronic acid and guluronic acid. The metal salts of alginic acid readily dissolve in cold water to yield viscous solutions.[4] Agars are polysaccharides derived from red seaweeds and consist of alternating D- and L-galactopyranose units. Carrageenan, in contrast to agar, is built up from D-galactopyranose units only.[4]

PHARMACOLOGY: Studies report that the seaweeds are used worldwide for many medicinal purposes. The brown seaweeds contain a polysaccharide fraction known as fucan sulfate that has antithrombin[6] and antiviral[7] activity. The red seaweeds have antiherpetic and laxative effects.[8] Furthermore, there are reports in the literature of antibiotic, antifungal, and insecticide properties associated with seaweeds. [3] It has been noted that their extracts exert a stimulatory effect on B lymphocytes and macrophages, which may be used clinically for the modulation of immune responses.[9,10]

In addition to these reports, substantial evidence exists for the following effects:

Ripening of the cervix: *Laminaria* tents have been used for many decades to dilate the uterine cervix. However, the technique fell into disrepute because of improper methods of sterilization and resulting uterine infection. With the use of gamma radiation for sterilization purposes, *Laminaria* tents once again were used in the 1970s for first- and second-trimester abortion.[11] Although the hydrophilic property of *Laminaria* may be considered the principal mechanism promoting cervical dilation, it also may alter levels of uterine prostaglandin F_{2a}.[12] Studies in the 1980s demonstrated that a combination of *Laminaria* with prostaglandin increased the success rate and decreased abortion time.[13,14] By the late 1980s, a synthetic tent had been developed, known as lamicel. This appeared to have greater convenience, lower rate of bleeding upon removal, lower cost per patient, and comparable efficacy. [15] *Laminaria* tents also have been used to ripen the cervix and induce labor. A small, randomized trial of 20 patients showed that *Laminaria* tents were more effective than PGE_2vaginal suppositories at cervical dilation. It has been proposed that *Laminaria* tents could be used in patients when PGE_2 has failed, when patients are intolerant of PGE_2, or where uterine contractions are undesirable.[16] However, studies also have illustrated problems associated with its use. Significant risk of maternal and neonatal infectious morbidity has been found. [17]

Wound management: A number of dressings and topical agents have evolved for use as a consequence of improved understanding of wound healing. Dressings now include alginates. These are naturally occurring polysaccharides found only in the brown seaweeds and come in the form of a loose, fibrous rope or pad. They are generally classified as hydrogels. Calcium alginate dressings are suitable for burns and extensive wounds where a normal dressing would be difficult to remove. [4] When applied to the wound, a network is formed around which a healthy scab may appear. The calcium ions found in the dressings interact with the sodium ions within the wound exudate to produce a fibrous gel. The hydrophilic gel provides a barrier to contamination and a moist wound environment that allows gaseous exchange. The bandage may be removed with a sodium chloride solution, which renders the alginate soluble in water. [18]

Anticancer effects: Breast cancer rates show dramatic differences in worldwide distribution; it appears that behavioral factors are involved. [19] Epidemiologic studies have shown that the rates of breast cancer incidence in premenopausal women in Japan is about 3 times lower and in postmenopausal women 9 times lower than those found in the United States. Not only do fewer Japanese women develop breast cancer, but when they do, they live longer than their counterparts in the United States. One explanation for this may be the much higher consumption of dietary seaweed in Japan.[5] The estimated per capita intake of seaweed in Japan ranges from 4.9 to 7.3 g/day.[5]

Research has led to the isolation of a number of polysaccharides from edible brown kelp seaweeds (*Laminaria angustata*, *japonica*, and *religiosa*), which slow the development of various induced cancers (in vitro). Their proposed mechanism of action is enhancement of the immunological defense of the organism against the carcinogen. Other explanations are that *Laminaria* is a source of nondigestible fiber (thereby increasing fecal bulk and decreasing bowel transit time) and that it contains an antibiotic substance that may influence fecal ecology. [19]

Antihypertensive effects: Low-sodium diets are widely reported to reduce blood pressure and are recommended by the American College of Cardiology in the treatment of mild hypertension. Seaweed preparations have been shown to decrease blood pressure by a mechanism involving ion exchange. In a double-blind, crossover study, 62 middle-aged patients with mild hypertension were given a potassium-releasing seaweed preparation. Mean blood pressure was reduced from 112 to 101 mm Hg after ingestion of 12 g/day seaweed.[20] However, evidence has not shown that seaweed reduces mortality; therefore, seaweed cannot be recommended for the treatment of hypertension.

INTERACTIONS: A single case report describes a change in the international normalized ratio (INR) in a patient taking warfarin who consumed a large quantity of sushi that contained a seaweed. This was thought to be caused by the high vitamin K content of the seaweed. [21]

TOXICOLOGY: The blue-green algae *Lyngbya majuscula*is known to be toxic and to colonize seaweeds that are common throughout the Pacific, Indian, and Caribbean oceans. There are a number of reports of this algae causing contact dermatitis, commonly known as "stinging seaweed dermatitis." An isolate from the algae, debromoaplysiatoxin, is a very potent inflammatory agent, producing a follicular, papular, and pustular reaction in minute concentrations. [22]

Two other seaweeds, *Gracilaria coronopifolia*and *G. tsudai*, usually are considered nontoxic but occasionally may produce poisons associated with GI symptoms when ingested. Extreme cases have resulted in death.[23] There also has been a report of cholera associated with eating raw seaweed. [24]

Excessive intake of dried seaweed has been reported to cause carotenodermia (yellowing of the skin). Hypercarotenemia is caused by excessive intake of carotene-rich vegetables or drinks. [25]

Seaweed is a rich source of iodine. In Japan, where seaweed is widely consumed, a number of cases of diet-induced goiter have been reported. The goiters appear to be only cosmetic and elimination of seaweed from the diet generally leads to shrinkage or disappearance of the goiter. Iodine concentrations in seaweed-containing dietary supplements vary widely. In some cases, the US maximum safe iodine intake of 1000 mcg/day easily could be exceeded. Whether this could prove harmful is difficult to ascertain because susceptibility to the effects of a high intake of iodine appears to vary among individuals. [26]

SUMMARY: There is limited information regarding the antithrombin and antiviral activity of brown seaweeds. The red seaweeds have antiherpetic and laxative effects. Furthermore, there are reports in the literature of antibiotic, antifungal, and insecticide properties associated with seaweeds. *Laminaria* tents have been used for many decades to dilate the uterine cervix. Additionally, wound dressings now include alginates. Epidemiological studies from Japan suggest that seaweed has a protective effect against breast cancer. However, toxicity from seaweed has been reported. In Japan, where seaweed is widely consumed, a number of cases of diet-induced goiter have been reported. Also, stinging seaweed dermatitis, a form of contact dermatitis, has been observed in swimmers exposed to seaweed.

PATIENT INFORMATION — Seaweed

Uses: Seaweed is used in calcium alginate dressings and for dilation of the cervix prior to gynecological procedures (although infections are a concern). There is limited information regarding its laxative, antibiotic, antifungal, and insecticide effects.

Interactions: Patients taking warfarin and consuming a large quantity of food containing seaweed may experience a change in INR because of seaweed's high vitamin K content.

Side Effects: Contact dermatitis, goiter, and, occasionally, GI effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SEAWEED

SENEGA ROOT

DATE OF ISSUE: APR 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Polygala senega* L. Family Polygalaceae (Milkworts)

COMMON NAME(S): Seneca snakeroot, Rattlesnake root, Milkwort, Mountain flax

BOTANY: Senega root is an uncommon perennial herb about 1 foot high that grows throughout eastern North America. The leaves are small, alternate, and narrowly lanceolate. Numerous pinkish-white or greenish-white flowers are crowded on a terminal spike. The root is twisted and has an irregular, knotty crown with a distinctive ridge. The variety *P. senega*var. *latifolia* Torr. & Gray has been distinguished, but occurs throughout the same habitat and differs from *P. senega* only in the size of leaves and flowers and in having a slightly later flowering period. The related species *P. tenuifolia* Willd., *P. reinii*Franch., *P. glomerata* Lour., and *P. japonica* Houtt. are used in Asia for similar purposes.

HISTORY: Senega root was used by eastern Native American tribes including the Seneca, from whom its name is derived. Snakeroot refers to the purported use in snakebite. However, even the early European observers gave little credence to this use. Senega root found use among the colonists and in Europe as an emetic, cathartic, diuretic and diaphroetic in a variety of pulmonary diseases such as pneumonia, asthma, and pertussis, and also in gout and rheumatism. [1] Its main use in the 19th century was as an expectorant cough remedy. It was official in the US Pharmacopeia from 1820 to 1936, and in the National Formulary from 1936 to 1960.

CHEMISTRY: Seneca snakeroot contains a series of saponins constructed from the 2,3,27-trihydroxy-oleanane 23,28-dioic acid triterpene skeleton (presenegenin), having a single sugar attached at position 3 and a 4 to 6 sugar chain appended at position 28. A variety of methoxy-cinnamate esters are attached at the internal sugar of the C-28 chain.[2,3,4,5,6,7,8,9] These saponins have been named senegins ?-?V and senegasaponins A-C. The senegins can be analyzed by HPLC. [10] Several other species of *Polygala* (see Botany) contain distinct but very similar saponins based on the same sapogenin. [11] An extensive series of ester oligosaccharides, senegoses A-O, have been isolated from *P. senega* var. *latifolia*.[12,13,14] The root also contains a small amount of methyl salicylate, which gives it a characteristic wintergreen odor.

PHARMACOLOGY: The antitussive effect of senega root has generally been attributed to the saponin content of the plant, which is consistent with the general detergent property of saponins in breaking up phlegm. In addition, senega is thought to act by irritation of the gastric mucosa, leading by reflex to an increase in bronchial mucous gland secretion.

The senega saponins have been shown to possess hypoglycemic activity in normal and diabetic mice, but not in streptozotocin-treated mice. [7,8,9,15,16,17] Thus, these compounds have activity relevant to non-insulin-dependent diabetes. This activity is quite potent when the saponins are injected intraperitoneally, but can also be detected with higher oral doses. The same saponins have also been found to substantially reduce alcohol absorption when given orally 1 hour before alcohol. [7,8,9]

The aqueous extract of the related species *P. tenuifolia* has been shown to have a potent effect in blocking inflammatory processes in cultured mouse astrocytes. Substance P and lipopolysaccharide-induced production of tumor necrosis factor and interleukin-1 was blocked by the saponin-containing extract at low concentration.[18] It is possible that a systemic anti-inflammatory effect may be the result of a similar mechanism.

No biological activity has been reported for the oligosaccharides. Senegose A was found to be inactive in the hypoglycemia model cited above. [17]

TOXICOLOGY: High doses of powdered senega root (> 1 g) or tincture have been reported to be emeteogenic and irritating to the GI tract. The use of senega root is contraindicated in pregnancy and in patients with peptic ulcer disease or inflammatory bowel disease. [19]

SUMMARY: Senega root is an antitussive herb with additional potential for use in non-insulin-dependent diabetes and in reducing alcohol absorption. While toxic at high doses, its emetic action makes further toxicity self-limiting.

Senega snakeroot is approved in the German Commission E monographs for catarrh of the respiratory tract. It is also monographed in ESCOP F-3, WHO volume 2, BHP volume 1.

PATIENT INFORMATION — Senega Root

Uses: Senega has been used as an antitussive.

Side Effects: High doses of powdered senega root or tincture are emetogenic and irritating to the GI tract.

Dosing: Antitussive dosage of senega root is 1 to 3 g/day. [20]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SENEGA ROOT

SENNA

DATE OF ISSUE: JULY 1998

REPLACES MONOGRAPH DATED: JAN 1989

SCIENTIFIC NAME(S): *Cassia acutifolia* Delile, syn. with *Cassia senna* L. Also includes references to *C. angustifolia* Vahl. Family: Caesalpinaceae

BOTANY: *C. acutifolia* is native to Egypt and the Sudan while *C. angustifolia* is native to Somalia and Arabia. Plants known as "wild sennas" (*C. hebecarpa* Fern. and *C. marilandica* L.) grow on moist banks and woods in the eastern US. This plant should not be confused with "cassia," a common name for cinnamon. Senna is a low branching shrub, growing to about 3 feet in height. It has a straight woody stem and yellow flowers. [1] The top parts are harvested, dried and graded. The hand-collected senna is known as Tinnevally senna. Leaves that have been harvested and graded mechanically are known as Alexandria senna. There are over 400 known species of cassia.[1]

HISTORY: Senna was first used medicinally by Arabian physicians as far back as the 9th century A.D. [1] It has long found use in traditional Arabic and European medicine as well, primarily as a cathartic. The leaves have been brewed and the tea administered for its strong laxative effect. Because it is often difficult to control the concentration of the active ingredients in the tea, an unpredictable effect may be obtained. Therefore, standardized commercial dosage forms have been developed, and these concentrates are available as liquids, powders and tablets in over-the-counter laxatives. The plant derives its name from the Arabic "sena" and from the Hebrew word "cassia," which means "peeled back," a reference to its peelable bark.

CHEMISTRY: Senna contains anthraquinones including dianthrone glycosides (1.5% to 3%), sennosides A and B (rhein dianthrones), sennosides C and D (rhein aloe-emodin heterodianthrones). Other numerous minor sennosides have been identified, and all appear to contribute to the laxative effect. The plant also contains free anthroquinones in small amounts including rhein, aloe-emodin, chrysophanol and their glycosides. [2,3]

Senna pods also contain the same rhein dianthrone glycosides as the leaves.

Carbohydrates in the plant include 2% polysaccharides, and ± 10% mucilage consisting of galactose, arabinose, rhamnose and galacturonic acid. [2,3] Other carbohydrates include mannose, fructose, glucose, pinitol and sucrose. [2]

Flavonols present include isorhamnetin and kaempferol. Glycosides 6-hydroxymusizin and tinnevellin are also found.

Other constituents in senna include chrysophanic acid, salicylic acid, saponin, resin, mannitol, sodium potassium tartrate and trace amounts of volatile oil. [2,4]

PHARMACOLOGY: Senna is a potent laxative. Its cathartic effects can be obtained from a tea prepared from one or two teaspoonfuls of dried leaves.

Senna's use in treating constipation is well documented. It is one of the most popular laxatives, especially in the elderly. [5] Many reports are available discussing senna's role in constipation,[6,7] its use in the elderly,[8,9,10,11,12] in psychiatric patients,[13] in spinal cord injury patients[14] and in pregnancy, where it is the stimulant laxative of choice.[15] In cancer treatment protocols, senna has also been noted to reverse the constipating effects of narcotics, and may prevent constipation if given with the narcotic.[16] It may, however, cause more adverse effects than other laxatives, primarily abdominal pain.[17] Castor oil was superior to senna for chronic constipation sufferers in another report. [18]

Senna may affect influence on intestinal transit time.[19,20,21] Its effectiveness as part of a cleansing regimen to evacuate the bowels in preparation for such tests as colonoscopies or barium enemas is documented.[22,23,24,25,26,27,28,29,30,31,32] Results from these studies include reduced ingestion of commercial *Golytely* solution and simethicone when given with senna,[27] and more effective colon cleansing with senna in combination with polyethylene glycol electrolyte lavage solution, compared to the solution alone.[28] Senna has also been studied in chronic constipation, [33] and for long-term laxative treatment.[34] Several mechanisms are postulated as to how senna acts as an effective laxative. The anthraquinone glycosides are hydrolyzed by intestinal bacteria to yield the active, freed anthraquinones. Alternately, it has been suggested that anthraquinones are absorbed in small quantities from the small intestine and hydrolyzed in the liver. The resultant anthraquinones are secreted into the colon. [35] One report using human intestinal flora finds sennoside A to eventually be converted to rheinanthrone, which is the active principle causing peristalsis of the large intestines. Sennosides A and B also play a role in inducing fluid secretion in the colon. Sennosides irritate the lining of the large intestine, causing contraction, which results in a bowel movement approximately 10 hours after the dose is taken. [1]

Prostaglandins may also be involved in the laxative actions. [2] One report suggests prostaglandin-mediated action of sennosides. [36] Indomethacin can partly inhibit the actions of sennosides A and B.[2] However, conflicting reports suggest that prostaglandins do not contribute to the laxative effect. [37,38] In addition, studies on the rat colon suggest that the laxative effect produced by senna may involve histamine formation. [39]

Metabolism of anthranoid laxatives has been reported, [40,41] as has the metabolism of sennosides.[42,43,44] The kinetics of senna constituents rhein and aloe-emodin have been investigated in man.[45]

The senna constituents, aloe-emodin and beta-sitosterol, possess inhibitory activity against cancer cells in mice. [2,4]

Senna was not found to have antidiabetic activity when tested in diabetic mice. [46]

TOXICOLOGY: Chronic use of any laxative, in particular irritant laxatives such as senna, often results in a "laxative-dependency syndrome" characterized by poor gastric motility in the absence of repeated laxative administration. Other reports of laxative abuse include laxative-induced diarrhea, [47,48] and osteomalacia and arthropathy associated with prolonged use of the product. [49]

The chronic use of anthroquinone glycosides has been associated with pigmentation of the colon (melanosis coli). Several cases of reversible finger clubbing (enlargement of the ends of the fingers and toes) have been reported following long-term abuse of senna-containing laxatives. [50,51,52] One report described a woman who developed finger clubbing following ingestion of from 4 to 40 *Senokot* tablets per day for about 15 years.[53] Clubbing reversed after the laxative was discontinued. The mechanism has been postulated to be related to either increased vascularity of the nail beds or a systemic metabolic abnormality secondary to chronic laxative ingestion.

Senna abuse has been associated with the development of cachexia and reduced serum globulin levels after chronic ingestion. [54]

Risk assessment for senna's use during pregnancy has been addressed.[55] One review suggests senna to be the "stimulant laxative" of choice during pregnancy and lactation.[15] Uterine motility was not stimulated by sennosides in one report in pregnant ewes. [56] None of the breast-fed infants experienced abnormal stool consistency from their mothers' ingestion of senna laxatives. The constituent rhein, taken from milk samples varied in concentration from 0 to 27 mg/ml, with between 89% to 94% of values = 10 mg/ml.[57,58] Nonstandardized laxatives are not recommended during pregnancy. [2]

Myenteric neurons in the rat colon are not destroyed by sennosides, as had been earlier suggested. [59,60,61] Anthraquinone purgatives in excess were said to have

caused degeneration of neurons. Toxicity studies separating toxic components of senna's anthraquinone derivatives have been performed. [62]

Generally, senna may cause mild abdominal discomfort such as cramping. Prolonged use may alter electrolytes. Patients with intestinal obstruction should avoid senna.[2]

Various case reports of senna toxicity are available, and include coma and neuropathy after ingestion of a senna-combination laxative, [63] hepatitis after chronic use of the plant,[64] occupational asthma and rhinoconjunctivitis from a factory worker exposed to senna-containing hair dyes, [65] and asthma and allergy symptoms from workers in a bulk laxative manufacturing facility.[66]

SUMMARY: Senna has been used for many years as an effective laxative. It is used to treat constipation and to cleanse bowels in preparation for certain procedures. It has many mechanisms of action including bowel irritation, increased peristaltic action, and fluid secretion. Toxicity includes laxative abuse and abdominal discomfort. Caution is advised for long-term use of "dietary teas" containing laxatives.

PATIENT INFORMATION— Senna

Uses: Senna is most commonly used as a laxative.

Side Effects: The chronic use of senna has resulted in pigmentation of the colon, reversible finger clubbing, cachexia and a dependency on the laxative.

Dosing: Senna leaves or pods have been used as a cathartic laxative at doses of 0.6 to 2 g/day, with a daily dose of sennoside B from 20 to 30 mg. Senna should not be used at higher doses or for extended periods of time.[67]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SENNA

SHA REN

DATE OF ISSUE: MAR 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Amomum xanthoides* or *A. villosum*. Family: Zingiberaceae

COMMON NAME(S): Tavoy cardamom, malabar cardamom, bastard cardamom, yang chun sha, chun sha ren, fructus amomi, grains of paradise[1]

BOTANY: The therapeutic action of *A. xanthoides*(sha ren) is associated with the fruit or seed. The soft, thin outer surface or peel of the fruit is brownish-red and covered with thorn-like projections. The flattened pyramid-shaped seeds are firm in texture and average 3 mm in length. Often there are 4 to 15 seeds in 3 cavities separated by 3 blunt ridges. The fruit has a strong aroma and a pungent, bitter taste. The plant species is native to tropical Asia, particularly southern India, and is cultivated throughout southwestern China.[1,2,3,4,5]

HISTORY: *A. xanthoides* has been used commercially and medicinally in China and India for > 3000 years. European, Latin American, and Middle Eastern countries use the plant as a spice. The seeds reportedly have been used in alcoholic liquors, veterinary medicine, cosmetics, perfumes, and as a fragrance in soaps. [1,3,6]

Hippocrates recommended its use in the treatment of coughs, abdominal pain, nervous disorders, sciatica, retention of urine, and venomous bites. Although the claims are unreferenced, *A. xanthoides*is considered a carminative and GI aid (eg, enteritis, dysentery, nausea, vomiting). *The British Herbal Pharmacopoeia* lists *A. xanthoides* for the treatment of flatulent dyspepsia.[1,2,7]

CHEMISTRY: The volatile oil of *A. xanthoides*contains the following terpenoids: Borneol, bornyl acetate, camphene, camphor, caryophyllene, limonene, linalool, myrcene, necrolidol, pinene, and terpinene. Borneol and bornyl acetate are the principal terpenoids. The stems of the plant also contain daucosterol and emodin monoglycoside.[1,8,9,10]

Beta-caryophyllene, alpha-humulene, and their epoxides account for the seed's aroma, while paradol is responsible for its pungency. *A. xanthoides* also contains calcium, iron, magnesium, potassium, sodium, and zinc.[3,8,9,10]

PHARMACOLOGY: Only animal and in vitro data are available on the efficacy of *A. xanthoides*. One study investigated the protective effect of an *A. xanthoides* extract against alloxan-induced diabetes in mice. The results indicate that the extract provides a protective effect against NFkappaB activation, which is considered a primary determinant in the progression of diabetes.[11] Human clinical trials are needed to substantiate the efficacy of *A. xanthoides*.

INTERACTIONS: In vivo drug-drug interaction data are not available.

TOXICOLOGY: Human clinical trials are needed to substantiate the toxicology of *A. xanthoides*. Because of the lack of scientific evidence, avoid use during pregnancy and lactation.

SUMMARY: The fruit or seed of *A. xanthoides*has been used commercially and medicinally for > 3000 years. Historical documentation supports the use of this plant species as a carminative and GI aid. Human clinical trials are needed to substantiate the historical uses of *A. xanthoides*.

PATIENT INFORMATION— Sha Ren

Uses: Historically, sha ren has been used as a carminative and GI aid. Human clinical trials are needed to substantiate its efficacy.

Side Effects: There is no information on the toxicology of sha ren. Avoid use during pregnancy and lactation.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SHA REN

SHARK DERIVATIVES

DATE OF ISSUE: SEP 1995

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Squalus acanthias* (spiny dogfish shark), *Sphyrna lewini* (Hammerhead Shark) and other shark species

COMMON NAME(S): Spiny dogfish shark, hammerhead shark and other species

HISTORY: Shark cartilage is prepared from the cartilage of freshly caught sharks in the Pacific Ocean. The cartilage is cut from the shark, cleaned, shredded, and dried. One of the main processing plants for dogfish shark is in Costa Rica. The finely ground cartilage is uniformly pulverized (in a 200 mesh screen), sterilized, and encapsulated. Gelatin capsules contain 740 mg, usually without additives or fillers, and are claimed to be "all natural." The 100% pure shark cartilage is also available in 200 g and 500 g capsules in safety-sealed bottles (eg, *Cartilade*©).[1,2]

Squalamine was originally isolated from shark stomachs, but has subsequently been synthesized. [1] This compound is still in the experimental stage and is not yet commercially available.

CHEMISTRY: Early claims were made that extracts of shark cartilage inhibited tumor angiogenesis when implanted in rabbit corneas. The active principle(s) has not been found, although some believe it might be a protein.[1,2] Several studies have been done on various sharks. Pettit and Ode [3] isolated and characterized sphyrnastatin 1 and 2 from the hammerhead shark. Neame et al[4] recently reported on the isolation of a protein from reef shark (*Carcharhinus springeri*) cartilage which bears a striking resemblance to human tetranectin. Moore et al [5] discovered a broad-spectrum steroidal antibiotic from the dogfish shark which they nemed squalamine; chemically it is 3-beta-N-1-(N-[3-(4-aminobutyl)]-1,3-diamino-propane)-7 alpha, 24 zeta-dihydroxy-5 alpha-cholestane 24-sulfate.

PHARMACOLOGY: Many claims have been made that shark cartilage can cure cancer. The rationale includes the fact that sharks rarely get cancer, that sharks are cartilaginous fish and that cartilage is avascular and contains agents that inhibit vascularization (angiogenesis). The reasoning then follows that sharks do not get cancer because the inhibited vascularization prevents the formation of tumors; hence, giving it to humans may inhibit tumor angiogenesis and thus cure cancer. [1]

In late 1992, incomplete and since nonreplicated clinical studies (unpublished) in Havana, Cuba, purported to show some progress in terminally ill cancer patients. The National Cancer Institute reviewed these studies and decided against researching shark cartilage. [1] Recently, however, the FDA granted an IND application for a shark cartilage product, *Benefin*, by Lane Labs-USA, Inc. to investigate benefits in prostate cancer and AIDS-associated Kaposi's sarcoma. [6]

Certainly, future work should continue to focus on the isolation of the responsible proteins or small molecules. The tetranectin-like protein from the reef shark is important since, in man, tetranectin enhances plasminogen activation catalyzed by the tissue plasminogen activator. It may also play a role in cancer metastasis. Research along these lines by Moore et al[5] has demonstrated the presence of a broad-spectrum aminosterol antibiotic in the dogfish shark which they named squalamine. It shows significant bactericidal activity against both Gram-negative and Gram-positive bacteria. It is also fungicidal and induces activity against protozoa.[5] This discovery implicates a unique steroid acting as a potential host-defense agent in vertebrates and provides unique concepts of chemical design for a new family of much needed broad-spectrum antibiotics.

TOXICOLOGY: No toxicity data has appeared in current literature on either shark cartilage or squalamine.

SUMMARY: Initial interest on the purported anticancer effects of cartilage from dogfish shark has waned since the National Cancer Institute decided against supporting studies on it. A few studies on related species show interesting active protein substances that may be useful as cancer control agents. However, the only active small molecule with promise is the aminosterol called squalamine. Its major experimental activity has been as a unique and potent antibiotic with fungicidal and antiprotozoal activity. Clinical data should be forthcoming.

PATIENT INFORMATION — Shark Derivatives

Uses: The shark cartilage was thought to be a cancer control agent, but no studies have proven this theory. Squalamine has been used as a potent antibiotic with fungicidal and antiprotozoal activity.

Side Effects: No adverse effects have appeared on either substance.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SHARK DERIVATIVES

SHARK LIVER OIL

DATE OF ISSUE: MAR 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Shark liver oil may be obtained from several species of sharks, including the deep sea shark (*Centrophorus Squamosus*), the dogfish shark (*Squalus Acanthias*), and the basking shark (*Cetorhinus Maximus*).

SOURCE: Shark liver oil (SLO) is commercially produced from several species of deep sea sharks' liver oil. The liver constitutes about 25% of the total shark body weight. SLO is a major natural source of squalene and alkyglycerols.[1]

HISTORY: SLO has been used for over 40 years for its therapeutic benefits. Initially, it was employed by Scandinavian fishermen to treat skin conditions and certain cancers. The active components, alkylglycerols, have been studied in a number of areas, including use as an immune system stimulant. [2]

CHEMISTRY: SLO contains alkylglycerols, squalene, pristane, vitamins A and D, esters of fatty acids, glycerol ethers, triglycerides, cholesterol, and fatty acids. [1] Alkylglycerols are a group of ether-linked glycerols and have been found in a number of shark species. For example, 1-O-(2-hydroxyalkyl) glycerols have been isolated from Greenland SLO.[3] Dogfish shark contains 40% to 70% SLO, containing 30% to 40% 1-O-alkyl diacylglycerol ethers. [4] Purification and characterization of deep sea shark, liver oil 1-O-alkylglycerols have been performed. The oil contained glycerol esters, 60% unsaponifiable matter, including squalene (45%) and cholesterol (4.5%).[5] Between ˜ 60% to 90% of liver weight in the *Centrophorus* species is oil, containing squalene that increases in concentration with the age of the shark. More than 50 fatty acids were identified, as well.[6]

Analyses concerning shark liver components from the late 1960s through the early 1970s include the following: Oil composition of the basking shark including sterols and glyceryl esters,[7,8] separation of neutral lipids from shark liver,[9] and hydrocarbon and fatty acid research.[10,11]

PHARMACOLOGY: SLO has been classified as a topical protectant.[1] An early use of alkylglycerols from SLO was to treat leukemia and to prevent radiation sickness from cancer X-ray therapy.[2] A Danish study reports less cases of irradiation damage in alkoxyglycerol-treated uterine cancer patients. [12] Another report suggests alkylglycerols' radioprotective effects may operate by a mechanism that may incorporate the substance into a pool of platelet-activating factors, increasing their biosynthesis.[13] Alkoxyglycerol also may increase leukocyte and thrombocyte counts in specific dosages. [12] The natural alkylglycerol level rises within tumor cells, apparently an attempt in controlling cell growth. An essential step in cell proliferation involves activating protein kinase C, which can be inhibited by alkyglycerols. SLO demonstrates inhibitory actions against cutaneous angiogenesis in certain cancer cells in mice, human kidney cancer, and human urinary bladder cancer cells including sarcoma L-1 syngeneic.[14] However, a conflicting report finds no documentation regarding inhibition of tumor growth in alkoxyglycerol-treated cancer patients, even though it is used in Denmark as a supplementary agent in cancer treatment.[12]

Another effect of alkylglycerols include the ability to stimulate the immune system. One mechanism involved may include activation of macrophages. [2]

Dietary SLO also has been studied for its effects on lipid and fatty acid composition in guinea pig hearts. [15] A glycerol monoether mixture from SLO was found to be an effective skin penetration enhancer when studied in mice.[16]

TOXICOLOGY: It has been stated that SLO has no side effects in dosages of 100 mg three times daily.[2] However, in Sweden, a SLO product (*Ecomer*) was prohibited by the National Board of Health and Welfare. [17] A report on SLO-induced pneumonia in pigs is described, [18] as well as a case report concerning shark oil pneumonia.[19]

SUMMARY: SLO has been used therapeutically for the past 40 years in the areas of skin conditions, cancer treatment, and prevention of radiation sickness. Few toxic effects from SLO use have been reported, although caution regarding SLO-induced pneumonia is advised.

PATIENT INFORMATION— Shark Liver Oil

Uses: SLO has been used to prevent radiation sickness, to treat skin conditions, and as a cancer treatment. Alkylglycerols have been studied as an immune system stimulant.

Side Effects: Few toxic effects have been reported; advise caution with SLO concerning SLO-induced pneumonia.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SHARK LIVER OIL

SHELLAC

DATE OF ISSUE: FEB 1998

REPLACES MONOGRAPH DATED: SEP 1987

SCIENTIFIC NAME(S): Family: Coccidae

COMMON NAME(S): Shellac, lac, gommelaque, lacca

SOURCE: Shellac is the purified product of lac, the red, hardened secretion of the insect *Laccifer (Tachardia) lacca*Kerr. This tiny insect sucks the sap of selected trees and bushes, and secretes lac as a protective covering. The name lac is said to derive from lakh, the Sanskrit word for one hundred thousand, a reference to the very large number of insects involved in producing appreciable amounts of the product. [1]

Lac is cultivated in India, Thailand, and Burma.

The whitest lac is produced by insects infesting the kusum tree (*Schleichera trijuga*). The harvester cuts twigs coated with lac into small pieces called sticklac. The crude material is ground and soaked in water to remove debris and insect bodies. The remaining material is soaked in sodium carbonate, which removes laccaic acid, a complex mixture of at least four structurally related pigments. The resulting granules retain the yellow pigment erythrolaccin and are dried to form seedlac. Further treatment by melting, evaporating, or filtering yields shellac. [2]

CHEMISTRY: The National Formulary XV of the USA recognizes four grades of shellac: Orange, dewaxed orange, regular bleached and refined wax-free bleached. The grades differ in the manner in which the seedlac is treated. Orange shellac is obtained by the evaporation of filtered ethanolic solutions of seedlac. It may be dewaxed by further filtration. Regular bleached shellac is obtained by dissolving the seedlac in aqueous sodium carbonate at a high temperature. After filtration, a bleaching agent (such as sodium hypochlorite) is added. The resin is removed by sulfuric acid precipitation. Refined wax-free bleached shellac adds another filtration step to remove the waxes.[3]

The exact chemical composition of shellac is unknown. It appears to be composed of a network of hydroxy fatty acid esters and sesquiterpene acid esters with a molecular weight of about 1000. Aleuretic acid, r-butolic acid, shellolic acid, and jalaric acid are the major constituents. The composition is a function of the source and time of harvest of the sticklac. Variability in the product may be a problem for commercial users of shellac. The physical properties of shellac also vary. For example, the reported melting point ranges from 77° to 120°C. Shellac is soluble in ethanol, methanol, glycols, glycol ethers, and alkaline water. [1]

PHARMACOLOGY: Shellac is most often used as a finish for fine furnitures. Further, the material has been used for almost 100 years by the pharmaceutical industry. Examples of shellac's role in this field include: Tablet coating formulations, [4,5,6,7] microencapsulation,[8,9,10,11,12] matrix formation,[13] enteric coating,[14] humidity tolerance,[15] and binding ability.[16] However, shellac undergoes an "aging effect" upon storage and thus has fallen into disfavor as an ingredient in some preparations.[2]

Dentistry has also used shellac in various ways.[17,18] Reported uses include binding agents for dentures, restorations, and mouldings and as a constituent in "artificial calculus" for training purposes in dental schools. [19,20,21,22,23]

Shellac has also been used as an ingredient in hair spray [24] and in other cosmetics[25] and as pretreatment against mushroom toxins in mice.[26]

TOXICOLOGY: Little data are available regarding toxicity. One study investigated the short-term inhalation toxicity in rabbits of a hair spray-containing shellac; the product did not induce any significant toxicologic problems. [27] Shellac NF is food grade and is listed as Generally Recognized as Safe (GRAS) by the FDA. One report discusses contact cheilitis to shellac. [28] Another report reviews bezoars (accumulations of foreign material in the stomach) such as shellac. This unusual collection in the GI tract, if untreated, may lead to anorexia, weight loss, bleeding, or perforation. [29]

SUMMARY: Shellac is a crude natural material composed of variable constituents. It is produced from insect *Laccifer* secretions, then treated to form the final product. Shellac is used in furniture finishing, tablet coatings and matrices, dentistry, and cosmetics. The crude product poses little health hazard, although commercial products that dilute shellac in solvents may pose a health problem.

PATIENT INFORMATION— Shellac

Uses: The most common use is as a furniture finish, but it has also been used in the pharmaceutical industry, in dentistry, and in cosmetics.

Side Effects: Little data are available. One report discusses contact cheilitis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SHELLAC

SLIPPERY ELM

DATE OF ISSUE: FEB 1999

REPLACES MONOGRAPH DATED: MAR 1991

SCIENTIFIC NAME(S): *Ulmus rubra* Muhl. Also known as *U. fulva* Michx. Family: Ulmaceae

COMMON NAME(S): Slippery elm, red elm, Indian elm, moose elm, sweet elm

BOTANY: The genus *Ulmus* contains 18 species of deciduous shrubs and trees.[1]

The slippery elm tree is native to eastern Canada and eastern and central United States, where it is found most commonly in the Appalachian mountains. The trunk is reddish brown with gray-white bark on the branches. The bark is rough, with vertical ridging. The slippery elm can grow to 18 to 20 meters in height. [2] In the spring, dark brown floral buds appear and open into small, clustered flowers at the branch tips. [3] White elm (*U. americana*) is 1 related species and is used in a similar manner.[2]

HISTORY: North American Indians and early settlers used the inner bark of the slippery elm not only to build canoes, shelter, and baskets, but as a poultice or as a soothing drink.[2,4,5] Upon contact with water, the inner bark, collected in spring, yields a thick mucilage or demulcent that was used as an ointment or salve to treat urinary tract inflammation and applied topically for cold sores and boils. A decoction of the leaves was used as a poultice to remove discoloration around blackened or bruised eyes. Surgeons during the American Revolution treated gun-shot wounds in this manner. [3] Early settlers boiled bear fat with the bark to prevent rancidity. [1,4] Late in the 19th century, a preparation of elm mucilage had been recognized as an official product by the United States Pharmacopoeia. [6]

CHEMISTRY: Slippery elm contains carbohydrates including starches with mucilage being the major constituent. It contains hexoses, pentoses, and polyuronides.[2,7] The plant also has phytosterols, sesquiterpenes, calcium oxalate, cholesterol, and tannins (3% to 6.5%) as constituents. [2,4,7] Isolation and structure of a cyanidanol glycoside has been reported from related species *U. americana*.[8]

PHARMACOLOGY: Slippery elm prepared as a poultice coats and protects irritated tissues such as skin or intestinal membranes. The powdered bark has been used in this manner for local application to treat gout, rheumatism, cold sores, wounds, abscesses, ulcers, and toothaches. [4,7] It has also been known to "draw out" toxins, boils, splinters, or other irritants.[2]

Powdered bark is incorporated into lozenges to provide demulcent action (soothing to mucous membranes) in the treatment of throat irritation. [9] It is also used for its emollient and antitussive actions, to treat bronchitis and other lung afflictions, and to relieve thirst. [1,2,3,5,7]

When slippery elm preparations are taken internally, they cause reflex stimulation of nerve endings in the GI tract, leading to mucus secretion. [2] This may be the reason they are effective for protection against stomach ulcers, colitis, diverticulitis, gut inflammation, and acidity. Slippery elm is also useful for diarrhea, constipation, hemorrhoids, irritable bowel syndrome, and to expel tapeworms. It also has been used to treat cystitis and urinary inflammations. [2,3,4,7]

The plant is also used as a lubricant to ease labor, [3,4] as a source of nutrition for convalescence or baby food preparations, [2] and for its activity against herpes and syphilis.[4] The tannins present are known to possess astringent actions. [7]

TOXICOLOGY: The FDA has declared slippery elm to be a safe and effective oral demulcent. [5] An oleoresin from several *Ulmus* species has been reported to cause contact dermatitis[6] and the pollen is allergenic. [4] Preparations of slippery elm had been used as abortifacients, a practice that has not remained popular. [1,7] Generally, there are no known problems regarding toxicity of slippery elm or its constituents. [7]

SUMMARY: Slippery elm has been used for more than 100 years in traditional American medicine. The plant contains mucilage as its major component, which can be therapeutic in a variety of conditions. It has been used to protect irritated skin or mucous membranes in wounds, GI irritations, and respiratory ailments. It is also a good nutrient and possesses antiherpetic and antisyphilitic activity. Slippery elm is usually nontoxic but may cause dermatitis or an allergic reaction.

PATIENT INFORMATION — Slippery Elm

Uses: Parts of slippery elm have been used as an emollient and in lozenges. It protects irritated skin and intestinal membranes in such conditions as gout, rheumatism, cold sores, wounds, abscesses, ulcers, and toothaches.

Side Effects: Extracts from slippery elm have caused contact dermatitis, and the pollen has been reported to be allergenic. The FDA has declared slippery elm to be a safe and effective oral demulcent.

Dosing: Slippery elm inner bark has been used for treatment of ulcers at doses of 1.5 to 3 g/day. It is commonly decocted with ethyl alcohol. No formal clinical studies support this dosage.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SLIPPERY ELM

SMOKELESS TOBACCO

DATE OF ISSUE: JUN 1990

REPLACES MONOGRAPH DATED: N/A

BOTANY: Smokeless tobacco (ST) products are derived from the same botanical source as smoking tobacco (*Nicotiana* species). Smokeless tobaccos are often flavored with sugar or artificial sweeteners.

HISTORY: Smokeless tobaccos have been used by men and women of all levels of society. In Europe, snuffing involves placing a small pinch of tobacco in the nostrils while inhaling slightly. In the United States and many other parts of the world, "snuff dipping" is the more common practice. In this case, the user places a "quid" of powdered tobacco in the buccal area between the gum and cheek and retains the material for a period of time, usually swallowing the resultant saliva. Quids are taken as loose portions or as small prepackaged bags of tobacco. In many parts of the world, the quid is mixed with other stimulants such as betel nut. Lastly, some users chew a "chaw" of ST.

Recent national data compiled from several large-scale studies indicate that 10 to 12 million Americans use some form of ST. [1] The use of ST is prevalent throughout the United States and users often begin at very early ages. From the responses of 3,725 high school students in the southeastern United States, 20% reported trying ST products at some time. Of these users, 44% reported a first use of ST before age 13. Family influences and peer pressure were major factors in initiating use. Of concern was the indication that 8.4% of the users felt they were addicted to the substance. [2] Another survey of children in grades 3 to 12 in a Pennsylvania school district found that experimentation with ST had begun as early as the third grade, with the prevalence of use increasing with age. Nearly half of the boys in grades 7 to 12 did not believe ST products to be harmful.[3]

Children are strongly influenced by role models regarding the use of ST. To this end a survey was conducted of major league baseball personnel during the 1987 season to determine their use and understanding of the hazards of ST. Twenty-five of 26 teams participated. The players (46%) "dipped" or "chewed," more than the managers (35%), followed by the trainers (30%). Although the users recognize the harmful potential of ST, its use remains high among baseball personnel. [4] ST use is generally more prevalent among males. It should be noted that in one study, the prevalence of snuff use by women in the general population of central North Carolina was 30% (compared to 1.3% of women and 2.5% of men in the general US population).[5]

Analysis of the personality characteristics of 289 college-age users of ST found them to be significantly more reserved, less socially outgoing, less sentimental, more conforming, and more group-dependent than non-ST users.[6]

PHARMACOLOGY: As with smoking tobacco, the pharmacologic effect of ST is related to its nicotine content. Blood nicotine levels are achieved rapidly (within 5 minutes) and reach 40 ng/ml, comparable to peak levels found in heavy cigarette smokers (who average approximately 35 ng/ml). [7] The use of ST, therefore, carries many of the risks and dangers of smoking tobacco. Although there does not appear to be an increased risk of lung cancer or pulmonary disease with its use.

Oropharyngeal risks: The oral problems associated with ST use include bad breath, discolored teeth and restorative materials, excessive tooth surface wear from abrasion, decreased ability to taste and smell, gingival recession, advanced periodontal soft and hard tissue destruction, tooth loss and soft tissue erythema. [1] A common pathologic change observed in ST users is oral leukoplakia. In a study of Navajo Indians (ages 14 to 19), 25% of the users compared with 4% of non-users had leukoplakia.[8] One in 20 cases of leukoplakia will undergo malignant transformation into an epidermoid carcinoma. Nitrosamines found in ST have been shown to be tumorogenic in animals.[9]

An increased incidence of cancers of the mouth and gums, pharynx, and salivary glands have also been reported in ST users. [10] Case-controlled analyses of chronic female snuff users in North Carolina found an exceptionally high mortality from oropharyngeal cancers. The relative risk associated with snuff dipping among nonsmokers was 4.2%; among chronic users the risk approached 50-fold for cancers of the gum and buccal mucosa.[11] Users of loose portion snuff exhibit increased thickening of the oral mucosa epithelium while portion bag users show variable thickened surface layers with evidence of keratinization. [12] In an analysis of more than 2000 patients with oropharyngeal cancers, chewing, smoking, or both accounted for 70% of the cancers of the oral cavity, 84% of the oropharynx, and 75% of the hypopharynx.[9]

Tooth loss and periodontal softening occurs with chronic snuff use. Extracts of ST have served as a growth substrate for three species of oral streptococci frequently associated with human dental caries.[13]

Other risks: Thromboangitis obliterans, a distinct clinical entity characterized by segmental inflammatory and proliferative lesions of the walls of small arteries and veins has been observed frequently in heavy cigarette smokers. At least one case has also been attributed to chronic snuff use. [14]

Approximately one-third of ST users swallow the salivary juices. Persistent hyperglycemia was observed in diabetic patients who used "candified" chewing tobacco and regularly swallowed the juice. Analysis of several brands found 50 to 150 mg of glucose per gram of tobacco. Blood sugar levels returned to normal once snuff use was discontinued.[15] Other investigators suggest that saccharin added to flavor some snuffs may pose an increased risk of bladder cancer. [16]

Nicotine per se is toxic. Its cardiovascular effects include vasoconstriction, hypertension, and tachycardia. Nausea and dizziness are often experienced by novice snuff users.[17]

SUMMARY: The use of ST is increasing in the United States and remains prevalent throughout the world. Flavored tobaccos are used orally or nasally. ST preparations deliver as much nicotine as cigarettes. The use of ST is associated with a constellation of side effects. The risk of oral leukoplakia is more than 5 times greater among snuff users, and the use of ST is a major determinant of most oropharyngeal cancers. Public Law 99-252 (the Comprehensive Smokeless Tobacco Health Education Act of 1986) was developed as a federal platform for disease prevention and health promotion with respect to ST use.

PATIENT INFORMATION— Smokeless Tobacco

Uses: Smokeless tobacco has not been used medically. Its recreational use carries many of the risks and dangers of smoking tobacco.

Side Effects: Smokeless tobacco has caused bad breath, discolored teeth, excessive tooth surface wear, decreased ability to taste and smell, gingival recession, advanced periodontal soft and hard tissue destruction, tooth loss, oral leukoplakia, and increased risk of cancers in the mouth and gums.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SMOKELESS TOBACCO

SNAKEROOT

DATE OF ISSUE: NOV 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Aristolochia serpentaria*L., *Aristolochia reticulata* Nuttall. Family: Aristolochiaceae (birthwort family)

COMMON NAME(S): Snakeroot, Virginia snakeroot, snakeweed, sangree root, sangrel, birthwort, pelican flower, Texas snakeroot, Red River snakeroot

BOTANY: Aristolochia is a genus comprising approximately 300 species of herbs and vines. *A. serpentaria* is a low-growing perennial (up to 0.6 m tall) found primarily in the rich woods of central and southern US, including Connecticut to Florida, Michigan, Missouri, Louisiana, Arkansas, and Texas. Snakeroot possesses a foul, fruit-like odor that attracts insects. Its exotic, brownish-purple flowers are tube-like and lined with hairs. Insects caught in this area become covered with pollen while struggling to escape and carry it to pollinate other flowers. The leaves of the plant are heart-shaped. The medicinal parts of the plant are the dried rhizome and the roots.[1,2,3,4] *A. reticulata* differs from *A. serpentaria* in having a larger rhizome with fewer, thicker rootlets and thicker leaves with more prominent reticulations and petioles.[1]

HISTORY: Snakeroot was used as a cure for snakebite, hence the common name. Native Americans chewed the root and also applied it to wounds. Colonial and European doctors were said to have used snakeroot for infectious fevers, malaria, and rabies. The heart-shaped leaves of the plant promoted its use as a heart tonic. Modern herbalists employ snakeroot as an aphrodisiac, to treat convulsions, and to promote menstruation. None of these claims, however, have been scientifically validated.[3,5] One source mentions that *A. serpentaria* was grown in England as far back as 1632.[4]

CHEMISTRY: *A. serpentaria* contains borneol, essential oil, and serpentarin (aristolochin), a bitter principle that is yellow in color. Aristolactone, aristolochine (an alkaloid), gums, resins, tannins, and starch are also present. Most interest lies in the toxin aristolochic acid, a non-alkaloidal, but naturally occurring, nitro-compound.[1,4,6] Aristolochic acids are found only among the Aristolochiaceae and also occur in butterflies that feed on the plants. [7] In these Taiwanese butterflies, aristolochic acid acts to protect them against birds. [8] Aristolactams, also present in the family, also are found in Annonaceae, Menispermaceae, and Monimiaceae. An extensive review discussing aristolochic acids and aristolactams, regarding specific structures from certain species and botanical occurrence is available.[7]

Other Aristolochia species containing aristolochic acid include *A. clematitis*;[9] *A. auricularia* (found to contain the highest reported amount of any species);[10] those species from Sudan and China, *A. bracteata*, *A. contorta*, *A. debilis*, *A. heterophylla*, and *A. mollissima*;[11] and those used as traditional Chinese medicine "Fanchi," including *A. fangchi*, *A. kwangsiensis*, *A. heterophylla*, and *A. moupinensis*.[12] A review of Taiwanese research in natural product medicine (from 1991 to 1996) includes Aristolochiaceae.[13] Quantitative analysis of aristolochic acids has been performed. [14]

PHARMACOLOGY: Snakeroot has been used as an aromatic bitter.[1] Its known effects include stimulation of gastric secretions and smooth muscle contractions of the GI tract and heart.[15] In small doses, snakeroot can promote appetite and tone digestive organs. Larger doses promote arterial action, diaphoresis, and diuresis. It is also said to be helpful in amenorrhea.[5] Unproven effects of the plant include increased circulation, heart stimulation, fever reduction, and in the treatment of dyspepsia and skin sores.[15] Folk uses of snakeroot include treatment of fever, prevention of convulsions, promotion of menstruation, and as an aphrodisiac. Snakeroot's effectiveness as an antidote for snakebite and rabies remains unproven. [3]

A. clematitis, a related species, is used to stimulate the immune system and to treat wounds.[9] Taliscanine, a component of *A. taliscana*, has been reported to treat Parkinson's and related diseases. [16] Tumor inhibiting properties are clearly due to aristolochic acids. [6]

TOXICOLOGY: Snakeroot should not be used in humans. Aristolochic acid is a known kidney toxin in rodents. [17] Several articles confirm aristolochic acid's nephrotoxic and carcinogenic effects in humans as well. Aristolochic acids from *A. fangchi*, *A. clematitis*, and others have been found to cause kidney damage or "Chinese herb nephropathy." Cases of interstitial renal fibrosis, urothelial lesions, malignancy, Fanconi's syndrome, and end-stage renal failure all have been extensively reported.[9,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36] A review with 108 references discusses this further.[37]

The structural basis for mutagenicity of aristolochic acid has been reported. [38] In large doses, constituent aristolochine also can affect the kidneys and irritate the GI tract, leading to coma and death from respiratory paralysis. [5,6]

No one should take snakeroot, especially those with any disease of the GI tract, including ulcer, reflux, or colitis, as well as those who are pregnant or breastfeeding.[15] Aristolochic acid also may cause genetic mutations; some countries ban the plant's sale. [3] A case report explains acute hepatitis from a tea mixture (including *A. debilis*) containing toxic aristolochic acids.[39]

SUMMARY: Snakeroot once was used as a cure for snakebite, a remedy for infection, and a heart tonic. The plant is one of many from the Aristolochiaceae family of approximately 300 species. Its use as an aromatic bitter and to stimulate gastric secretions has been reported. Some uses, including wound healing and menstruation promotion, are unproven. Many reports confirming the constituent, aristolochic acid, discuss its nephrotoxic and carcinogenic effects, which can lead to end-stage renal failure. No one should use snakeroot because of its toxic effects.

PATIENT INFORMATION — Snakeroot

Uses: Do not use snakeroot because of its toxicity. Snakeroot stimulates gastric secretions and smooth muscle contractions. In small doses, snakeroot can promote appetite and tone digestive organs, and larger doses promote arterial action, diaphoresis, and diuresis.

Side Effects: Aristolochic acid, a component of snakeroot, can affect the kidneys and irritate the GI tract, and may also cause genetic mutations. Snakeroot should not be used, especially in those with diseases of the GI tract and in women who are pregnant or breastfeeding.

Dosing: While *Aristolochia* formerly was used as a bitter tonic at 1 g dosage, in view of the nephrotoxicity of aristolochic acid derivatives, it cannot be recommended at any dose.[18]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SNAKEROOT

SOAPWORT

DATE OF ISSUE: JUL 1993

REPLACES MONOGRAPH DATED: NOV 1989

SCIENTIFIC NAME(S): *Saponaria officinalis* L. Family: Caryophyllaceae

COMMON NAME(S): Bruisewort, Bouncing Bet, Dog Cloves, Fuller's Herb, Latherwort, Lady's-Washbowl, Old-Maid's-Pink

BOTANY: Common to pastures and roadsides from coast to coast, soapwort is a perennial herbaceous plant growing to a height of 1 to 2 feet, with a single smooth stem and lanceolate leaves. Its five-petaled flowers appear during late July through September in the form of fragrant clusters varying from white to pale lavender in color.[1]

HISTORY: Soapwort was originally native to northern Europe and was introduced to England during the Middle Ages by Franciscan and Dominican monks who brought it as "a gift of God intended to keep them clean."[2] By the end of the 16th century the herb had become widespread in England, where it was used as a soap for cleansing dishes and laundry. John Gerard's Herbal (1597) recommended it as a topical disinfectant for "green wounds" and "filthy diseases."[2] Soapwort also has been administered topically for the treatment of acne, psoriasis, eczema and boils. An extract of the roots is still a popular remedy for poison ivy. While an exact time of its arrival in North America cannot be established, there is little doubt that the Puritans brought it with them to the New World. Once established, the herb spread and can now be found wild throughout the United States and southern Canada. The herb was used extensively in the early textile industry as a cleaning and sizing agent. This process, known as fulling, accounts for the name "Fuller's Herb." Another use for the product was found by the Pennsylvania Dutch who used it to impart a foamy head to the beer they brewed. To this day some beer makers use saponins, a component of the plant, to provide and maintain that foamy head.[1]

CHEMISTRY: Soapwort contains a natural source of water-soluble steroidal saponins, which allow it to form a soaplike lather. These active principles are found in all parts of the plant[1] and act as surface active agents to facilitate cleaning.

TOXICOLOGY: Saponins tend to be highly toxic (usually hemolytic) only if injected. Most are relatively inocuous when ingested orally, unless there is an underlying disease of the mucosa (ie, ulcers). Ingestion of soapwort has led to severe vomiting and diarrhea.[3] For this reason, ingestion is to be avoided.

SUMMARY: While once used internally as a diuretic, laxative, and expectorant, soapwort lacks these pharmacological actions once attributed to it by herbalists or pharmacologists.[3] Its chief use today is as a source of natural saponins to be used in making "natural" soaps and shampoos. These soaps are extracted from the rhizomes and leaves of the plant and find their chief use in brightening and cleaning delicate fabrics.

PATIENT INFORMATION — Soapwort

Uses: Soapwort is generally used to make "natural" soaps and in brightening and cleaning delicate fabrics.

Side Effects: Soapwort adverse effects are usually experienced only if taken internally, causing severe vomiting and diarrhea.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SOAPWORT

SOD

DATE OF ISSUE: JUL 1995

REPLACES MONOGRAPH DATED: DEC 1989

SCIENTIFIC NAME(S): Superoxide dismutase, orgotein

CHEMISTRY: Superoxide dismutase (SOD, orgotein) is an ubiquitous enzyme that has received attention because of its therapeutic activity and because of claims that its ingestion may improve health and lengthen the human lifespan.

PHARMACOLOGY: A highly reactive superoxide free radical is generated as a toxic metabolite in a wide range of normal biological reactions that reduce oxygen. Since the superoxide radical is toxic to normal living cells, the enzyme superoxide dismutase which is present in all cells catalyzes the conversion of superoxide to the harmless components oxygen and hydrogen peroxide.[1]

At least three distinct types of the compound are found in humans and other mammals.[2] In mammals, SOD is usually confined to intracellular areas; only traces of the enzyme are found extracellularly.[3]

White blood cells involved in the acute inflammatory response release large amounts of superoxide, which appears to contribute to the destruction of bacteria. Similarly, the amount of superoxide released at the site of an inflamed joint has been shown to cause extensive and rapid degradation of synovial fluid. SOD generally protects the fluid against this degradation. Furthermore, it protects the leucocytes themselves from free radical damage. [4]

Low levels of SOD at birth appear to be related to the development of infant respiratory distress syndrome. [2] Furthermore, alterations in the superoxide level and the activity of SOD have been implicated in the development of a wide variety of chronic disorders, including diabetes and renal diseases. [5]

Although intravenous infusion of SOD has little anti-inflammatory activity due to its rapid renal clearance, the local injection of SOD has proven to be an effective treatment for a variety of inflammatory disorders. SOD's mechanism of action remains speculative. It protects leukocytes and macrophages against lysis induced by phagocytosis, probably by stabilizing membranes involved in the inflammatory events. In turn this reduces the spillage of cellular inflammants, thereby interrupting the cycle that maintains inflammation.[6]

Veterinary uses: Parenteral SOD is approved for the treatment of soft tissue inflammation in horses and dogs. The compound has been used successfully in a variety of veterinary disorders including canine allergic dermatitis, canine lick granuloma, and upper respiratory infections in cats.

Clinical uses: Similarly, superoxide has been successfully used to treat human inflammatory diseases. In West Germany, where orgotein has been in general medical use for some years, the drug is injected locally for the management of osteoarthritis, sports injuries, [7] and knee joint osteoarthritis.[8]

In a placebo-controlled study in patients with osteoarthritis of the knee, intra-articular orgotein, given as two 16 mg doses, was effective in reducing symptoms for up to 3 months after treatment.[9] One double-blind study showed that intra-articular (IA) orgotein was superior to IA aspirin (a nontraditional route of administration) in the treatment of rheumatoid arthritis of the knee.[10] The anti-inflammatory effectiveness of IM orgotein is good but less effective than that of IM gold in the treatment of active rheumatoid arthritis (52% improvement with orgotein vs 86% with gold after 6 months of treatment); the investigators concluded that SOD is a safe and effective drug for the short-term treatment of rheumatoid arthritis.[11]

In some countries, the drug has also been approved for local use in the treatment of chronic bladder inflammations including radiation-induced and interstitial cystitis.[12,13] SOD therapy has also been suggested for the treatment of hyperuricemic syndromes[14] and the management of acute paraquat poisoning.[15] Studies are underway to evaluate the effects of orgotein therapy in aiding cancer patients to tolerate radiation therapy.

SOD is currently in Phase III clinical trials to improve rejection rates after kidney transplantation and has been thought to be of use in the managment of "reperfusion injury" following an acute myocardial infarction. A recent study, however, found no clinical benefit for the intravenous administration of SOD to patients with acute myocardial infarction who underwent percutaneous transluminal angioplasty; no improvement in left ventricular function was observed in these patients, suggesting that the effects of SOD in this population may be limited. [16]

SOD has been investigated for the treatment of infant respiratory distress syndrome. While initial studies were criticized because the SOD preparation could not effectively penetrate into pulmonary cells, subsequent experiments with SOD encapsulated in liposomes and SOD complexed with polyethylene glycol have enhanced the effectiveness of this treatment. In addition, transgenic mouse cells that express superoxide may be administered by inhalation in the near future; this "gene therapy" would increase the SOD-producing capacity of pulmonary epithelial cells in patients at risk for developing oxygen-associated lung disorders. [2]

Other studies are currently underway to investigate the effectiveness of SOD in reducing oxygen radical damage following myocardial infarction or surgery where perfusion is reduced, including renal transplants. [2,17]

The superoxide radical has been implicated in the development of hepatic cirrhosis, and a reduction in the concentration of this radical by SOD treatment could be a theoretical way to limit the progression of this disease. [18]

SOD is obtained for clinical use through genetically engineered biotechnology sources.

Health food claims: Several reports have described an association between free radicals and aging. One researcher suggested that lifespans could be increased by 5 to 10 years by reducing body weight and increasing the levels of free-radical scavengers such as ascorbic acid, selenium and alpha-tocopherol. [19] Some data indicate that longer-lived animal species have a higher internal degree of protection against free radicals. [20]

Based on such reports, some health food manufacturers have promoted products containing SOD as a nutritional supplement. These oral supplements have been said to remove wrinkles and age lines, slow the aging process, and give a longer, healthier life.

There is no published data to support these claims. SOD is a labile enzyme that is rapidly degraded by gastric acids when ingested. It is essentially unabsorbed after oral administration even when enteric coated, and confers no pharmacologic activity when taken orally. While many foods (red meats, vegetables) are rich in SOD, their SOD is degraded when ingested and is rendered enzymatically inactive. The inactivity of oral SOD supplementation has been confirmed by at least one team that examined the effect of an oral SOD supplement on tissue SOD levels in mice. The animals received a diet containing 0.004% SOD, equivalent to 10 times the "recommended" intake for humans. No differences were found in the levels (activity) of two forms of SOD in tissue or blood between the control and treated groups. [21] Additionally, the analysis of 12 brands of SOD tablets purchased from health food stores indicated that one product contained zero activity and ten contained less than 20% of the labeled activity claim.[22]

TOXICOLOGY: The safety of SOD has been investigated in numerous animal models using doses up to 40,000 times the average human clinical dose of 0.1 mg/kg/day. Abnormalities were noted rarely following acute or chronic parenteral administration in mice, rats, dogs and monkeys. SOD did not induce embryonic or teratogenic changes in rats or rabbits. Parenteral administration resulted in occasional allergic sensitization in guinea pigs, but did not cause allergic reactions in horses treated for up to 6 months.[23] No immune suppression was noted after doses of up to 50 mg/kg. SOD has not been found to cause drug interactions with a variety of antibacterial agents or steroidal and nonsteroidal anti-inflammatory drugs in animals and man. [6] Pain at the injection site is usually the most common clinical complaint.

The minimal lethal dose in animals was greater than 40,000 times the anticipated human clinical dose. [24]

SUMMARY: SOD is a common enzyme found in essentially all living cells. It scavenges the toxic superoxide radical, preventing cellular damage. When administered parenterally, SOD has a local anti-inflammatory effect that has been used clinically in the management of arthritic disorders. SOD may be effective in the management of a variety of oxygen-related disorders, but significant additional research will be needed to verify its activity. To date, SOD has only shown clinical activity following parenteral and not oral administration.

Although claims have been made that the ingestion of SOD can improve health and extend life, there is no evidence that SOD is absorbed orally or that it can result in any of the claimed benefits. Even following parenteral administration, SOD is a remarkably nontoxic compound.

PATIENT INFORMATION— SOD

Uses: Sod has been used for the treatment of soft tissue inflammation in horses and dogs, human inflammatory diseases, and chronic bladder inflammations.

Side Effects: Sod has been recognized as a remarkably nontoxic compound, whereas the main complaint seems to be pain at the injection site.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SOD

SOUR CHERRY

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Prunus cerasus* L. (*Cerasus vulgaris* Mill.) Family: Rosaceae.

COMMON NAME(S): Sour cherry, morello cherry, tart cherry, pie cherry, red cherry

BOTANY: There are ˜ 270 varieties of sour cherries, a handful of which are of commercial importance (eg, Montmorency, Richmond, English morello). The sour cherry tree is smaller than the sweet cherry tree (*Prunus avium*) and is more tolerant of extremes in temperature.[1] The sour cherry originated in Europe, but is widely cultivated in America. The trees may reach ˜ 13 yards in height, with a trunk diameter of 30 to 45 cm. The bark is a grayish-brown, flowers are white to pale pink, and leaves are ovate with serrated edging.[2,3] Sour cherry fruits can grow to 20 mm in length and 18 mm in width. They are cordate drupes by nature, with color ranging from light to dark red. This fruit envelops a light brown seed. [4]

HISTORY: The Greek botanist Theophrastus described the cherry circa 300 BC; although it is believed to have been cultivated even earlier than this time. In 70 AD, Pliny indicated locations of cherry trees to be in Rome, Germany, England, and France. By the mid-1800s, cherries were being cultivated in Oregon. The first commercial cherry orchard was planted in the late 1800s. By the early 1900s, the sour cherry industry was flourishing. As of the late 1900s, 100,000 tons of sour cherries are produced in the US each year.[1,5]

CHEMISTRY: Cherries contain 80% to 85% water. Sour cherries have 58 calories per 100 grams, which contain 1000 IU vitamin A (per 100 g) as compared to 110 IU in sweet cherries.[1] Nutrients and other constituents found per 100 g of dried tart cherries include potassium, vitamin A, vitamin C, calcium, iron, phosphorus, sugars, fiber, and carbohydrates.[5] Citric acid, amygdalin, malic acid, tannin, dextrose, sucrose, quercetin, and anthocyanin are all present in juice preparations of the fruit.[3] The antioxidants kaempferol and quercetin are found in the fruits, as are ˜ 15 other compounds with antioxidant properties. [5]

Older studies have determined the presence of coumarin derivatives, [6] glycoside 2,3-dihydro-wogonin-7-mono-beta-D-glucoside, [7] and flavonoids in tart cherries.[8]

More recent studies have determined other compounds. The pigment cyanidin-3-glycoside has been isolated from the tart cherry. [9] Polyprenol patterns have been found in the leaves of the plant.[10] Chlorogenic acid methyl ester and the new compounds 2-hydroxy-3-(0-hydroxyphenol) propanoic acid, 1-(3´,4´-dihydroxycinnamoyl)-cyclopenta-2,3-diol and 1-(3´,4´-dihydroxycinnamoyl)-cyclopenta-2,3-diol have also been identified by spectral data. [11]

PHARMACOLOGY: Cherries were traditionally used by Cherokee Indians as a remedy for arthritis and gout. Today, we are finding components of the plant responsible for this anti-inflammatory and antioxidant activity. [11] Michigan State University studies indicate tart cherry compounds (eg, cyanidin) to be 10 times more active than aspirin, without the side effects. Antioxidant activity has been studied as well. Tart cherry's anthocyanins have the potential to inhibit tumor growth, slow cardiovascular disease, and possibly retard the aging process. [5]

The juice of tart cherries is used in the formulation of cherry syrup, USP, as a vehicle for unpleasant-tasting drugs. [3,4]

TOXICOLOGY: Little information concerning the toxicology of tart cherry was found in recent literature searches. One document reports in an analysis of fruits and vegetables, the contamination percentages of the mycotoxin, patulin, in sour cherry. [12]

SUMMARY: There are ˜ 270 varieties of sour cherries. They originated in Europe, but are widely cultivated in America. Sour cherries contain more vitamin A than sweet cherries. Other nutrients include potassium, vitamin C, and carbohydrates. Sour cherries contain compounds that have both anti-inflammatory and antioxidant activities; studies are continuing in these areas. Tart cherry juice is used in the popular pharmaceutical vehicle, cherry syrup. Few reports of tart cherry toxicity exist.

PATIENT INFORMATION — Sour Cherry

Uses: A study has been done on the anti-inflammatory and antioxidant properties of sour cherries. Tart cherry's anthocyanins have the potential to inhibit tumor growth, slow cardiovascular disease, and possibly retard the aging process. Tart cherry juice is used to mask the unpleasant taste of some drugs.

Side Effects: Little information exists; one document reports the contamination percentages of the mycotoxin, patulin, in sour cherry. [12]

Dosing: There is no dosage information available for sour cherry.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SOUR CHERRY

SOY

DATE OF ISSUE: APR 2003

REPLACES MONOGRAPH DATED: SEP 1998

SCIENTIFIC NAME(S): *Glycine max*. Family: Fabaceae

COMMON NAME(S): Soy, soybean, soya

BOTANY: Legumes are able to transform free nitrogen from the air into a form they can use to grow, providing the bacteria *Rhizobium japonicum* is present. The soybean is an annual plant that grows from 0.3 to 1.5 m tall. The bean pods are covered with short, fine hairs, as are the stems and leaves of the plant. The pods contain up to 4 oval seeds that can be yellow to brown in color. The cotyledons account for most of a seed's weight and contain nearly all the oil and protein. [1]

HISTORY: Soybeans were cultivated in China as far back as the 11th century BC. Described by Chinese emperor Shung Nang in 2838 BC, they were said to have been China's most important crop at this time. Cultivation of the plant went to Japan, then Europe, and eventually to the US in the early 1800s. The US now produces 49% of the world's soybeans.[1,2,3] Soy foods have become increasingly popular among health-conscious individuals since the early 1990s. In 2000, approximately 27% of US consumers reported using soy products at least once a week, nearly double the 1998 figure. [4]

CHEMISTRY: Soybeans are high in nutritional value and can contain up to 25% oil, 24% carbohydrate, and 50% protein. [1] Isolation of certain proteins and protein determination methods may be used to characterize soybeans and their products.[5] Fatty acids in beans include linoleic (55%), palmitic (9%), stearic (6%), and others. The soybean is also rich in minerals and trace elements, including calcium, iron, potassium, amino acids, and vitamins. It is also a good fiber source. [1,2] Soybeans also contain compounds known as isoflavones, which have structures molecularly similar to natural body estrogens (phytoestrogens). Genistein and daidzein are the most abundant isoflavones in soybeans.[4] Glycitein and equol are other isoflavones found in the plant. [4]

PHARMACOLOGY: Dietary phytoestrogens have been extensively studied for their proposed roles in cancer prevention, treatment of menopausal symptoms, osteoporosis, cardiovascular disease, and GI disorders.

Isoflavones, the phytoestrogens from the soybean, are similar to the main female hormone estradiol; therefore, they have similar effects, including hormonal and nonhormonal actions.[4] Hydrolysis of these isoflavones by intestinal glucosidases yields genistein, daidzein, and glycitein. These compounds undergo further metabolism to equol and p-ethyl phenol. This metabolism is highly variable and may depend, for example, on carbohydrate intake altering intestinal fermentation. Isoflavones are secreted into bile via the enterohepatic circulation. Plasma half-life of genistein and daidzein is approximately 8 hours, with peak concentration being achieved in 6 to 8 hours in adults. Elimination is via the urine, primarily as glucuronide conjugates. [6]

Anticancer effects: In some studies, soybeans appear to exert modest anticancer activity.[7] Inhibition of early cancer markers in human epithelial cells has been demonstrated by genistein.[8] Another report found genistein to retard growth of implanted tumors both in vivo (mice) and in vitro. [9] These anticancer effects of genistein may be related to its ability to reduce expression of stress response related genes. Induction of stress proteins in tumor cells protects them against cell death, so inhibition of this stress response by the isoflavone is beneficial. [10]

Breast cancer: Isoflavones are considered to be selective estrogen receptor modulators but also possess nonhormonal properties. In 1990, The National Cancer Institute was prompted to hold a workshop following reports of decreased chemically-induced rat mammary cancer after the addition of soy protein to a typical laboratory diet. The low breast cancer mortality rates in Japan and other Asian countries where soy is commonly consumed added to this intriguing discovery. In 1991, a case-controlled study reported a 50% reduction in premenopausal breast cancer risk that was associated with soy consumption. [4] However, there are conflicting data as other investigators have reported that the isoflavones in soy may actually stimulate breast tumor growth through their estrogenic activity. [11] Studies of 1-year duration indicated that isoflavone supplements do not affect breast tissue density in premenopausal women and may decrease density in postmenopausal women. These effects are opposite to those of hormone replacement therapy (HRT). Overall, the data are not persuasive that adult consumption of soy affects the risk of developing breast cancer or that soy consumption affects the survival of breast cancer patients. Nonetheless, if breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them.[4] Several organizations, including the American Cancer Society, American Dietetic Association, and American College of Obstetricians and Gynecologists, have commented on the consumption of soy in breast cancer patients. However, none of these statements appear to be the result of a comprehensive evaluation of the relevant literature.

Prostate cancer: Prostate cancer incidence appears to decrease with increasing isoflavone intake. [12] Genistein has been shown to decrease prostate cancer in vitro. Asian men consuming low-fat, high-fiber, soy-based diets have a lower incidence of prostate cancer than European or North American men. Isoflavones present in prostatic fluid, and the metabolic data on these males has been reported. [13]

Food allergy/intolerance in infants: Cow's milk allergy affects approximately 2.5% of children. Allergy is characterized by a specific IgE response. In clinical practice, alternative protein sources from vegetable proteins, such as soy, are substituted for cow's milk. [14] Food intolerance does not imply a specific mechanism but is a reproducible adverse reaction to a specific food. In infants, cow's milk protein intolerance is most common. It has been suggested that exposure to cow's milk early in life may predispose the infant to an increased risk of allergy or intolerance. There is insufficient evidence to suggest that substitution with soy milk can prevent the development of atopy. Many infants with food intolerance become tolerant over time, with the risk of persisting intolerance increased with evidence of atopy. [15]

Menopausal symptoms: Women of menopausal age suffering from symptoms of decreased estrogen production may benefit from HRT, a combination of estrogen and progesterone. However, a 5-year study has shown that HRT increases the risk of heart disease and breast cancer. [16] Soy products may offer a favorable alternative to conventional HRT. Hot flashes and postmenopausal symptoms, including bone mineral loss, can be reduced by a daily intake of 45 g of soy flour. [2] Hot flashes were decreased by 45% in one report in postmenopausal women given soy powder, as compared with 30% reduction with placebo powder. [6]

Osteoporosis: Evidence for an estrogenic, bone-preserving effect of isoflavones has been provided in a number of studies. In a Japanese study evaluating daily intakes of isoflavones in 478 postmenopausal women, there was evidence of increased bone mineral densities. However, data also exist that demonstrate no effect on bone.[12] Thus, evidence in this area is weak, especially when taking into account that no studies have examined reduction in fracture rates in osteoporotic women.

Osteoarthritis (OA): Current treatments for OA generally consist of pain relief. Avocado/soybean unsaponifiables (ASU) are made of one-third avocado oil and two-thirds soybean oil. Preclinical studies showed this combination to have some anti-OA activity, possibly via effects on interleukin-1 and collagen synthesis. In one study, patients with OA (N = 164) of the knee or hip were entered into a randomized controlled trial with a 6-month treatment period and a 2-month posttreatment follow-up. Patients were given ASU or placebo. Greater improvement in pain scores and functional indices was noted for the active treatment group. The authors suggest that ASU may be useful, when prescribed before NSAIDs, in slowing the symptomatic activity of OA. However, because no radiographs were performed in the trial, no comments can be made on the effects of ASU relating to structure-modifying properties. [17]

Cardiovascular disease/lipid alterations: Atherosclerosis begins in adolescence as fatty streak lipid deposits in the arterial wall. High concentrations of total plasma cholesterol and low-density lipoprotein (LDL) cholesterol accelerate atherogenesis in the teenage years and lead to cardiovascular disease. Phytosterols are in the forefront of research on the development of food products that lower plasma cholesterol concentrations. Soybean phytosterols have been shown to lower total and LDL cholesterol in a randomized, controlled trial of males with elevated LDL cholesterol. [18] Increased consumption of soy in Asian populations is associated with decreased rates of cardiovascular disease.[19] A vegetarian diet consisting of soy-based products was given to 32 patients with coronary heart disease who discontinued their conventional hyperlipidemic medications. The diet resulted in normalization of serum lipids, with the best results associated with the group who maintained this diet for the longest period of time. [20]

A meta-analysis of 38 trials showed a decrease in LDL cholesterol.[21] The average soy protein consumed to achieve these benefits was 47 g per day. This supports the FDA-approved health claim that 25 g of soy protein per day, along with a low-fat diet, may reduce the risk of heart disease.[22] Soy protein also has been shown to have a beneficial effect on triglycerides but does not appear to benefit HDL cholesterol. Overall dietary replacement of animal protein with soy protein may have a favorable yet variable effect on serum lipid values in men and women. The addition of soy protein to the diet may be useful for patients requiring only modest reductions in cholesterol.[23] The precise mechanism by which soy improves the blood lipid profile is unknown. One possible mechanism is altered hepatic metabolism, with enhanced removal of LDL and very low density lipoprotein (VLDL) cholesterol by hepatocytes.[22]

GI effects: Beneficial effects on large bowel function were found in rats given a mixture of soybean and cereals vs a standard diet. Soybean fiber can prevent constipation, reducing the incidence of bowel diseases.[2] The use of fiber-supplemented soy formula in one report reduced the duration of diarrhea in 44 infants.[24] Soy also has been investigated in studies for the treatment of infantile colic[25] and recurrent abdominal pain in childhood.[26] However, there is no evidence to suggest soy has any beneficial effect in these 2 conditions.

Food use: Soy is an important food source and has been used in Asian cultures for thousands of years. These cultures consume 60 to 90 g/day of soy, as compared with Western diets that contain about one tenth of that amount.[3] Soybean products are numerous and include milk, flour, curd, sufu, tofu (cheese-like cake high in protein and calcium), tempeh (Indonesian ingredient), miso (fermented soybean paste), sprouts, soy sauce, soybean oil, textured soy proteins (in meat extenders), soy protein drinks, and livestock feeds. Because of its low cost, good nutritional value, and versatility, soy protein also is used as part of food programs in less developed countries.[1]

INTERACTIONS: A subtherapeutic international normalized ratio (INR) was reported in a 70-year-old man stabilized on warfarin after he started drinking soy milk.[27] The INR returned to the therapeutic range when he stopped drinking soy milk.

TOXICOLOGY: Tolerance to soy preparations in one study (N = 164) was reported to be good to excellent for most patients.[17] However, both toxicity and allergy have been reported in the literature.

The effects of phytoestrogens in soy-based infant formulas are of concern and could have clinical consequences.[28,29] In one report, daily exposure of infants to the isoflavones in soy-based formula was found to be 13,000 to 22,000 times higher than estradiol concentrations in early life,[30] whereas the contribution of isoflavones from breast milk and cow's milk are negligible. Additionally, scientific reports of the goitrogenic effects of soy have been reported since the 1930s. A study by Japanese researchers concluded that intake of soy (30 g/day) could cause enlargement of the thyroid and suppress thyroid function. It has been proposed that the soy-formula-fed infant is at risk of thyroid dysfunction. Alteration of thyroid levels during the neonatal period may lead to disorders of the CNS and abnormal psychomotor development. In 1998, the US Environmental Protection Agency suggested the phytoestrogen content of soy formulas required priority research.[31]

Inhalation of soy dust caused an asthma epidemic in 26 patients exposed to an unloading of the product. This incident was confined only to Barcelona, Spain. Skin prick tests confirmed exposure to soy in all cases. Specific immunoglobulins, such as IgE, are associated with this type of "soy bean asthma."[32]

Soy and peanut are phylogenetically and antigenetically similar to each other and to other beans. Exposure to both is widespread, and thus, they are an exceedingly common cause of food allergy. It is not uncommon to find positive tests for IgE antibody to these foods in individuals who are clinically reactive to one or the other. However, there is not enough data to recommend soy avoidance in peanut allergic patients.[33]

Soybeans treated with the appropriate proteases reduces allergenicity of the soybeans themselves.[34] Reports also are available that describe how fatal allergic reactions from soy can be prevented.[35]

SUMMARY: The soybean is a versatile legume and has been used by Asian populations for thousands of years. Soybeans are high in nutritional value and are an excellent source of protein, vitamins, and minerals. The effects of phytoestrogens found in soybeans are hormonal and nonhormonal. Soy exerts a small but beneficial effect on total and LDL cholesterol. It also may alleviate menopausal symptoms, improve bone mineral density in osteoporosis, and regulate the bowel. Soy intake is generally well tolerated in most individuals. Cross-sensitivity exists with peanuts. Soy can be substituted for cow's milk in infants with allergy. However, more research is needed in infants consuming soy-based formulas.

PATIENT INFORMATION— Soy

Uses: Soy is commonly used as a source of fiber, protein, and minerals. The isoflavone compounds in soybeans may be useful to alleviate menopausal symptoms, possibly improve bone mineral density in osteoporosis, and treat some minor GI problems. Soy exerts a small but beneficial effect on total cholesterol and LDL cholesterol.

Interactions: For potential interactions, refer to the Evidence-Based Herb-Drug Interactions appendix.

Side Effects: Overall tolerance to soybeans is good to excellent for most patients. Although there are no robust studies, the effects of phytoestrogens (found in soy-based infant formulas) on CNS and psychomotor developmental processes are a concern.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SOY

SPINACH

DATE OF ISSUE: MAR 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Spinachia oleracea*. Family: *Chenopodiaceae*[1]

COMMON NAME(S): Spinach

BOTANY: The *Chenopodiaceae* family consists of 100 species. They are evergreen or semi-evergreen annuals, perennials, and shrubs. Other members of this group include beet and chard.[1] Spinach reaches edible maturity quickly (37 to 45 days) and thrives best during the cool, moist seasons of the year. There are a number of varieties of spinach, all of which have large, dark-green leaves on upright plants. The leaves are the most frequently used parts of spinach. [2]

CHEMISTRY: Spinach contains a number of antioxidants including carotenoids, polyphenols, [3] and flavonoids.[4] The carotenoids are composed of 2 main classes, carotenes (beta-carotene) and xanthophylls (lutein). [5]

PHARMACOLOGY: The main components in spinach, carotenoids, polyphenols, and flavonoids, provide many of its actions. These compounds possess antioxidant properties.

Age-related macular degeneration: Xanthophylls are abundant in green leafy vegetables such as spinach. Lutein and its isomer zeaxanthin are xanthophylls, which exert their action by powerful inhibition of lipid peroxidation and its chemical oxidation by free radicals. For more than 200 years, controversy has surrounded the yellow coloration in the central 3 mm of the retina known as the macula lutea. Studies in the 1940s and 1950s showed that the xanthophylls improved night vision and adaptation to dusk. Lutein and zeaxanthin now are known to be present in the lens of the eye and to have a role in cataract prevention. Furthermore, studies have shown that lutein intake can lower the prevalence of age-related macular degeneration. [5,6]

Cancer: It has been suggested that phytoestrogens, hormone-like compounds found in plant foods, might play a protective role in the etiology of cancer. One mechanism by which these plant foods could have protective effects is by exerting antioxidant activity. Polyphenols and carotenoids have such properties. In 1 study, 23 healthy volunteers were given juices from tomatoes, carrots, and spinach powder daily for a 2-week period. All 3 products appeared to be capable of suppressing DNA strand breaks. It has been proposed that these plant products exert their cancer-protective effect via a decrease in oxidative and other damage to human DNA. [3]

Epidemiological studies have demonstrated an inverse relationship between premenopausal breast cancer risk and spinach, onion, and lettuce intake. These foods are rich in the flavonoid quercetin, which inhibits the proliferation of human breast cancer cells in vitro and mammary tumorigenesis in vivo. Potential mechanisms for the anticarcinogenic effects of quercetin might include its capacity to bind with type ?? estrogen receptors and its potent antioxidant activity. [4,7] The effects of spinach have been studied in a variety of different cancers. It has been suggested that it may decrease the risk of prostate cancer. [8]

Papillomas: The naturally occurring polyphenolic antioxidants have received increased attention as cancer-preventive agents. Natural antioxidant (NAO) is found in spinach leaves. NAO is a water-soluble mixture of polyphenols and flavonoids that is a free radical scavenger. NAO has been shown to reduce the multiplicity of papillomas in a mouse model ($P < 0.01$).[9]

Cardiovascular disease: Analysis of the Framingham study showed that an increased frequency in the consumption of fruit and vegetables, the dominant source of folate in the human diet, was associated with higher levels of plasma folate, lower levels of plasma homocysteine, and a reduced risk of cardiovascular disease. Spinach consumption can increase plasma folate concentration.[10] However, spinach is probably only one of many dietary factors.

Neurological dysfunction: Common components thought to contribute to age-related neurological dysfunction are increased susceptibility to long-term effects of oxidative stress and inflammatory insults. Spinach fed to aged rats was found to reverse certain age-related deficits in neuronal and behavioral parameters (eg, learning, memory). This has been attributed to polyphenolics found in spinach. The findings indicate potential associations with neurotransmission and/or receptor function, possible immunomodulatory effects, and alteration in the antioxidant status of the brain. [11]

Immune system effects: Oxidative stress resulting from the cumulative damage caused by reactive oxygen species (ROS) is present throughout life and thought to be a major component of the aging process. The immune system is particularly vulnerable to oxidative damage because many immune cells produce those reactive compounds as part of the body's defense mechanisms. Antioxidants intercept or scavenge free radicals, preventing the formation of ROS. Among the dietary antioxidants are the carotenoids, including beta-carotene, lycopene, and lutein. Spinach is a source of two of these, beta-carotene and lutein. Thus, carotinoids might help maintain immune cell integrity by reducing damage by ROS to cell membranes and their associated receptors and modulating immune cell function by influencing the activity of redox-sensitive transcription factors and the production of cytokines and prostaglandins. [12]

INTERACTIONS: Spinach has a high vitamin K content and, as such, can decrease the international normalized ratio (INR) in patients taking warfarin. Warfarin interferes with the hepatic synthesis of vitamin K-dependent coagulation factors. Because of this mechanism of action, fluctuations in vitamin K intake can cause changes in anticoagulant response.[13]

TOXICOLOGY: Uric acid is a product of purine catabolism. Some purines are made in the body, while others come from food. Spinach contains moderate amounts of purines. Because gout is caused by high levels of uric acid with crystals forming in the joints, dietary measures to reduce purine intake may be appropriate. [14]

An IgE-mediated allergy to spinach has been reported. A 48-year-old woman experienced an episode of uvular edema, oropharyngeal itching, and facial angioedema while eating fresh spinach. This was reported as oral allergy syndrome (OAS) resulting from direct contact between food and oral mucosa. It appears to be related to the very high concentration of mast cells in the oropharyngeal mucosa, leading to extensive contact between the allergen and specific IgE bound on the mast cell surface. Allergy to fresh fruits and vegetables is the most frequent cause of OAS. It normally affects patients who are allergic to pollen and only occasionally is associated with this allergy. Additionally, spinach contains histamine, which can cause pseudoallergic reactions. [1]

Cross-allergy between spinach and latex and mushrooms also has been reported. [15,16]

SUMMARY: The main effects of spinach are related to its main chemical components: Carotenoids, polyphenols, and flavonoids. These agents possess antioxidant properties and scavenge free radicals, preventing oxidative stress associated with cell aging. Several studies have proposed a role for these antioxidants in the prevention of macular degeneration in the eye, cancer, cardiovascular disease, or degeneration of the immune and neurological systems.

PATIENT INFORMATION — Spinach

Uses: Many of the actions of spinach are related to its antioxidant properties. Prevention of cancer, cardiovascular disease, macular degeneration in the eye, and degeneration of the immune and neurological systems have been reported.

Interactions: In patients taking warfarin, vitamin K intake can cause changes in anticoagulant response. Patients on long-term warfarin therapy should limit their intake of foods containing vitamin K (eg, spinach). Cross-allergy between spinach and latex and mushrooms also as been reported.

Side effects: Cases of allergic reactions to spinach have been reported rarely. Because gout is caused by high levels of uric acid with crystals forming in the joints, dietary measures to reduce purine intake may be appropriate.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SPINACH

SPIRULINA

DATE OF ISSUE: MAY 2003

REPLACES MONOGRAPH DATED: FEB 1998

SCIENTIFIC NAME(S): *Spirulina spp.* Family: Oscillatoriaceae.

COMMON NAME(S): Spirulina, dihe, tecuitlatl, blue-green algae

BIOLOGY: Spirulinas are blue-green algae (cyanophytes) that take the form of microscopic, corkscrew-shaped filaments. The cell dimensions, degree of coiling, and length of the filaments vary with the species.[1] There are 35 species of spirulina,[2] with *S. platensis* and *S. maxima* most commonly used as food sources.[1] They live in high-salt alkaline water in subtropical and tropical areas. [2] In some locations, they impart a dark-green color to bodies of water. They are noted for their characteristic organism behavior in carbonated water and their energetic growth in laboratory cultures. [3]

HISTORY: Spirulina has been documented in literature since the 16th century. Spanish explorers found the Aztecs harvesting a "blue mud" that probably consisted of spirulina. The mud, which was dried to form chips or cheese-flavored loaves, was obtained from Lake Texcoco in what is now Mexico. Spirulina was similarly harvested by natives of the Sahara Desert where it was known by the name dihe. Thus, over the ages, 2 populations approximately 10,000 km apart, independently discovered and utilized the nutritional properties of spirulina. [4] Spirulina has been sold in the United States as a health food or food supplement since about 1979. [5]

CHEMISTRY: Spirulina consists of approximately 65% crude protein,[6] high levels of B-complex vitamins,[6] and ß-carotene.[2] The protein content includes all 22 amino acids, but the balance of these is not as desirable as that in many types of animal protein. High levels of the polyunsaturated fatty acid, gamma linolenic acid, are present.[7] Spirulina preparations contain iron at levels of 300 to 400 ppm dry weight. Unlike many forms of plant iron, this iron has a high bioavailability when ingested by humans. A dosage of 10 g/day can contain 1.5 to 2 mg absorbable iron. Trace elements present at high levels include manganese, selenium, and zinc. Also, concentrated in the organisms are calcium, potassium, and magnesium.[8] Spirulina is the first prokaryote found to contain a ferredoxin. [9] Ferredoxin obtained from *S. maxima* is a stable, easily extractable plant type. A superoxide dismutase has been isolated from *S. platensis*.[6]

PHARMACOLOGY

Food supplement: Several authors have reported that spirulina can be used as a weight loss aid. The theory is that high levels of phenylalanine act to inhibit the appetite. However, an FDA review found no evidence to support this claim.[10,11]

Spirulina's role as a nutritional supplement has been well documented in animal studies. A study in rats found that *S. maxima* is a good protein source, as indicated by weight gain, but the rats showed no sign of reduction of total caloric intake.[12] The nutritional value of spirulina depends on the method of processing; protein in concentrates prepared from disintegrated cellular material has greater bioavailability than preparations of whole cells. [4,13] An examination of 3 commercial preparations of spirulina indicated that more than 80% of what is thought to be vitamin B_{12} may actually be analogs that have little or no nutritional value for humans.[14] *S. fusiformis* is a valuable source of vitamin A in rats.[15] Spirulina as a ß-carotene source is questionable compared with standard sources, but spirulina-fed rats exhibit better growth patterns than those fed standard diets.[16] *S. maxima*'s alteration of vitamins A and E storage and utilization have been reported in rats. [17] Availability of iron from spirulina fed to rats is comparable with rats being fed standard ferrous sulfate. [18] Spirulina alone or in combination with iron supplements is also a good dietary supplement during pregnancy in animals.[19]

Cancer: Extract of spirulina and dunaliella algae injected into induced oral carcinoma in animals resulted in 70% partial tumor regression. [20] A similar study reported the absence of gross tumors in experimental oral cancer in hamsters.[21] Tumor regression is accompanied by induction of tumor necrosis factor, suggesting a possible mechanism of tumor destruction.[22] A later evaluation confirms spirulina's chemopreventive effects in human oral leukoplakia in tobacco chewers in India (45% lesion regression vs 7% placebo).[23]

Immune system: Studies on the consumption of food-grade microalgae have reported enhanced immune function in animals and humans. Dietary spirulina has been shown to exhibit chemopreventive and antiviral effects in humans. The active component for these effects has been investigated; it appears that several types of polysaccharides exhibit biological activity.[24] However, efficacy after oral administration is highly unlikely because of poor absorption and rapid breakdown. Calcium spirulan inhibits replication of several enveloped viruses. These include herpes simplex, cytomegalovirus, mumps and measles viruses, influenza A virus, and HIV-1. Inhibition of virus entry into host cells appears to be the mechanism.[25] Another polysaccharide found in spirulina, immunlina, has been shown to activate monocytes and macrophages.[24]

Cytokines are proteins produced by lymphocytes that affect the behavior of immune cells. The interferons and interleukins are 2 such cytokines that regulate the balance between macrophage activation and antibody production to a particular immune stimulus. Addition of spirulina to peripheral blood mononuclear cells can augment the production of interleukin-4, interleukin-1ß, and interferon-?. The greatest effect is on interferon-?, thus indicating a shift toward a cell-mediated immune response. Therefore, it may be suggested that spirulina appears to be a strong agent for conferring protection against intracellular pathogens and parasites. [26]

The authors of these studies propose that successful development of these microalgal polysaccharides would add to the arsenal of available agents for immunotherapy in the treatment of cancer and infectious diseases.[24]

Type 2 diabetes mellitus: Diabetes mellitus is a chronic disorder affecting the metabolism of carbohydrates, fats, and proteins. Development of secondary complications and multiple organ failure is directly related to hyperglycemia caused by nonenzymatic glycation of serum proteins. Ninety percent of diabetic patients are noninsulin-dependent and this syndrome can be effectively controlled with prudent diet therapy. Thus, research into natural foods such as spirulina has progressed. One such study investigated the long-term effect of spirulina supplementation (2 g/day). Twenty-two patients with type 2 diabetes mellitus were enrolled, with 15 patients allocated to the spirulina group and 7 serving as controls. After 2 months of treatment, fasting blood sugar was reduced 27%, triglycerides 22%, and total cholesterol 11%.[27] These results have been supported in another small trial (N = 25). [28]

Studies show that spirulina exerts hypoglycemic effect because of its fiber content. However, another theory is based on the possible action of peptides and polypeptides generated by the ingestion of spirulina proteins. These peptides may act as a stimulating agent for insulin. The actions on lipids have been attributed to gamma linolenic acid found in spirulina.[27]

Hyperlipidemia in nephrotic syndrome: Hyperlipidemia is a recognized feature of proteinuria and nephrotic syndrome. The common lipid abnormalities frequently encountered are hypercholesterolemia and increased low density lipoprotein. Hyperlipidemia is thought to be an important factor in the progression of renal failure via glomerulosclerosis. The pathogenesis is complex but there is general agreement that hepatic synthesis of lipids is increased and clearance is altered. Additionally, large amounts of protein are lost in the urine. Many lipid-lowering agents have been tried in patients with nephrotic syndrome. Two studies report the effects of spirulina.

In one study, 40 patients with nephrotic syndrome caused by primary glomerulonephritis were enrolled; 20 received spirulina 5 g/day, and 20 served as controls. After 8 weeks' treatment, total cholesterol decreased 40%, triglycerides 22%, and LDL cholesterol 22.4%. A decrease in urine protein excretion also was noted in the spirulina-treated group. The cause of decreased proteinuria could be caused by a direct effect of dietary manipulation or by the effect of decreased hyperlipidemia. [29] A similar small study (N = 23) in children (average, 7.5 years of age) with nephrotic syndrome also demonstrated reductions in total cholesterol, triglycerides, and LDL-cholesterol.[30]

Further studies are required before a recommendation can be made on the therapeutic use of spirulina in this area.

Fatty liver: The addition of spirulina maxima (5%) to a purified diet has been shown to prevent fatty liver. In this study, 25 rats had spirulina added to their diet (25 received no spirulina). No increases in liver cholesterol were noted in the spirulina-fed rats. The authors suggest a potential hepatoprotective role of spirulina. [31]

Asthma: Asthma is characterized by hyperresponsiveness of the bronchi. It is currently treated by inhaled corticosteroids and bronchodilators. However, because of the side effects of these drugs, research is ongoing into the effects of using natural alternatives for this condition. Gamma linolenic acid (GLA) is one such therapy. In humans, linolenic acid (LA) is converted to GLA via enzymatic action. However, this can be limited and produce GLA deficiency. This, in turn, results in lack of prostaglandin E_1, proposed as having a possible role in asthma pathogenesis. Spirulina has a high GLA content; 1 g contains 14 mg of GLA. In a small study (N = 34), patients with mild to moderate asthma were divided to receive conventional drugs only, spirulina (1 g/day) only, or both for a 2-month period. Improvement in lung function was observed in patients receiving spirulina supplementation and conventional therapy. [32] However, it should be noted that this study was small and no long-term studies in patients with asthma have been performed.

Rheumatoid arthritis (RA): RA is a chronic systemic autoimmune disease characterized by progressive joint damage and cartilage destruction. The inflammation results from an unregulated cascade of complex cell-to-cell interactions initiated by macrophages. *Zymosan*, a product consisting of purified bakers yeast, induces a similar reaction. In mice with chemically-induced arthritis, as measured by an increased level of ß-glucuronidase activity in the synovial fluid, spirulina (100 to 400 mg/day) can suppress enzymatic activity. Triamcinolone also abolishes the enhanced ß-glucuronidase activity. It has been reported that phycocyanin, a protein found in spirulina, exerts a scavenging action against reactive oxygen species and anti-inflammatory activity. The effects of spirulina may be mainly caused by its constituent phycocyanin. Because it has been demonstrated that spirulina can be consumed safely, it has been proposed that further preclinical and clinical studies be performed to determine its place as a potential drug for the treatment of RA. [33]

Spirulina also has been reported to reduce gastric secretory activity, [34] and provide radioprotection (against gamma radiation) in mouse bone marrow cells. [35]

Costs: Spirulina has been touted as a food source. Cost is, therefore, a consideration in choosing it as a food. Studies have shown the protein content of spirulina to be no better than protein from sources such as meat or milk. The cost of spirulina protein is about 17 cents per gram, compared with only a half cent per gram of beef. Dietary iron of spirulina is highly bioavailable but could be costly as well. [36]

TOXICOLOGY: Nutritional tests have established spirulina as nontoxic to humans. [5] However, spirulina can contain amounts of mercury as high as 10 ppm. Consumption of 20 g of spirulina per day could produce a mercury consumption above the maximum 180 mcg considered prudent for safety. [8] Reported mean heavy metal levels include arsenic 0.42 ppm, cadmium 0.1 ppm, lead 0.4 ppm, and mercury 0.24 ppm. Microbial contamination may occur if spirulina is grown on the effluent of fermented animal wastes. [37] Spirulina can concentrate radioactive di- and trivalent metallic ions. [38] Some spirulina manufacturers report that microbiological data for standard plate counts, fungi, yeasts, and coliforms conform to US standards for spray-dried powdered milk.

SUMMARY: Spirulina is a blue-green algae that is used as a food and food supplement. It contains high levels of protein and B-complex vitamins; the nutritional value, particularly of the latter, has been questioned. Spirulina represents an expensive source of dietary protein and iron. Reports find spirulina effective in tumor regression, chemo- and radioprotection, virus inhibition, and enhancing antibody production. Recent research indicates a possible role in the treatment of asthma and RA. Spirulina seems to be nontoxic in humans but may harbor some contaminants, such as heavy metals or microbes.

PATIENT INFORMATION — Spirulina

Uses: Spirulina is sold in the United States as a health food or health food supplement and also has been reported to enhance the immune system, improve dietary hyperlipidemia, exert a positive effect on liver triglycerides, and cause tumor regression. Recent research indicates a possible role in the treatment of asthma and rheumatoid arthritis. There is limited information to recommend blue-green algae for any indication.

Side Effects: Spirulina is nontoxic in humans.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SPIRULINA

SQUILL

DATE OF ISSUE: APR 1991

REPLACES MONOGRAPH DATED: APR 1989

SCIENTIFIC NAME(S): European or white squill (*Urginea maritima* L. Baker); Indian squill (*U. indica*Kunth.). Commercial samples of Indian squill are often mixtures of *U. indica* and *Scilla indica*Roxb. Red squill (*U. maritima* var. *pancratium* Stein Baker). Referred to in some texts as *U. scilla* Steinh. Family: Liliaceae

COMMON NAME(S): European squill, Mediterranean squill, white squill, Indian squill, red squill, sea onion, sea squill

BOTANY: Squill is a perennial herb that is native to the Mediterranean. It often grows in sandy soil. The bulbous portion of the base is harvested and the dried inner scales of the bulb are used. White squill has sometimes been adulterated by the inclusion of Indian squill.

HISTORY: Some varieties of squill have been known for more than a thousand years to be effective rodenticides. In man, extracts of the bulb have been used as a cardiotonic for the treatment of edema, as an expectorant, and as an emetic. Today it continues to find use as an expectorant in some commercial cold preparations. [1] Due to the popularity of the digitalis glycosides, squill components are rarely used as cardioactive agents.

CHEMISTRY: Squill contains several related steroidal cardioactive glycosides. Those found in the greatest concentration in the bulb include scillaren A and proscillaridin A (the aglycone of both is scillarenin). In addition, glucoscillaren A, scillaridin A, and scilliroside have been characterized. In one study, the most common components identified in dried bulbs were scilliroside (appr. 45 ppm) and scillaren A (appr. 38 ppm); [2] others have found proscillaridin A in the greatest concentration.[3] Scillaren B has been used to describe a mixture of squill glycosides as opposed to pure scillaren A. [4] Squill bulbs contain more than a dozen unique flavonoids. Components of squill tissue cultures appear to vary significantly in quantitative composition from whole bulb extracts. [5] Further, the extracts from fresh bulbs can vary significantly by season.

PHARMACOLOGY: Squill extracts cause peripheral vasodilation and bradycardia in anesthetized rabbits. [5]

Squill glycosides have cardiotonic properties similar to digitalis. However, squill components are generally poorly absorbed from the gastrointestinal tract and are less potent than digitalis. Some preparations do exist for oral administration and these are enteric coated to prevent degradation by gastric acidity. A semisynthetic derivative, meproscillaren derived from proscillaridin, is absorbed orally and may be effective in some patients.

The strength of squill preparations and extracts may vary and therefore must be used with caution. An analysis of the comparative potencies of extracts of *U. maritima* and *U. indica* based on a British Pharmacopoeial assay for digitalis found no significant differences between the species when activity was expressed as ml tincture/kg of guinea pig weight.[6]

Squill induces vomiting by both a central action and local gastric irritation. Vomiting may be preceded by a generalized increase in the flow of secretions, and therefore these compounds appear to exert an expectorant effect in sub-emetic or near-emetic doses.

Methanolic extracts of red squill have been said to be effective as hair tonics in treating seborrhea and dandruff, the activity being ascribed to scilliroside. [4] In general, red squill is not employed medicinally. The powdered dried bulbs of red squill find their main use as rodenticides. Death is due to the centrally-induced convulsant action of scilliroside rather than direct cardiotoxicity. Rats lack the vomit reflex and are insensitive to the emetic action of these glycosides. Because squill-laced bait is vomited by domestic animals before a lethal dose can be absorbed, it is often considered to be a rat-specific agent.

Squill has been used traditionally as a cancer remedy, and silliglaucosidin has shown activity in an experimental cancer cell line. [7]

TOXICOLOGY: Although white squill and its extracts have the potential to induce life-threatening cardiac effects in relatively low doses, they have not generally been associated with human toxicity. Vomiting is often induced as a reflex in cases of overdosage, minimizing the absorbed dose. The toxic dose of squill soft mass (a galenical extract form used to make certain squill preparations) in guinea pigs is 270 mg/kg; tinctures made from Indian squill caused death at a dose of 36 mg/kg. [8] Red squill may induce central nervous system effects resulting in convulsions. Fresh bulbs contain a vesicant. [7]

SUMMARY: Squill and its extracts have been used for centuries in medicine and as a rat poison. White squill continues to find use in some traditional medicine preparations for its digitalis-like cardiotonic effects, although this use is almost extinct. Squill extracts do continue to find some use in low doses as expectorants. Red squill is used as a rodenticide, causing death via a centrally-induced convulsant action.

PATIENT INFORMATION— Squill

Uses: Squill has been used in hair tonics treating seborrhea and dandruff, as a cancer remedy, and as a rodenticide.

Side Effects: Side effects related to squill include vomiting and convulsions.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SQUILL

ST. JOHN'S WORT

DATE OF ISSUE: AUG 2000

REPLACES MONOGRAPH DATED: NOV 1997

SCIENTIFIC NAME(S): *Hypericum perforatum*L. Family: Hypericaceae

COMMON NAME(S): St. John's wort, klamath weed, John's wort, amber touch-and-heal, goatweed, rosin rose, and millepertuis

BOTANY: St. John's wort is a perennial native to Europe but is now found throughout the US and parts of Canada. The plant is an aggressive weed found in the dry ground of roadsides, meadows, woods, and hedges. It generally grows to a height of 1 to 2 feet, except on the Pacific coast where it has been known to reach heights of 5 feet.[1] The plant has oval-shaped leaves and yields golden-yellow flowers, which bloom from June to September. The petals contain black or yellow glandular dots and lines. Some sources say that the blooms are at their brightest coincidental with the birthday of John the Baptist (June 24). [2] There are ˜ 370 species in the genus *Hypericum*, which is derived from the Greek words, hyper and eikon meaning "over an apparition," alluding to the plant's ancient use to "ward off" evil spirits. *Perforatum* refers to the leaf's appearance; when held up to light, the translucent leaf glands resemble perforations. [4,5] Harvest of the plant for medicinal purposes must occur in July and August; the plant must be dried immediately to avoid loss of potency. [3] The dried herb consists of the plant's flowering tops. [4]

HISTORY: This plant has been used as an herbal remedy for its anti-inflammatory and healing properties since the Middle Ages. [2,3] Many noteworthy ancient herbalists, including Hippocrates and Pliny, recorded the medicinal properties of St. John's wort. It was noted for its wound-healing and diuretic properties as well as for the treatment of neuralgic conditions such as back pain. In 1633, Gerard recorded the plant's use as a balm for burns. The oil of the plant was also popular during this time.[4] An olive oil extract of the fresh flowers that acquires a reddish color after standing in the sunlight for several weeks has been taken internally for the treatment of anxiety but has also been applied externally to relieve inflammation and promote healing. Its topical application is believed to be particularly useful in the management of hemorrhoids. Although it is often listed as a folk treatment for cancer, there is no scientific evidence to document an antineoplastic effect. [2,3]

Although it fell into disuse, a renewed interest in St. John's wort occurred during the past decade, and it is now a component of numerous herbal preparations for the treatment of anxiety and depression. The plant has been used in traditional medicine as an antidepressant and diuretic and for the treatment of gastritis and insomnia. Since 1995, St. John's wort has become the most prescribed antidepressant in Germany. Sales have increased from $10 million to over $200 million in the past 8 years in the US. Since 1997, St. John's wort has been one of the leading herbal products; estimated sales of St. John's wort worldwide total $570 million. [6]

CHEMISTRY: Several reports regarding the chemical components in St. John's wort are available. [7,8,9] The most commonly described constituents are naphthodianthrones, flavonoids, phloroglucinols, and essential oils.

Naphthodianthrones occur in St. John's wort in concentrations of < 0.1 to 0.15%. The anthraquinone derivatives hypericin and pseudohypericin (also emodin-anthranol and cyclo-pseudohypericin) are the best known components of the plant. Isohypericin and protohypericin are also present. The reddish dianthrone pigment hypericin (hypericum red) is found in a concentration ranging from 0.02% to 2.5%, [2] depending on harvesting period, drying process, and storage. [3,10] Hypericin content also varies widely among growing regions. [11] Hypericin concentration varies among plant parts: Flowers, buds, top leaves, and secondary stems yielding the highest amount.[4] Microscopic evaluation finds hypericin to accumulate in secretory cell globules within these plant structures. [12] Several reports concerning determination and analysis (ie, HPLC) of hypericin in St. John's wort exist. [13,14,15,16,17,18,19,20] Liposoluble pigments from the plant, including hypericin, carotenoids, and chlorophylls, have also been reported. [21]

Flavonoid concentrations in St. John's wort occur at < 12% in flowers and ˜ 7% in leaves/stalks. [4] Flavonoids include kaempferol, quercetin, quercitrin, isoquercitrin, amentoflavone, luteolin, myricetin, hyperin, hyperoside, and rutin. [3,4,10] The proanthocyanidins (˜ 12% of aerial parts) are certain forms of catechin and epicatechin. [4] Other flavonoids found are miquelianin and astilbin. [22]

Hyperforin and adhyperforin are in the phloroglucinol class of compounds. [4,5,23] Hyperforin appears in St. John's wort in concentrations of 2% to 4%. Isolation, purity, and stability of this compound have been reported. [24] Recovery of hyperforin in plasma has been measured. [25] Related structure furohyperforin, an oxygenated analog of hyperforin has been isolated from the plant, [26] as have other hyperforin analogs. [27]

The essential oil component of St. John's wort is reported to be between 0.05% and 0.9%. [4,5] It consists of mono- and sesquiterpines, mainly 2-methyl-octane (16 to > 30%), n-nonane, alpha- and beta-pinene, alpha-terpineol, geraniol, and traces of myrecene, limonene, caryophyllene, and others. [3,4,10]

Other compounds present in St. John's wort include xanthones (1.28 mg/100 g) and tannins (3% to 16%). One study reports that tannin content (in extracts) is influenced by parameters such as temperature of maceration. [28] Phenol constituents include caffeic, chlorogenic, and p-coumaric acids, and hyperfolin. Other plant constituents include acids (eg, nicotinic, myristic, palmitic, stearic), carotenoids, choline, pectin, hydrocarbons, and long-chain alcohols. Amino acids include cysteine, GABA, glutamine, leucine, lysine, and others.[3,4,5,10]

Because St. John's wort products are classified as dietary supplements, they are not regulated by the FDA. [29] Several reports evaluating commercial preparations of St. John's wort have found inconsistencies in active ingredients such as variations from 47% to 165% of labeled hypericin concentrations, [30] different concentrations of major components between brands,[31] and marked deviations in hyperforin (and adhyperforin) amounts in certain St. John's wort preparations. [32] Several reports are available addressing these issues, with various proposed standardization methods. [33,34,35,36] One such method has been developed by Paracelsian Inc., a private biotechnology company (http://www.paracelsian.com/). Their *Biofit* (bio functional integrity tested) quality assurance method has tested several St. John's wort products for structure and function claims of mood support on *otc* labeling. This testing process evaluated the product's ability to inhibit reuptake of serotonin and dopamine.

PHARMACOLOGY

Depression: Early research focused on the hypericin constituents in St. John's wort. Originally, hypericin was thought to exert its tranquilizing effect by increasing capillary blood flow. Later studies in rats found hypericin to be a strong inhibitor of the enzyme monoamine oxidase (MAO). [37] However, in the mid-1990s, two studies examined *H. perforatum* fractions in vitro and ex vivo and reported no evidence of any relevant MAO inhibition, concluding that St. John's wort's antidepressant effects cannot be explained by this mechanism alone.[38,39]

Many reports have postulated certain mechanisms and behavioral characteristics of *H. perforatum*, concentrating mostly on hypericin as the active ingredient. The following are major findings: Inhibition of serotonin uptake by postsynaptic receptors has been confirmed in a number of reports; in rat synaptosomes, *H. perforatum*caused a 50% inhibition of serotonin uptake;[40] neuroblastoma cells treated with the extract demonstrated reduced expression of serotonin receptors; [41] *H. perforatum*extract inhibited both serotonin and norepinephrine uptake in astrocytes, the cells surrounding synaptic terminals that regulate neurotransmission by their uptake systems;[42] and *H. perforatum* has also increased brain dopamine function in humans. [43] St. John's wort extract has been found to modulate interleukin-6 (IL-6) activity, linking the immune system with mood. IL-6 is involved in cell communication within the immune system and in modulating the hypothalamic-pituitary-adrenal (HPA) axis. St. John's wort has the ability to reduce IL-6 levels, which reduce HPA axis elevations and certain hormones, which if elevated, are associated with depression.[39] Sigma receptor binding of hypericin has been demonstrated.[44] *H. perforatum* does not act as a classical serotonin inhibitor but resembles reserpine's properties. Its antidepressant effects are unlikely to be associated with serotonin, benzodiazepine, or GABA receptors. [45] In addition, *H. perforatum* differs from other

selective serotonin reuptake inhibitors (SSRIs) by failing to enhance natural killer cell activity (NKCA). [46] Other effects on neurotransmitters from hypericin include inhibition of dopamine-beta-hydroxylase[47] and inhibition of metekephaline and tyrosine dimerization.

Hyperforin is the major lipophilic constituent in the plant and is also a potent inhibitor of serotonin, noradrenaline, and dopamine uptake, increasing their concentrations in the synaptic cleft. Some identify it as the major active principle for its efficacy as an antidepressant. [48,49,50,51] Antidepressant activity was found in rodent models given extracts containing hyperforin (< 39%) but devoid of hypericines. Hyperforin's spectrum of central activity, however, is affected by other constituents, as proven by alteration of serotonergic effects using different extracts of the plant. [52,53] Hyperforin is confirmed to be a major neuroactive component of *H. perforatum* extracts; modulating neuronal ionic conductances is only one of many mechanisms of action it possesses. [54] Hyperforin inhibits serotonin uptake by elevating free intracellular sodium, not seen with conventional SSRIs. [55] In a clinical trial involving 147 patients with mild-to-moderate depression, subjects given *H. perforatum* extract containing greater concentrations of hyperforin exhibited the largest Hamilton Rating Scale for Depression (HAMD) reduction compared with those given lower concentrations or placebo, confirming that the therapeutic effects of St. John's wort depend on its hyperforin content. [56]

St. John's wort continues to be a topic of interest because of its antidepressant effects. [57,58] Reports from 1994 to 1996, including a study using the HAMD, evaluate St. John's wort as clinically effective in the treatment of depression, [59,60,61] rating close to 70% in treatment response. [62] A meta-analysis evaluating 23 randomized trials, including 1757 mildly or moderately depressed patients, was conducted to investigate St. John's wort (vs placebo and other conventional antidepressants). Results found St. John's wort to be superior to placebo. Side effects occurred in ~ 20% of patients on *H. perforatum* and 53% of patients on standard antidepressants. [63] Other reviews described similar outcomes; lower doses of standard antidepressants were used. [3,59,64]

Review articles and meta-analyses concerning *H. perforatum*'s antidepressive effects have become available from 1998 to 2000, [65,66,67,68,69,70,71,72,73] of which the most notable are the following: Question and answer format in common language containing tables summarizing clinical trials; [74] a review of clinical studies, most commonly using 300 mg 3 times daily of 0.3% hypericin (600 mg in severe depression); a review of *H. perforatum*'s equivalence in efficacy to numerous antidepressants with fewer incidences of side effects; [75] meta-analyses on *H. perforatum* finding a response rate of 60% to 70% (estimate of pooled data) in patients with mild-to-moderate depression, [76] and its use resulting in 1.5 times the likelihood to observe antidepressant response than placebo, along with equivalence in efficacy to tricyclic antidepressants (TCAs); [77] a clinical trial review confirming greater efficacy vs placebo and equal efficacy to TCAs, MAO inhibitors, and SSRIs, with superior side-effect profile; [71] a review of 20 clinical trials including 1787 patients, describing similar outcomes; [78] and a broad-based literature search from 1980 to 1998, yielding ~ 1300 records confirming St. John's wort's increased efficacy over placebo in treating mild-to-moderate depressive disorders. [79] Some opposing views mention a lack of information regarding long-term effects, use in other depressive states, the use of different preparations, [80] and the exact mechanism of action being unknown with more definitive data being needed. [81] Mechanisms of action similar to SSRIs or MAO inhibitors are seen in *H. perforatum*, but its clinical efficacy is probably attributable to the combined contribution of several mechanisms. [82]

Other literature concerning the antidepressant effects of St. John's wort includes the following: Ongoing confirmation of *H. perforatum*'s benefits for depression; dose-dependent response rates were seen using 3 different standardized extracts; [83] different population-type trials, including adolescents with psychiatric problems, [84] elderly patients experiencing dementia such as Alzheimer's disease, [85] and mild-to-moderate depression; [86] *H. perforatum* compared with conventional antidepressant medications was found to have effects similar to the antidepressant properties of TCAs, imipramine, and fluoxetine; [87] 800 mg of a certain St. John's wort extract compared with 20 mg fluoxetine proved to be equally effective in ~ 150 depressed elderly patients (both groups experiencing adverse reactions, however); [88] certain dosages of St. John's wort significantly increased latency to REM sleep without affecting other sleep patterns, consistent with other antidepressants' mechanisms of action; [89] and seasonal affective disorder (SAD), a type of depression in which symptoms occur in fall/winter and resolve in spring/summer, benefited from St. John's wort, in combination with light therapy. [90]

There are a few overall limitations to the studies that make drawing conclusions about St. John's wort's efficacy in treating depression difficult. In most of the studies, the antidepressant doses used were low, the diagnosis of depression was not uniformly documented, and the trials were of short duration (average: 4 to 6 weeks). In addition, the studies standardized St. John's wort to hypericin that varied widely among studies, and there is evidence that hyperforin might be the active ingredient, which was not quantified in the studies. [56]

Pharmacokinetic studies of hypericin and pseudohypericin performed in humans found that, while similar in structure, they possess substantial pharmacokinetic differences. [91] Single-dose and steady-state pharmacokinetics have also been evaluated. [92] A daily dose of *H. perforatum*, as determined by trials and studies, is 200 to 900 mg of alcohol extract, [3] or 300 mg 3 times daily of a 0.3% hypericin-containing, standardized extract. [74]

HIV: Hypericin is still in the early stages of clinical trials investigating its effects against certain viruses, including HIV. One study found 16 of 18 patients had improved CD4 cell counts over a 40-month period. CD4/CD8 ratios also improved in the majority of patients. Hypericin and pseudohypericin inhibit a variety of encapsulated viruses, including HIV. [4]

The FDA sanctioned hypericin as an investigational new drug, making it eligible to be tested on humans. It is in Phase 1/Phase 2 clinical trial testing and is being developed under the name *VIMRxyn*. In late 1996, its developers (VIMRx Pharmaceuticals, Inc.) announced "a well tolerated oral dose with no untoward toxicity or cutaneous photosensitivity." Viral load measured in a 12-patient population ranged from no change to 97% reduction. [93,94] Another report in 1999 of a Phase 1 study evaluating hypericin's effects concluded hypericin had no antiretroviral activity (in a 30-patient trial), with phototoxicity being observed. [95]

Antiviral: Hypericin and pseudohypericin exert effects against a wide spectrum of other viruses, including influenza virus, herpes simplex virus types 1 and 2, Sindbis virus, poliovirus, retrovirus infection in vitro and in vivo, murine cytomegalovirus, and hepatitis C. [3,4,10,96] Hypericin and pseudohypericin have been found to exert unique and uncommonly effective antiviral actions, possibly due to nonspecific association with cellular and viral membranes. It has been reported more than once that the antiviral activity involves a photoactivation process. [4] Recent reports find that exposure of hypericin to fluorescent light markedly increases its antiviral activity. [3] *H. perforatum* has been considered as a photodynamic agent and may be helpful in future therapeutics and diagnostics. [97]

Antibacterial: Extracts of the plant have been active against gram-negative and gram-positive bacteria in vitro. [98] Reports have documented antimicrobial effects against such organisms as *S. equinus*, *K. pneumoniae*, *E. coli*, *B. lichteniforms*, and *S. flexneri*. [99] Antibacterial activity of constituent hyperforin against *S. aureus* and other gram-positive bacteria has also been reported. [100] In another study, *H. perforatum* extract showed bacteriostatic activity at a dilution of 1:200,000 and bactericidal action at 1:20,000. [3] St. John's wort has also been used in a 20% tincture form to treat otitis. The tannin component of the plant probably exerts an astringent action that contributes to the plant's traditional use as a wound-healing agent. [5]

Other uses: Other uses of the plant include the following: Wound-healing effects, including burn treatment; [3,4,101] oral and topical administration of hypericin for treatment of vitiligo (failure of skin to form melanin) [102] and other skin diseases; [103] anti-inflammatory and anti-ulcerogenic properties from the component amentoflavone (a biapigenin derivative); [5,104] treatment for hemorrhoids, [3] alcoholism, [87] bedwetting, [5] glioblastoma brain cancer, [105] and menopausal symptoms of psychological origin. [106] St. John's wort is capable of increasing and suppressing immunity. [107] Hypericin has been shown to inhibit T-type calcium channel activity. [108] *H. perforatum* enhances coronary flow and also may be useful in treating certain headaches. [4] Fibromyalgia, causing chronic musculoskeletal pain and fatigue, may also benefit from St. John's wort extracts by keeping serotonin levels high and decreasing pain sensations. Other neuralgias may also benefit from the plant. [5,74]

INTERACTIONS: Several recent articles concerning drug interactions with *H. perforatum* include the following: A meta-analysis of St. John's wort and other herbs possessing potentially unsafe effects; [109] reviews regarding similar issues; [110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135] and a letter. [113] More specific reports include drug interactions with St. John's wort and theophylline, [114] digoxin [115] (decreasing bioavailability in both), and indinavir. St. John's wort reduced the AUC of this HIV-1

protease inhibitor 57% in 16 patients, indicating possible treatment failure or drug resistance issues. [116] An interaction between St. John's wort and cyclosporine caused acute rejection in 2 heart transplant patients. [117] At least 7 cases of a decrease in the anticoagulant effects of warfarin have been reported. [136] Central serotonergic syndrome was reported among elderly patients combining St. John's wort with other prescription antidepressants. [118] The use of St. John's wort along with SSRIs, venlafaxine HCl, and various TCAs (with close monitoring of symptoms) has been successfully undertaken. Avoidance of tyramine-containing foods during coadministration of St. John's wort and MAO inhibitors has been recommended; recent information proving lack of MAO inhibition does not justify this. [74]

Since St. John's wort may induce the isozymes cytochrome P450 1A2, 2C9, and 3A4 in addition to inducing p-glycoprotein transporter, numerous other drug interactions with St. John's wort are possible. [135] Research is needed to determine the magnitude and clinical importance of these potential drug interactions.

Women taking oral contraceptives and St. John's wort have experienced breakthrough bleeding. [137]

TOXICOLOGY: When ingested, hypericin can induce photosensitization characterized by inflammation of the skin and mucous membranes following exposure to light, which was recognized in animals grazing on the plant. [119,120] Mice given 0.2 to 0.5 mg of herb also developed severe photodynamic effects. [10] Phototoxic activity by *H. perforatum* has been observed when tested on human keratinocytes. [121] A review of the chemistry of phenanthroperylene quinones from hypericin reveals photosensory pigments. [122] After oral administration, concentrations of hypericin in human serum and blister fluid have been detected. [123] Most reports of photosensitivity, however, have been limited to those taking excessive quantities of *H. perforatum*, primarily to treat HIV. [74] For example, both IV (eg, 0.5 mg/kg twice weekly) and oral dosing (eg, 0.5 mg/kg/day) of *H. perforatum* caused significant phototoxicity in 30 HIV patients tested, with 16 of 30 discontinuing treatment for this reason. [95]

A number of studies report no serious adverse effects. In a 22-patient study evaluating St. John's wort, 50% reported no side effects. Those reported include jitteriness, insomnia, change in bowel habits, or headache. [124] In a study of 3250 patients taking St. John's wort for 1 month, fewer than 3% suffered from dry mouth, GI distress, or dizziness. [125] In another review of clinical trials, St. John's wort was associated with fewer and milder adverse reactions as compared with any other conventional antidepressant. Adverse effects from *H. perforatum* were "rare and mild." No information on overdose was found. [126] A case report describes acute neuropathy after sun exposure in a patient using St. John's wort. [127] A review on photodermatitis in general is available, discussing mechanisms, clinical features, and treatment options. [128] Various other reports regarding other adverse effect studies concerning St. John's wort are available. A 7-patient evaluation reports St. John's wort to be unlikely to inhibit cytochrome P-450 enzymes 2D6 and 3A4 activity. [129] Reports of mania induction have been associated with St. John's wort. [130,131] Uterotonic actions also have been reported. [132] A letter discussing St. John's wort's use during pregnancy has been published. [133] Due to lack of toxicity data in this area, St. John's wort is best avoided during pregnancy. [10] Potent inhibition of sperm motility was observed from in vitro experimentation of St. John's wort. [134] The volatile oil of St. John's wort is an irritant. [10]

SUMMARY: St. John's wort has been used traditionally as an herbal treatment in the management of anxiety and depression. Several constituents acting by different mechanisms may contribute to its potent antidepressant activity. Clinical trials concerning use of St. John's wort to treat AIDS and certain cancers are ongoing. *H. perforatum* possesses antiviral and antibacterial actions, making it potentially useful in treating skin diseases and in wound healing. Side effects from St. John's wort are rare in standard dosing. With higher dosing, photosensitivity is observed. Drug-drug interactions have been documented with theophylline, digoxin, indinavir, cyclosporine, and SSRIs. Hyperforin appears to be a major active antidepressive agent.

PATIENT INFORMATION — St. John's Wort

Uses: St. John's wort has been primarily studied for its potential antidepressant and antiviral effects. There is information to show that St. John's wort is more effective than placebo, but evidence is still lacking regarding its efficacy compared to the standard antidepressants, partially due to ineffective dosing. In addition, at least 3 studies have shown that commercially available St. John's wort products vary considerably in content and may be standardized to the wrong component (hypericin instead of hyperforin). St. John's wort is still in the early stages of clinical trials investigating its effects against certain viruses, including HIV.

Interactions: St. John's wort has been reported to decrease the efficacy of theophylline, warfarin, and digoxin and reduce AUC of indinavir (and potentially other protease inhibitors). Known interactions to cyclosporine have occurred. Concomitant use with prescription antidepressants is not recommended. Use with oral contraceptives may cause breakthrough bleeding but has not been reported to result in unexpected pregnancy.

Side Effects: Side effects are usually mild. Potential side effects include the following: Dry mouth, dizziness, constipation, other GI symptoms, and confusion. Photosensitization may also occur. In clinical trials, side effects and medication discontinuation with St. John's wort were usually less than that observed with standard antidepressants. Other possible rare side effects include induction of mania and effects on male and female reproductive capabilities.

Dosing: Traditional use of St. John's wort herb indicated 2 to 4 g/day doses. However, most clinical studies have been conducted on extracts, with hypericin content of 0.3% the earliest form of standardization. With the discovery of hyperforin's bioactivity, a content of 3% to 5% hyperforin has been used as a new standard. Some of the many products include *LI 160*(Lichtwer, 0.3% hypericin), *Kira*(Lichtwer, 300 mcg hypericin in 125 to 225 mg extract tablets), *Hyperiforce* (Bioforce, 0.33 mg hypericin in 60 mg extract/tablet), *Ze 117*, *WS 5573* (300 mg extract, 0.5% hyperforin), *WS 5572* (300 mg, 5% hyperforin), *STEI 300*(Steiner, 0.2% to 0.3% hypericin and 2% to 3% hyperforin), *Psychotonin*, *Esbericum*, *Neuroplant*, *Sedariston*, and *Hyperforat*. Doses of the extracts have ranged from 500 to 1800 mg/day. [56,62,83,91,106,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    ST. JOHN'S WORT

STEVIA

DATE OF ISSUE: SEP 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Stevia rebaudiana* Bertoni. Family: Asteraceae

COMMON NAME(S): Stevia, Sweet Leaf of Paraguay, Caa-he-e, Ca-a-yupi, Eira-caa, Capim doce

BOTANY: Stevia is a perennial shrub indigenous to northern South America, but commercially grown in areas such as Central America, Israel, Thailand, and China. The plant can grow to 1 m in height, with 2- to 3-cm long leaves. The leaves are the parts of the plant used. [1]

HISTORY: Stevia has been used to sweeten tea for centuries, dating back to the Guarani Indians of South America. For hundreds of years, native Brazilians and Paraguayans have also employed the leaves of the plant as a sweetening agent. Europeans learned about stevia in the 16th century, whereas North American interest in the plant began in the 20th century when researchers heard of its sweetening properties. Paraguayan botanist Moises Bertoni documented stevia in the early 1900s. Glycosides responsible for the plant's sweeteners were discovered in 1931. Stevia extracts are used today as food additives by the Japanese and Brazilians as a non-caloric sweetener. In the US, however, use is limited to supplement status only. [1,2]

CHEMISTRY: Eight of stevia's glycosides were discovered and named in 1931.[3] Recently, the glycosides have been analyzed by capillary electrophoresis. Rebaudioside A and steviobioside have been isolated by HPLC methods.[4] Glycoside stevioside determination has been reported.[5] The main glycosides of stevia include stevioside and rebaudioside. Two glucosyl transferases acting on steviol and its glycosides have been isolated. [6] Stevioside (6 to 18% in leaves) is the sweetest glycoside and was tested and found to be 300 times sweeter than saccharose in one report.[7] Steviol hydroxylation has been reported.[8] Sterols in stevia include stigmasterol, beta-sitosterol, and campesterol.[9] Isolation of the principal sugars of stevia has also been studied. [10]

Also found in stevia are certain vitamins (C, B, A), minerals (iron, zinc, calcium), electrolytes (sodium, potassium), protein and others. [1]

Cultivation studies have been performed on the plant[11,12] as has tissue culture experimentation.[13]

PHARMACOLOGY: Stevia has been used for centuries as a natural sweetener.[1] The plant contains sweet ent-kaurene glycosides,[14] with the most intense sweetness belonging to the *S. rebaudina* species.[15] Stevia has been evaluated for sweetness in animal response testing.[16] In humans, stevia as a sweetening agent works well in weight-loss programs to satisfy "sugar cravings," and it is low in calories. The Japanese are the largest consumers of stevia leaves and employ the plant to sweeten foods (as a replacement for aspartame and saccharin) such as soy sauce, confections, and soft drinks. [1]

Stevia may be helpful in treating diabetes. Steviol, isosteviol, and glucosilsteviol decreased glucose production in rat renal cortical tubules. [17] Oral use of stevia extract in combination with chrysanthemum to manage hyperglycemia has been discussed.[18] Aqueous extracts of the plant increased glucose tolerance in 16 healthy volunteers, as well as markedly decreasing plasma glucose levels.[19]

Stevia's effects on blood pressure have been reported. The plant displayed vasodilatory actions in both normo- and hypertensive animals. [20] Stevia has also produced decreases in blood pressure, and has increased diuretic and natriuretic effects in rats. [21,22] The plant has cardiotonic actions, which normalize blood pressure and regulate heartbeat.[1]

Stevia extract has exhibited strong bactericidal activity against a wide range of pathogenic bacteria, including certain *E. coli* strains.[23] Steviol, stevia's aglycone, is mutagenic toward salmonella and other bacterial strains, under various conditions and toward certain cell lines. [24,25,26,27] Stevia may also be effective against *Candida albicans*.[1] One report addresses stevia's role against dental plaque. [28]

Certain metabolic aspects of stevioside have been described, including rat liver effects, [29,30,31] and cell membrane transport.[32]

TOXICOLOGY: Stevia has been shown not to be mutagenic or genotoxic.[1] One report indicates that constituents of stevioside and steviol are not mutagenic in vitro.[33] Stevioside was found to be nontoxic in acute toxicity studies in a variety of laboratory animals. [1] Chronic administration of stevia to male rats had no effect in fertility vs. controls.[34] Another report concludes that stevioside in high doses affected neither growth nor reproduction in hamsters of both sexes. [35]

SUMMARY: The use of stevia as a sweetening agent is centuries old and it is still used today as a natural sweetener. Other effects of the plant include hypoglycemic, hypotensive, and bactericidal. Stevia is not mutagenic and was found to be nontoxic, having no effect on growth reproduction or fertility in animal experimentation. More studies are needed to determine if it is an acceptable sweetening agent, as well as an effective agent against dental plaque.

PATIENT INFORMATION — Stevia

Uses: Stevia is used as a sweetening agent. It has also been found to have hypotensive, hypoglycemic, and bactericidal properties.

Side Effects: No major contraindications, warnings, or side effects have been documented.

Dosing: Stevia leaf is used ad lib for sweetening foods.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    STEVIA

STILLINGIA

DATE OF ISSUE: SEP 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Stillingia sylvatica*Garden ex L. Family: Euphorbiaceae (Spurges)

COMMON NAME(S): Stillingia, queen's delight, queen's root, silverleaf, nettle potato, yaw-root, marcory, cockup-hat, Indian flea root

BOTANY: *Stillingia* is a perennial herb that grows in the sandy soils of pine barrens from Texas and Oklahoma east to Virginia and Florida. When broken, the stems exude an acrid white sap, as do many spurges. The small yellowish flowers are borne on a terminal spike, with the few female flowers at the base below the more numerous male flowers. The three-chambered seedpod forcibly ejects the ripe seed. The rootstock and rhizome are large and woody. The scientific name honors the English botanist A.B. Stillingfleet. The genus was monographed in 1951. [1] Oil of stillingia is a fixed oil derived from the Chinese tree *Sapium sebiferum*, which was formerly classified as a species of *Stillingia*.[2]

HISTORY: American Indians used the root to repel fleas; Creek Indian women were reported to consume the boiled, mashed roots after giving birth. [3,4] The root was used in the southern United States for constipation, as a purgative, and to treat syphilis and liver, skin, and lung diseases. [4] The dried root is considered to be less toxic than the fresh root. *Stillingia*was used by the Eclectic medical movement and is an optional ingredient in the controversial Hoxsey cancer formula. [5,6] It has also been used in homeopathy.

CHEMISTRY: Only 1 modern chemistry study of the plant has been published in which a series of 8 daphnane and tigliane phorbol esters were isolated based on their irritancy to mouse ear.[7] Six of these compounds were novel, while prostratin and gnidilatidin were previously isolated from other plants. No report of their possible tumor promoting properties was made, although it should be noted that prostratin was found in another study to antagonize TPA-mediated tumor promotion in a classical Berenblum experiment.[8]

Positive alkaloid tests have been reported, but have never been substantiated by elucidation of the proposed alkaloid "stillingine." [9] A number of 19th century studies were published on analysis of *Stillingia* root,[10,11,12,13] while the plant has been largely ignored recently, even though it remained in the *National Formulary* until 1947.[14] A related species of *Stillingia* was reported to be cyanogenetic; however, this has not been confirmed. [15]

PHARMACOLOGY: No pharmacologic studies have been reported on the plant or its extracts. With the exception of prostratin, the other *Stillingia*factors are likely to be tumor promoters and to possess the typical pleiotropic effects possessed by most other phorbol esters. The observation of purgative properties would place this plant in league with croton oil, although it is perhaps less potent.

TOXICOLOGY: There are reports of sheep poisoned by *Stillingia*in Florida.[16] Because of the reported phorbol esters,[7] this plant should not be ingested or used topically in human medicine. Observe particular caution with the fresh root, which appears to be more toxic than the dried product.

SUMMARY: *Stillingia* was official in the *U.S. Pharmacopeia* from 1850 to 1920 and in the *National Formulary* from 1926 to 1947. *Stillingia*root is a purgative and irritant product that should be avoided because of a high likelihood of tumor promotion and documented severe irritancy to skin.

PATIENT INFORMATION— Stillingia

Uses: With the exception of prostratin, the other *Stillingia* factors are likely to be tumor promoters and to possess the typical pleiotropic effects possessed by most other phorbol esters.

Side Effects: Do not ingest or use topically in human medicine. Observe particular caution with the fresh root, which appears to be more toxic than the dried product. *Stillingia* root is a purgative and irritant product that should be avoided because of a high likelihood of tumor promotion and documented severe irritancy to skin.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    STILLINGIA

STORAX

DATE OF ISSUE: APR 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Liquidambar orientalis*, *L. styraciflua* Family: Hamamelidaceae

BOTANY: Levant storax (*L. orientalis* Mill.) is obtained from a small tree native to Turkey. American storax is obtained from *L. styraciflua* L., a large tree found near the Atlantic coast from New England to as far south as Central America.[1] Also known as the sweet gum tree, red gum, bilsted, star-leaved gum, styrax, and the alligator tree.[2,3,5]

HISTORY: The bark of the tree is mechanically ruptured in early summer, then stripped as late as autumn. The bark is then pressed in cold water alternating with boiling water, and crude liquid storax obtained from this process is collected. The crude balsam is then dissolved in alcohol, filtered, and collected in a manner so as not to lose the volatile constituents.

Storax has been used as an expectorant, especially in inhalation with warm air vaporizers. It has also been used to treat parasitic infections. The leaves are rich in tannins and have been used to treat diarrhea and to relieve sore throat.[2] In Latin America, the gum is used to promote sweating and as a diuretic. It is also applied topically to sores and wounds.[2] Storax had been used in the US as a component of hemorrhoid preparations, but today its only official use is as an ingredient in compound tincture of benzoin,[2] where it is used as a topical protectant.[3] Resins derived from storax have been used in perfumes, incense and as food flavors.

The reddish-brown wood of the tree, called satin walnut, is used in furniture making.

CHEMISTRY: Crude storax is a gray, thick liquid with a pleasing odor but a bitter taste. About 85% of the crude material is alcohol soluble.[1] Purified storax forms a brown semi-solid mass that is completely soluble in alcohol. Storax is high in free and combined cinnamic acid. Purified storax yields up to 47% total balsamic acids.[1] Its major components include phenylethylene (styrene), cinnamic esters, and vanillin.[1]

Upon steam distillation, the leaf yields an oily liquid containing about three dozen components, the major ones being terpinen-4-ol, alpha-pinene, and sabinene.[4] Benzaldehyde is produced from certain chemical reactions with the cinnamic acid in storax. Storax also contains an aromatic liquid (styrocamphene).[2]

PHARMACOLOGY: The leaf oil is rich in terpinen-4-ol, and the oil has a composition that is similar to that of the essential oil of *Melaleuca alternifolia* (Australian tea tree oil, see monograph), which has been investigated clinically as a topical antiseptic. Although the leaf oil of *Liquidambar styraciflua* has not yet been bioassayed, its similarity in composition indicates that it may demonstrate similar antibacterial and protectant properties to tea tree oil.[4]

TOXICOLOGY: No significant toxicity has been reported following the use of storax, although some persons may display sensitivity to compound tincture of benzoin.

SUMMARY: Storax has been used in traditional medicine for many years and continues to be used topically as a skin protectant. It is also widely used as a flavor and in perfumes.

PATIENT INFORMATION — Storax

Uses: Although not yet proven, storax may demonstrate similar antibacterial and protectant properties such as those of tea tree oil. Presently it is used topically as a skin protectant, as a flavor, and in perfumes.

Side Effects: There have been no demonstrated adverse effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    STORAX

SWEET VERNAL GRASS

DATE OF ISSUE: OCT 1996

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Anthoxanthum odoratum* L., Family: Graminae

COMMON NAME(S): Grass, spring grass, sweet vernal grass

BOTANY: Sweet vernal grass is a fragrant plant in the grass family that has flat leaves and narrow spike-like panicles of proterogynous flowers. It grows perennially in tufts, without stolons or basal scaly offshoots. The culms are slender, erect, and 2 to 10 dm high. Its spikelets are brownish-green, 8 to 10 mm long, and spread at the time of flowering. The grass is originally native to Eurasia and Africa, but is common in American fields, pastures, and waste places as far north as southern Ontario and as far south as Louisiana.[1]

HISTORY: Like many aromatic plants, sweet vernal grass has been used historically as a flavoring agent because of its vanilla-like aroma. In Russia and related countries, it was used in the manufacture of special brandy.[2]

CHEMISTRY: Except where veterinary poisoning has shown the presence of dicoumarol in its hay, very few chemical studies have been carried out directly on sweet vernal grass.[3]

PHARMACOLOGY: An outbreak of a hemorrhagic diathesis has been reported in cattle fed home-produced sweet vernal grass hay. The same syndrome was later reproduced experimentally in calves fed the same hay.[3] The poisoning is characterized by increased prothrombin and partial thromboplastin times, while the leukocyte and erythrocyte counts stayed normal until the terminal hemorrhage was evidenced. Symptoms include rapid onset of progressive weakness, mucosal pallor, stiff gait, tachypnea, tachycardia, and hematomata, quickly ending in death. Necropsy revealed no blood coagulation, but petechial, ecchymotic, and free hemorrhages were observed in most organs. Most striking were the massive ecchymotic hemorrhages on the peritoneal rumen surface. Each kidney was enveloped by a bloody gelatinous mass. A second feeding trial was undertaken to see if vitamins K_1 and K_3 were antidotal. No trichothecene mycotoxins were found in the hay.

A multi-allergen dipstick IgE assay to skin-prick test and RAST tests have been compared. Generally, immunological sensitivity to sweet vernal grass is low. [4]

Based on the current warnings about the use of natural sources of coumarin and dicoumarol, and their known anticoagulant properties, use of *A. odoratum* for flavoring should be discouraged. Coumarin is widely distributed in plants, and the FDA has banned its use for flavoring purposes. [5]

Other than historical reference to the use of sweet vernal grass as a flavoring, no other pharmacological or toxicological studies are found in the recent literature.

SUMMARY: Historically, sweet vernal grass has been used as a flavoring. However, recent veterinary experiences on its anticoagulant principle (dicoumarol) should discourage its use for this purpose. The FDA has banned coumarin for flavoring purposes.

PATIENT INFORMATION — Sweet Vernal Grass

Uses: Sweet vernal grass is used as a flavoring and sometimes in the manufacture of brandy. Recent veterinary poisonings show reason to discourage its use in humans.

Side Effects: In cattle, hay made from sweet vernal grass has caused progressive weakness, stiff gait, breathing difficulties and hemorrhage followed by quick death. This reaction has been attributed to the dicoumarol content of the hay and makes human consumption dangerous.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "S" MONOGRAPHS
    SWEET VERNAL GRASS

"T" MONOGRAPHS

TAHEEBO

DATE OF ISSUE: NOV 1999

REPLACES MONOGRAPH DATED: JULY 1990

SCIENTIFIC NAME(S): *Tabebuia avellanedae* Lorentz ex Griseb. Family: Bignoniaceae (Trumpet creepers). This species is synonymous with *T. impetiginosa* Mart. ex DC., *T. heptaphylla* Vell. Toledo, and *T. ipe* Mart. ex Schum. The distinct related species *Tecoma curialis* Solhanha da Gama is sometimes marketed under the same names.

COMMON NAME(S): Taheebo, Pau d'Arco, Lapacho morado, Lapacho colorado, Ipe Roxo

BOTANY: *Tabebuia* is a large genus of tropical trees that grows worldwide. According to one source, the correct name for the source species is *T. impetiginosa*;[1] however, the majority of biological and chemical studies of the plant refer to *T. avellaneda*. The commercial product is derived from the inner bark. The tree grows widely throughout tropical South America, including Brazil, Paraguay, and northern Argentina. It has a hard, durable, and attractive wood that is extremely resistant to insect and fungal attack.

HISTORY: Taheebo has been promoted for many years as an anticancer herb, and lay reports have claimed efficacy in a variety of cancers. [2] Antifungal and antibiotic properties are also claimed in promotional literature, with both topical and oral dosing for candidiasis.

CHEMISTRY: The naphthoquinone lapachol was isolated from the heartwood of the species in 1882, [3] and other related naphthoquinones (lapachones) have also been found in the wood.[4] Their structures were elucidated by Hooker[5] and others[6] and lapachol was synthesized by Fieser in 1927.[7] The inner bark has a distinct group of furanonaphthoquinones not found in the wood, [8,9,10] and these compounds are more likely to be responsible for the bioactivity observed in commercial samples of taheebo than lapachol and lapachones. [11,12] Analysis of commercial samples has found only trace amounts of lapachol and lapachones. [8] HPLC methods have been published about the analysis of taheebo bark [13] and wood.[14] The furanonaphthoquinones have been produced in good yield in callus and cell suspension cultures of *T. avellanedae*.[15] They are found in a number of species of *Tabebuia* and related Bignoniaceae.[16,17,18]

Other constituents of taheebo bark include 3 iridoid glycosides [19] and a number of simple benzoic acid derivatives.[9] A series of anthraquinones was also isolated from the wood.[20]

PHARMACOLOGY: Lapachol was extensively evaluated as an anticancer agent by the US National Cancer Institute and the Pfizer Co. in the 1960s. [21,22] It showed reproducible activity in mouse cancer models.[22] While oral absorption in humans was relatively poor, peak blood levels of 14 to 31 mcg/ml were attained with doses of 30 to 50 mg/kg.[21] Extensive modifications of the lapachol structure have been performed in pursuit of better antitumor activity, [23] in the search for antimalarial drugs,[24] and for antipsoriatic drugs.[25] Lapachol has also been reported to have modest antifungal and antibacterial activity, [26] as well as anti-inflammatory activity[27] and weak estrogenic action.[28]

Active ß-lapachone has been found in tumor models.[29] It inhibits both murine leukemia virus reverse transcriptase and DNA polymerase-a, but not DNA polymerase-ß and several other related enzymes.[30]

While having apparent potential for drug development, the biological activity of lapachol and ß-lapachone is not relevant to the use of taheebo bark, because the bark contains little of these constituents. Instead, the furanonaphthoquinones are the important constituents, having cytotoxic, [16,17] antifungal, antibacterial, [11,18] and rather potent immunomodulatory activity.[12] Stimulation of host response to cancer cells or microbial infection may be responsible, at least in part, for the activity of the bark extract in vivo.

Despite the promising activity shown by the furanonaphthoquinone constituents, there do not appear to be clinical studies to support the use of taheebo for any of the indications mentioned.

TOXICOLOGY: The toxicology of lapachol was studied in detail by Morrison et al., [31] who found hemolytic anemia to be the principle limiting toxicity in dogs, monkeys, rats, and mice. Human toxicity because of lapachol was seen at doses > 1.5 g/day, with an elevated prothrombin time that was reversed by administration of vitamin K.[21] Because lapachol is not a major constituent of taheebo bark, these studies are not entirely relevant to the commercial product. No toxicology has been reported for either the bark extract or its main constituents.

SUMMARY: Taheebo, also known as Pau d'Arco and Ipe Roxo, is derived from the inner bark of *Tabebuia avellanedae* and related species. Lapachol has been mistakenly identified as the active constituent, whereas the furanonaphthoquinones appear to be responsible for the biological activity of the product. Widely used in alternative cancer therapy without sufficient scientific proof, it may be more useful in antifungal applications, although no clinical trials appear to have been conducted for any indication. There are no reports of serious adverse effects; however, it should not be used with anticoagulants.

PATIENT INFORMATION — Taheebo

Uses: Taheebo is widely used in alternative cancer therapy without sufficient scientific proof. It may be more useful in antifungal applications, although no clinical trials have been conducted for any indication.

Interactions: Do not use taheebo with anticoagulants.

Side Effects: There are no reported serious side effects.

Dosing: Taheebo bark has been used as an alternative cancer treatment; however, there are no clinical studies to support a specific dose.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TAHEEBO

TANNING TABLETS

DATE OF ISSUE: NOV 1991

REPLACES MONOGRAPH DATED: N/A

HISTORY: A variety of over-the-counter tablets and capsules containing the pigments beta-carotene and canthaxanthin have been available for more than a decade and have been promoted to give the user a natural-looking skin tan. These products have long been available in Europe and Canada, and "tan" by systemically pigmenting the skin. Today, they can be found in many tanning salons throughout the US.

CHEMISTRY: The natural pigments beta-carotene and canthaxanthin (beta-carotene-4,4'-dione) form the basis for orally administered tanning products. [1] The majority of these products contain synthetic versions of these carotenoid pigments, which are responsible for much of the yellow, orange, and red coloration in plants.[2] Canthaxanthin, a highly lipid soluble, deep red-orange pigment, is often the only color in these tanning preparations; it is sometimes referred to as Food Orange 8,[3] carophyll red or roxanthin red 10.[4]

NONCLINICAL USES: In the US, these pigments are approved as color additives for use in food and drugs, but are unapproved for use as ingested agents intended to color the body. The typical dietary intake of beta-carotene and canthaxanthin added during food manufacturing is 0.3 mg and 5.6 mg, respectively. [2] A recommended maximum daily intake of canthaxanthin is 25 mg/kg.[1] In monkeys, canthaxanthin concentrates preferentially in the liver and spleen. [5]

CLINICAL USES: Antineoplastic effects: Epidemiologic evidence suggests that the incidence of cancers may be slightly lower among individuals with an above-average intake of beta-carotene and other carotenoids. These compounds may deactivate reactive chemical species such as singlet oxygen and free radicals. [6] They may also have some slight pro-vitamin A effect that may contribute to the neoplastic protectant effect. [7] Mice supplemented with beta-carotene for 5 weeks prior to and 26 weeks after the administration of a nitrosamine derivative to induce bladder cancer developed significantly fewer tumors than did unsupplemented mice. Mice receiving canthaxanthin showed no protection.[8] Mice receiving canthaxanthin, retinyl palmitate or a combination developed fewer cutaneous tumors following exposure to ultraviolet irradiation.[9] Dietary supplementation of canthaxanthin inhibited the initiation of experimental breast tumors in mice, but did not slow their spread.[10]

Porphyrias: Beta-carotene and canthaxanthin administration help prevent photosensitivity in people with inherited erythropoietic protoporphyria. This skin disorder is characterized by burning, itching skin often with ulceration, following exposure to sunlight. Beta-carotene effectively protects against photosensitivity but does not protect from ultraviolet-induced sunburn.[2,11]

Dermatologic uses: Canthaxanthin has been used for the treatment of vitiligo, a disorder in which the melanocytes cease to synthesize melanin and disappear from the involved areas. When given orally to 48 patients with vitiligo, self-rating showed that 54% were not satisfied, 35% were satisfied and 10% were very satisfied with the results of canthaxanthin pigmentation.[1]

Tanning effects: Labeling for over-the-counter products recommends taking several tablets a day for 2 to 3 weeks, then smaller periodic doses to maintain the coloration. The skin color accumulates over a 2-week period, then fades in about as much time when the product is stopped. Ingestion of too much pigment can make the palms of the hands turn orange.[1] One brand of tablets contains 4 mg of beta-carotene and 36 mg of canthaxanthin per dose; the resulting daily intake of beta-carotene and canthaxanthin would be 12 to 16 mg and 108 to 144 mg, respectively.[2] Ingestion of these large amounts of pigment results in the accumulation of dyes in adipose tissue with a resultant yellow discoloration of the skin. The "tan" has a distinct orange tinge and affords no protection against sunburn. [1]

TOXICOLOGY: Both beta-carotene and canthaxanthin are classified as "Generally Recognized As Safe (GRAS) " substances by the FDA. [12] The conversion of beta-carotene to vitamin A is limited by physiologic requirements and, therefore, the ingestion of these tablets does not pose a threat of hypervitaminosis A. Canthaxanthin is not metabolized to vitamin A in humans, and some question exists as to whether it may interfere with the conversion of carotene to vitamin A. [2]

In short- and long-term animal studies, the LD_{50} for canthaxanthin in mice, rats, and dogs has been found to be greater than 10,000 mg/kg. [1]

A small amount of the drug is absorbed and large quantities are excreted, imparting a brick-red color to the stool, a side effect that may mask the presence of rectal bleeding.[1]

There have been no reports of teratogenicity, carcinogenicity, or histotoxicity. [1] No toxicity was noted in volunteers who ingested 180 mg/day of beta-carotene for 10 weeks.[13] These dyes afford no protection to sunburn and patients should be instructed to take adequate precautions against exposure. Severe orange discoloration of plasma has been noted by blood collection agencies in blood samples obtained from subjects who ingested tanning tablets, although toxic levels of vitamin A were not found in the samples.[14]

The most common non-dermatologic adverse effects include nausea, cramps and diarrhea, which occurred in about one-third of patients receiving these pigments as treatment for photosensitivity. The Food and Drug Administration has received reports of a drug-induced hepatitis and a case of severe itching and welts, which may have been related to oral tanning products.[2]

Amenorrhea has been reported among women receiving carotenoid therapy, although with a very low prevalence. [15] A survey of 50 patients who took more than 200 tanning tablets over a period of time found golden crystalline deposits in the inner layers of the retina and around the macula in 12%. [16] No alterations in visual acuity were observed, but the long-term implications of these deposits are not understood. Retinopathy does not appear to develop in patients taking beta-carotene alone. [12] A recent report described a 20-year-old woman who died secondary to developing aplastic anemia after ingesting a course of high-dose canthaxanthin-containing tanning tablets. Although supportive measures may have saved the patient, her religious beliefs precluded the use of these interventions. [17]

SUMMARY: Tanning tablets containing a combination of beta-carotene and canthaxanthin are available over the counter to promote the development of a "suntan." This is accomplished by pigmenting the skin with an orange-red color accumulated in subcutaneous fat deposits. Side effects include discoloration of the stool, gastrointestinal discomfort and at least one case of aplastic anemia. These products cannot be recommended for use as tanning agents because of the unknown safety associated with their long-term use. Carotenoids such as these may impart a cancer-protective effect, although they offer no protection against the development of sunburn.

PATIENT INFORMATION — Tanning Tablets

Uses: Tanning tablets have been used to give a natural-looking skin tan, prevent photosensitivity in people with inherited erythropoietic protoporphyria, and in the treatment of vitiligo.

Side Effects: Some adverse effects reported with tanning tablets include discoloration of the stool, GI discomfort, and at least one case of aplastic anemia.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TANNING TABLETS

TANSY

DATE OF ISSUE: FEB 2004

REPLACES MONOGRAPH DATED: SEP 1992

SCIENTIFIC NAME(S): *Tanacetum vulgare* L. (also referred to as *Chrysanthemum vulgare* [L.] Bernh.) Family: Asteraceae (daisies)

COMMON NAME(S): Tansy, garden tansy[1], scented fern, stinking willie, bitter[2] or golden[1] buttons, parsley fern.[2] Do not confuse with other plants referred to as "tansy," such as the tansy ragworts (*Senecio* species).

BOTANY: Tansy (also referred to as *Chrysanthemum vulgare* [L.] Bernh.) is indigenous to Europe and was introduced to North America, probably for use in folk remedies or as an ornamental plant. It is an invader of disturbed sites and is commonly found on roadsides and waste areas throughout temperate regions of North America.[1] Tansy is listed as a noxious weed in several states.[3]

The hardy, aromatic, perennial plant grows erect in large clusters usually about one-half to 1 m in height but occasionally near 2 m. Stems are smooth or mostly hairless, often purplish-red in color and branch extensively at the top. The stalkless leaves grow alternately around the stem and are narrow, lance-shaped, and finely divided into leaflets, giving a fern-like appearance. From July to October mature plants bear dense, flat-topped clusters of small, button-like, yellow flowers, about one-half inch wide.[4] Seeds are yellowish-brown with short, 5-toothed crowns. The plant emits a strong, aromatic odor when crushed, described by some as unpleasant. Tansy ragwort (*Senecio jacobea*) can be distinguished from common tansy by its ray flowers (petals), absence of sharp-toothed leaves, and the long fringe of soft, white hairs on the seeds.[1]

HISTORY: Tansy has been used extensively in traditional medicine for centuries, despite its recognized potential for toxicity. Records exist of the use by Charlemagne and Swiss Benedictine monks in the 8th century for treatment of intestinal worms, rheumatism, fevers, and digestive disorders. Large doses were used to induce abortions. Conversely, smaller doses were thought to enhance fertility and prevent miscarriages. [1] Other indications included treatment of gout, hysteria, kidney weakness, flatulence, and, in moderate doses, as an antispasmodic. Medieval records also note tansy as a culinary agent used to replace nutmeg and cinnamon and as a bitter-tasting tea. Tansy pudding was a delicacy commonly associated with the Lenten fast.

Early American history records the use of tansy for funeral shrouds and wreaths. In 1668, the first president of Harvard University was buried in a tansy-lined coffin, wearing a tansy wreath. When the Harvard cemetery was relocated in 1846, the tansy in the coffin still held its shape and fragrance. [1] Colonial Americans exploited the preservative properties of tansy, using it for packing meat and other perishable goods. A 17th century governor of Massachusetts listed tansy as a necessary plant for colonial herb gardens. American Indians reportedly used tansy as an insect repellant. [5]

Tansy is also reputed to have had a place in Greek funeral rites. Ganymede, a beautiful Trojan prince, was supposedly immortalized by taking tansy after Zeus, enamored by Ganymede's physical perfection, carried him away to Mount Olympus. The name tansy is said to derive from the Greek word *athanon* or immortal, either because of the flower's long-lasting nature or because of its ability to preserve dead bodies from corruption.

CHEMISTRY: Analysis of tansy plant extracts has identified more than 30 chemotypes that are distinguished by the components of their essential oil. [6] Fresh tansy yields between 0.2% and 0.6% volatile oil of highly variable composition. [7] Variability is further increased, both quantitatively and qualitatively, by the extraction method used.[5] The volatile oil is dominated by terpenes. In plants grown in the United States, Canada, and England, the major constituent is ß-thujone. [5,7] Some genotypes contain as much as 95% thujone,[8,9] while other varieties are almost thujone free.[10] Major constituents of other genotypes include camphor, isopinocamphone, trans-chrysanthenyl acetate, sabinene, bornyl acetate, or germacrene D. [11] Sesquiterpene lactones, principally parthenolide, are primary components of strains devoid of thujone.[8] The presence of flavones eupatorin, jaceosidin,[12] apigenin, diosmetin, jaceidin, jaeosidin, and quercetin also has been recorded.[8]

The association between morphological attributes and chemical composition has been investigated in Finnish tansy. [7] Strains with the tallest shoots were associated with high yields of camphor and 1,8-cineole. Mixed chemotypes had the shortest shoots.

PHARMACOLOGY: Evidence to support the use of tansy for any pharmacologic indication is lacking. Although roundworms are stunned by thujone and then expelled by the peristaltic action of the intestine, the risk of toxicity is too high to justify use as an anthelmintic. Similarly, use as an emmenagogue-abortifacient is dangerous.[8]

Anti-inflammatory: Parthenolide, the major component of some genotypes, impairs platelet activation, induces cyclo-oxygenase-2 expression in macrophages, and activates the nuclear transcription of ?B.[12] Mouse-ear edema was inhibited 93% by a parthenolide-rich fraction of a tansy extract. Similar inhibition occurred with indomethacin (85%) and a jaceosidin-rich fraction (80%). Effects against carrageenan-induced paw edema were more modest (25% and 8% for parthenolide and jaceosidin fractions, respectively).[12]

Antiulcer: Sesquiterpene lactones have a cytoprotective effect against gastric ulcers, possibly related to interactions between the a-methylene-?-lactone group and thiol constituents in the gastric mucosa. Additionally, flavonoids isolated from tansy may have a topical effect on ulcers. [13] A dose-dependent reduction in ethanol-induced gastric lesions in rats was seen with a chloroform extract of a parthenolide-rich genotype of *T. vulgare*. Ulcer inhibition was similar for animals given chloroform extract or parthenolide (71% and 91% ulcer inhibition, respectively, at a dose of 40 mg/kg).

Antimicrobial: Tansy has some degree of in vitro antimicrobial activity against both gram-positive [14,15] and gram-negative bacteria.[15] Organisms susceptible to a hydroalcoholic extract of *T. vulgare* include *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Some activity against *Candida krusei* and *C. tropicalis* was also observed. Aqueous extracts of the plant partially inactivate tick-borne encephalitis virus in vitro but have been found to induce resistance to the virus in infected mice.[16]

Research reveals no clinical data regarding the use of tansy as an antimicrobial, anti-inflammatory, or antiulcer agent.

Insecticidal: Oil of tansy has a strong, insect-repellent activity, but the acaricidal activity is affected by the method of extraction. Bioassays have associated the presence of 1,8-cineole, bornyl acetate, ?-cymene, ?-terpinene, and camphor with the strongest repellent activity [6] and ß-thujone with insecticidal properties. [5] Colorado potato beetles (*Leptinotarsa decemlineata*) were strongly repelled by a commercial oil of tansy and a steam distillate of fresh leaves and flowers of tansy. [6] Inhibition of the feeding activity of the cabbage aphid (*Brevicoryne brassicae*) by a preparation of sesquiterpene lactones isolated from *T. vulgare* was 80% to 100%. High activity against the flour beetle (*Tenebrio molitor*), greenhouse whitefly (*Trialerodes vaporariorium*), and *Teranychus urtiae Koch* was also noted.[17]

The extraction process affected mortality of spider mites treated with a 4% extract of tansy. Mortality rates for extracts obtained by distillation in water or steam was 60.4% and 75.6%, respectively, compared with 16.7% for a microwave-assisted extraction process. LC_{50} values were 0.054 and 0.046 mg/cm^2 for water and steam-assisted distillation processes, respectively. LC_{50} values for the microwave-assisted process were inconclusive. The active agent in this study was probably ß-thujone, the main component in all 3 extracts (87% to 92%).[5]

INTERACTIONS: No evidence associating tansy with interactions has been documented.

TOXICOLOGY: As little as 10 drops of the oil may be lethal, but recovery has been reported after ingestion of 15 mL. [11,18] The tea also has been fatal.[18] Symptoms of internal tansy poisoning include rapid and feeble pulse, severe gastritis, violent spasms, and convulsions and uterine bleeding; treatment with gastric lavage or

emesis has been suggested, followed by symptomatic treatment.[19] Thujone is probably responsible for much of the toxicity associated with the plant. Chronic poisoning from prolonged use is also likely.

Pregnancy/lactation: Tansy, especially in the form of the essential oil, is a potent abortifacient and use during pregnancy is contraindicated. Information on use in breastfeeding is lacking.

Adverse reactions: Ingestion of tansy and its extracts has been reported to cause serious systemic toxicity in animals and humans. Fatalities have occurred.

Prolonged exposure to tansy may cause contact dermatitis[20] ; an extract of tansy is routinely included in the standard testing mixture for Compositae allergy. [21,22] A strong cross-sensitivity between chrysanthemum and tansy exists. The presence of parthenolide in both species may be a possible cause [22] ; arbusculin-A and tanacetin have also been indicated as sensitizing agents. [11] Prevalence of hypersensitivity to tansy has been reported as 60.6% [21] and 77%[22] of patients sensitive to Compositae (approximately 2% of the European patient population tested). Patients exhibiting the contact dermatitis may be exposed to the plants either occupationally (flower trade), in their own gardens, or by use of natural cosmetics, soaps, or shampoos. Clinically, lesions occur most on the face, fingers, hands, and forearms.[21]

SUMMARY: Tansy is a common plant having no role in herbal medicine because of its potential toxicity. Use in aromatherapy [23] and to prepare teas and flavor foods should be discouraged. Allergic dermatitis is common. Use as an insect repellent may be considered, although repellent and insecticidal activity against the target species may vary with different genotypes.[5]

PATIENT INFORMATION— Tansy

Uses: Tansy has no role in modern herbal medicine. Although it is toxic, tansy has been used as a vermifuge, emmenagogue, and antispasmodic. Effectiveness has not been proven.

Dosing: Safe dosing has not been established; do not use this herb.

Pregnancy/Lactation: Avoid use during pregnancy, as tansy is a known abortifacient.

Interactions: No evidence associating tansy with any interactions has been documented.

Adverse Reactions: Tansy may cause contact or airborne dermatitis.

Toxicology: Internal poisoning may occur with symptoms of rapid and feeble pulse, severe gastritis, violent spasms, and convulsions. Deaths have been associated with ingestion of the essential oil and tansy infusion (tea).That

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TANSY

TEA TREE OIL

DATE OF ISSUE: NOV 1997

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Melaleuca alternifolia* (Cheel)

COMMON NAME(S): Tea tree oil

BOTANY: There are many plants known as "tea trees," but species *melaleuca alternifolia* is responsible for the "tea tree oil," which has recently gained popularity. Native to Australia, the tea tree is found in coastal areas. It is an evergreen shrub that can grow to 6 meters tall. Its narrow, 4 cm, "needle-like" leaves release a distinctive aroma when crushed. The fruits grow in clusters, and its white flowers bloom in the summer.[1]

Other related species include *M. quinquenervia* (Cav.) S.T. Blake (*M. viridiflora* sol.) from the Caledonian evergreen tree yielding "niaouli oil" and *M. leucaden* L. and *M. cajuputi* Powell (= *M. minor* sm.) yielding "oil of cajuput." These oils contain similar constituents resembling camphor and peppermint and are used in aromatherapy.[2,3]

HISTORY: Tea tree oil (TTO) was first used in surgery and dentistry in the mid-1920s. Its healing properties were also used during World War II for skin injuries to those working in munition factories. Tea tree oil's popularity has resurfaced within the last few years with help from promotional campaigns and may be present in soaps, shampoos, and lotions.[1]

CHEMISTRY: The essential oil is normally obtained by steam distillation of the leaves.[2] The main constituent is tea tree's essential oil, terpin-4-ol, present in concentrations of 40% or more.[1,2] The related species contain eucalyptol, cineole, nerolidol, viridiflorol, or phenylpropanoids.[2,3] Listings of chemical compositions of tea tree oils have been reported.[4,5] An essential oil overview, use and purity issues are also available on this topic.[6]

PHARMACOLOGY: Tea tree oil has been used mainly for its antimicrobial effects without irritating sensitive tissues. It has been applied to cuts, stings, acne, and burns. In hospitals, TTO has been used in soap form and soaked in blankets to make an antibacterial covering for burn victims. When run through air-conditioning ducts, TTO has been shown to exert bactericidal effects.[1] A considerable amount of literature has become available on this topic.

Disc diffusion and broth microdilution methods have been used to determine antimicrobial effects against eight TTO constituents. Terpin-4-ol was active against all test organisms including *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Other constituents of the oil (such as linalool and alpha-terpineol) had some antimicrobial activity as well.[7,8] In addition, constituents terpin-4-ol, alpha-terpineol, and alpha-pinene were found to possess antimicrobial effects against *Staphylococcus epidermidis* and *Propionibacterium acnes*.[9]

TTO may be useful in removing "transient skin flora while suppressing but maintaining resident flora."[10] TTO was also shown to be an effective topical treatment of monilial and fungal dermatoses and superficial skin infections in 50 human subjects over a 6-month period with minimal or no side effects reported.[11] A report suggests TTO to be useful in treatment of "methicillin-resistant *S. aureus* (MRSA) carriage." In this evaluation, all 66 isolates of *S. aureus* were susceptible to the essential oil (64 isolates being MRSA, 33 being mupirocin-resistant).[12]

TTO's activity against anaerobic oral bacteria has been surveyed.[13] A case report exists, discussing antibacterial efficacy of TTO in a 40-year-old woman with anaerobic vaginosis.[14]

In a randomized, double-blind study comparing the efficacy of 10% (w/w) tea tree oil cream with 1% tolnaftate (and placebo creams) against *tinea pedis* (athlete's foot), TTO was found to be as effective as tolnaftate in reducing symptoms but no more effective than placebo in achieving mycological cure.[15] In a report on *onychomycosis* (nail fungus), TTO (100%) vs clotrimazole solution (1%) application yielded similar results in treatment. Both therapies, however, had high recurrence rates.[16]

TTO can be added to baths or vaporizers to help treat respiratory disorders. Related species oil has been used for nasal antiseptic purposes, pulmonary anti-inflammatory use, and for coughs.[1,2,3] TTO is also used in perfumery and aromatherapy.[2]

TOXICOLOGY: Allergic contact eczema was found to be caused primarily by the a-limonene constituent (in TTO) in 7 patients tested. In this same report, alpha-terpinene and aromadendrene additionally caused dermatitis in 5 of the patients.[17] Eucalyptol was found to be the contact allergan in a Dutch report.[18] Contact allergy due to TTO may be related to cross-sensitization to colophony.[19] A case report describes a petechial body rash and marked neutrophil leukocytosis in a 60-year-old man who ingested ± $^{1}/_{2}$ teaspoonful of the oil (for common cold symptoms). He recovered 1 week later.[20]

TTO in comparison to conifer resin acids was found to exhibit no cytotoxic activity in vitro using human epithelial and fibroblast cells.[21]

Another case report describes ataxia and drowsiness as a result of oral TTO ingestion (< 10 ml) by a 17-month-old male. He was treated with activated charcoal, which was only paritally successful, but after a short time appeared normal and was discharged 7 hours after ingestion.[22]

Various additional reports on TTO toxicity can be referenced.[23,24,25]

SUMMARY: Tea tree oil from species *Melaleuca alternifolia*native to Australia has recently gained popularity. Since the mid-1920s, its remarkable healing properties have been known. TTO's antimicrobial effects have been well documented, and its therapeutic use has been beneficial for skin infection treatment, respiratory disorders, and aromatherapy. Possibility of contact dermatitis exists. Do not ingest the oil. Adverse effects have been reported.

PATIENT INFORMATION— Tea Tree Oil

Uses: Tea tree oil has been used mainly for its antimicrobial effects. TTO should be applied topically. Do not ingest orally.

Side Effects: Use of tea tree oil has resulted in allergic contact eczema and dermatitis.

Dosing: TTO has been studied for its topical antifungal activity incorporated in cream formulations of 5% and 10% and as the neat oil. Standardized tea tree oil contains less than 10% cineole and greater than 30 percent terpinen-4-ol. Dosage should initially start low to avoid irritation caused by cineole. CNS toxicity has been observed at internal doses of 10 to 70 mL.[15,16,26]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TEA TREE OIL

TERMINALIA

DATE OF ISSUE: JAN 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Terminalia arjuna*, *Terminalia bellirica* (*T. belerica*), *Terminalia chebula*.

COMMON NAME(S): Arjuna, Axjun, Argun (T. arjuna); Behada, Bahera (Bahira), Balera (T. belerica); Hara, Harada, Hirala, Myrobalan, Haritaki (T. chebula); Bala harade (T. chebula black variety). Family: Combretaceae. [1,2,3,4,5]

BOTANY: The *Terminalia* species are evergreen trees. *T. arjuna* reaches ~ 30 meters, has light-yellow flowers, and cone-shaped leaves. *T. belerica* has clustered oval leaves, and greenish, foul-smelling flowers with brown, hairy fruit about the size of walnuts. *T. chebula* grows ~ 21 meters in height with white flowers and small, ribbed fruits.[2]

T. arjuna is used for its bark. In other *Terminalia* species, the fruit is the plant part used.[1] For example, in India, 100,000 metric tons of *T. chebula* fruit was produced in 1 year.[6]

A traditional Ayurvedic herbal combination dating back 5000 years is a mixture of 3 herbs, 2 of which are terminalia species: *T. belerica* (for health-harmonizing qualities), *T. chebula* (to normalize body balance), and *Emblica officinalis* (for vitamin C content; see separate monograph).[3]

HISTORY: Arjuna bark has been used in Indian medicine for at least 3000 years as a remedy for heart ailments. *T. chebula* also has been used by this culture as a digestive aid.[2] This species, referred to as "King of Medicine" by Tibetans is often depicted in the extended palm of Buddha. The *Emblica officinalis*/*T. chebula*/*T. belerica* herbal combination product is said to have been formulated by Ayurvedic physicians thousands of years ago. [3]

CHEMISTRY: *T. chebula* contains tannins, anthraquinones, chebulic acid, resin, and fixed oil. [2] Other constituents include amino acids, fructose, succinic acid, and beta sitosterol.[3] This specific species is an important source for industrial tannins. [6] One source lists *T. chebula* as having 32% tannin content.[1]

T. arjuna contains tannins, flavonoids, and sterols. *T. belerica* contains tannins and anthraquinones.[2] Gallic acid also has been isolated from this species. [7]

PHARMACOLOGY: Some similarity in pharmacologic actions exist among the 3 species. *T. arjuna's* traditional use as a cardiotonic has been confirmed by modern research. Although some results of these studies (performed since the 1930s) appear conflicting, (eg, increases and decreases in heart rate or blood pressure), the herb seems to work best when blood supply to the heart is compromised as in ischemic heart disease or angina [2] Ayurvedic medicine employs *T. arjuna* to restore balance of the "3 humors."[3] *T. arjuna* also has been used as an aphrodisiac, diuretic, and for earaches. [1,2] This species has reduced cholesterol levels, as well. [2] Studies done on *T. arjuna* combinations find the herb to be the most potent hypolipidemic agent compared with *T. belerica* and *T. chebula*. *T. arjuna* may also play a role as an anti-atherogenic.[8]

T. belerica has been studied for its effects on similar disease states. In combination with *E. officinalis* and *T. chebula*, *T. belerica* has reduced cholesterol-induced atherosclerosis in rabbits.[5] In another report, *T. belerica* reduced lipid levels in hypercholesterolemic animals.[9] The herb has also exhibited protective effects against myocardial necrosis in rats.[10] *T. belerica's* role in treating liver disorders is also apparent. [1] Constituent gallic acid displays significant hepatoprotective effects. Marked reversal of most altered parameters was shown including lipid peroxidation, drug metabolizing enzymes, and others. [7] *T. belerica* has also been used as primary treatment for digestive and respiratory (eg, cough, sore throat) problems. [2] Other uses include the following: As an astrigent, laxative, [2,11] lotion for sore eyes, [2] and retroviral reverse transcriptase inhibitory activity in murine leukemia enzymes. [12]

T. chebula is used in Indian medicine to treat digestive problems. It improves bowel regularity, thus making it possibly useful as a laxative and to treat diarrhea and dysentery.[1,2] Other uses include as a mouthwash/gargle, astringent, and douche for vaginitis. [2]

T. chebula and *T. belerica* have demonstrated antimicrobial properties.[13,14] *T. chebula* has also been evaluated for activity aganist methicillin-resistant *Staphylococcus aureus*.[15]

Certain *Terminalia* species demonstrate antifungal[16] and antiviral[17,18,19,20] activities, as well.

TOXICOLOGY: Few reports were found from recent literature searches regarding *Terminalia* species and toxicity. One source warns against taking *T. belerica* and *T. chebula* during pregnancy.[2]

SUMMARY: *Terminalia* species have been used in Indian medicine for thousands of years. Certain species are used for cardiac effects, anti-atherogenic and hypolipidemic actions, hepatoprotection, GI problems, and as antimicrobials. Little information on toxicity is available.

PATIENT INFORMATION — Terminalia

Uses: *T. arjuna's* traditional use as a cardiotonic has been confirmed by modern research. It has also been used as an aphrodisiac, diuretic, and for earaches, [1,2] it may play a role as an anti-atherogenic,[8] and has reduced cholesterol. *T. belerica* has been used in treating liver disorder[1] and as a primary treatment for digestive and respiratory (eg, cough, sore throat) problems.[2] Other uses include the following: As an astringent, laxative, [2,11] lotion for sore eyes,[2] and retroviral reverse transcriptase inhibitory activity in murine leukemia enzymes [12] *T. chebula*is used in Indian medicine to treat digestive problems. Other uses include as a mouthwash/gargle, astringent, and douche for vaginitis.[2] *T. chebula* and *T. belerica*have demonstrated antimicrobial properties.[13,14] Certain *Terminalia* species demonstrate antifungal[16] and antiviral[17,18,19,20] activities.

Side Effects: Few toxicity reports exist; do not use during pregnancy.

Dosing: Daily doses of 0.5 to 1.5 g of powdered *Terminalia* bark have been studied for their clinical effects on heart failure and serum cholesterol levels. A 10% solution also has been used as a mouthwash.[21,22,23]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TERMINALIA

THUNDER GOD VINE

DATE OF ISSUE: MAY 1998

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Tripterygium wilfordii* Hook.

COMMON NAME(S): Lei-kung t'eng, lei gong teng (Chinese), thunder god vine, huang-t'eng ken (yellow vine root), tsao-ho-hua (early rice flower)

BOTANY: *Tripterygium* is a perennial twining vine that grows in southern China, usually close to water sources. It is native to the Hunan province. It has reddish-brown branches with oval leaves. In the summer, small white terminal flowers bloom.[1]

HISTORY: The thunder god vine has been used for centuries in traditional Chinese medicine to treat fever, boils, abscesses, and inflammation. It has also been put to use as an insecticide to kill maggots or larvae and as a rat and bird poison. [1]

CHEMISTRY: Triterpene compounds (eg, tripterygone) have been isolated from thunder god vine roots. [2] Also found in the plant's roots are diterpenoid triepoxides, triptolide, and tripdiolide.[3] A new diterpene triepoxide, 16-hydroxytriptolide, has been isolated from the leaves of the plant. [4] A nortriterpenoid has also been isolated.[5] An anti-HIV constituent, neotripterifordin, has been recently identified. [6] Six diterpene epoxides have been identified, and listed as triptolide, tripdiolide, triptolidenol, tripchlorolide, 16-hydroxytriptolide, and one other unpublished structure. [7]

PHARMACOLOGY: Pharmacology of thunder god vine includes reports in the areas of antifertility, autoimmune disease, antiviral, antitumor, and other effects.

Antifertility: During the late 1980s and early 1990s, human studies evaluating thunder god vine for rheumatoid arthritis and psoriasis treatment revealed an unexpected side effect in male subjects. It was discovered that thunder god vine had reversible effects on sperm, producing fewer of them and making them less mobile. This suggested the plant's use as a possible "male antifertility" drug. [1] A number of thunder god vine constituents are responsible for these potent antifertility actions, including triptolide and tripdiolide. [8] One report suggests 6 compounds of the plant to show antifertility effect in mice. [9] A later report confirms the 6 antifertility compounds in both rats and man. These compounds act primarily on sperm development (eg, sperm head-tail separation), other than affecting testosterone levels. [1,7] Fertility is reversible after termination of thunder god vine preparations. Sperm returned to normal 6 weeks later. [7] A review of thunder god vine's fertility regulatory effects is available.[10]

The effective antifertility dose is 1/3 the recommended dose for treatment of arthritis or skin diseases, which may be associated with less adverse effects when thunder god vine is taken for antifertility. [10]

One report compared 1 thunder god vine constituent to gossypol, finding inhibition of spermatogenesis, "turnover of basic nuclear protein in late elongated spermatids" and head-tail separation (among other antifertility effects) to be more pronounced in the thunder god vine constituent than in gossypol. [11]

Autoimmune disease: Thunder god vine has been reported to be effective in treating autoimmune diseases in in vitro models and in animal and human studies.

In vitro, immunosuppressive activity was shown to be caused by the constituents tripchlorolide and tribromolide. [12] Another report analyzes T2 (a chloroform methanol extract of the plant) and an ethyl acetate extract, both of which contained triptolide and tripdiolide as the major immunosuppressive diterpenoids. [13] A new immunosuppressive component has been determined and was found to be phenolic nortriterpene demethylzeylasteral. [14]

In vitro analysis indicates thunder god vine to inhibit transcription of cytokine genes IL2 and gamma interferon. [15] The plant is also capable of inhibiting several other immune functions in vitro, including response of human mononuclear cells and generation of cytotoxic T-cells. [16] Another report measures ability of thunder god vine to affect cytokine secretion from monocytes or T-cells, prostaglandin E2 secretion from monocytes and other parameters of immune response. Results confirmed powerful suppressive effects in vitro, suggesting its use in rheumatic disease. [17] A similar study examining the mechanism of thunder god vine's effectiveness in rheumatoid arthritis isolates human peripheral blood mononuclear cells, then separates them into monocytes, T-cells, and B-cells. Thunder god vine alcoholic extract inhibited T-cell and B-cell proliferation, IL2 production by T-cells, and immunoglobulin production by B-cells. [18] Peripheral blood mononuclear cells from rheumatoid arthritic patients and control patients were studied for effects of thunder god vine polyglycosides. The thunder god vine preparation was found to act on both monocytes and lymphocytes, again confirming the immunosuppressive activity of the plant.[19]

In mice, thunder god vine isolate triterene inhibited antibody response and inhibited granuloma growth in rats. [20] Also in rodents, results of another report indicated six diterpenes (triptolide, tripchlorolide, triptonide, tripdiolide, triptolidenol, and 16-hydroxytriptolide) all to possess anti-inflammatory and immunosuppressive actions in vivo. The constituent triptriolide had anti-inflammatory activity only. [21] A thunder god vine isolate in different concentrations was studied for its anti-inflammatory effects. It markedly inhibited increased vascular permeability in mice, inhibited hind paw edema and also inhibited proliferation of granuloma, suggesting the isolate's ability to stimulate pituitary-adrenal axis. [22] In another report, it was suggested that the suppressive effect of thunder god vine may be mediated by substance P, when studied in rat spinal dorsal horn.[23]

Human clinical trials evaluating the beneficial effects of thunder god vine preparations to treat autoimmune diseases are very promising. An analysis of 165 cases of thunder god vine's actions on rheumatoid arthritis is available. [24] Later reports confirm the plant's efficacy, as well. In a prospective, controlled double-blind crossover study in 70 rheumatoid arthritis patients, polyglycoside constituent "T2" from thunder god vine had "impressive, curative effects." [25] Multi-glycosides of TGV, 30 mg/day, in 32 rheumatoid arthritis patients, resulted in "significant improvements in clinical and laboratory variables." [26] Oral tablets containing thunder god vine had obvious "anti-inflammatory, analgesia and immunosuppressive actions" in both standard and sustained release forms, when evaluated in a 226-patient, prospective, multi-center study.[27]

Antiviral: Neotripterifordin has been found to show potent anti-HIV replication activity in vitro. [6,28] Triptofordin C-2 and other sesquiterpene components of thunder god vine, have been evaluated for their antiviral activity including human cytomegalovirus. [29]

Antitumor: It has been demonstrated that low doses of the diterpene triptolide isolate from thunder god vine possesses antileukemic activities in rodents [30] Additionally, it shows marked antitumor activity in mice.[30,31] Demethylzeylasteral (a nortriterpenoid isolate of thunder god vine) inhibits proliferation of vascular endothelial cells 30 times more effectively than for the proliferation of human tumor cells, suggesting the isolate to be useful in treating highly vascularized and metastatic tumors.[5] Effects of thunder god vine on tumor necrosis factor have been reported.[32]

Other: Other effects studied on thunder god vine include therapeutic actions in 12 cases of menorrhagia [33] and as treatment for multiple sclerosis.[34] A review is available on clinical uses of thunder god vine. [35]

TOXICOLOGY: The triptolide constituent of thunder god vine exhibited non-specific cytotoxicity in cultured mammalian cell lines. Treatments of 50 mcg/mouse 3 times weekly in one preparation were lethal.[30]

Gastrointestinal upset, infertility and suppression of lymphocyte proliferation are the usual side effects of thunder god vine. [36] Rash symptoms and alimentary canal

incidences were experienced in one report, more so with a higher dose of the drug than with a lower dose. [26] Similarly, adverse reactions from a sustained release formulation of thunder god vine was approximately 20% in 226 rheumatoid arthritis patients, as opposed to a 70% side effect rate from standard release tablets. [27]

Fourteen female rheumatoid arthritis patients developed amenorrhea after treatment with "T2" (thunder god vine constituent), suggesting its site of action to be the ovary. These effects were reversible after discontinuation of the drug. [37]

Little information about lethal toxicities has been reported; however, one case report describes an incidence of death (in a seemingly young and healthy male) 3 days post-ingestion of the drug. Later investigation found some incidence of coexisting cardiac damage. Prior to death, the patient experienced profuse vomiting, diarrhea, leukopenia, renal failure, hypotension, and shock. [36]

SUMMARY: The thunder god vine has been used in ancient Chinese medicine for centuries. Most studies evaluate its role in autoimmune diseases such as arthritis, but recently its antifertility effects in men have been of interest. The plant also possesses antiviral and antitumor actions. Side effects of the drug include GI upset and lymphocyte proliferation. Amenorrhea and at least one death have been reported from ingestion.

PATIENT INFORMATION— Thunder God Vine

Uses: Thunder god vine has antifertility properties. In clinical trials it has been effective in treating autoimmune disease. Thunder god vine has shown antiviral and antitumor activity.

Side Effects: Side effects include gastrointestinal upset, infertility, suppression of white blood cells, amenorrhea, and one incidence of death.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    THUNDER GOD VINE

TINOSPORA CORDIFOLIA

DATE OF ISSUE: MAR 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Tinospora cordifolia*(Willd.) Miers. Family: Menispermaceae (Moonseeds)

COMMON NAME(S): Guduchi, amrita(Sanskrit), giloe, gulancha(Bengali), giloya (Hindi), gado, galo (Gujarati), duyutige, teppatige (Telugu), heartleaf moonseed(English)

BOTANY: *Tinospora cordifolia* is a glabrous, succulent, climbing shrub native to India. It also is found in Burma and Ceylon. It thrives easily in the tropical region, often attains a great height, and seems to be particularly fond of climbing up the trunks of large neem trees. The bark is gray or creamy-white in color, deeply cleft spirally and longitudinally, with the space in between spotted with large, rosette-like linticels. The wood is white, soft, and porous, and the freshly cut surface quickly assumes a yellow tint on exposure to air. The branches bear smooth heart-shaped leaves, unisexual greenish flowers (summer), and red berries (winter). Long thread-like aerial roots arise from the branches as well. The viscous sap has a light yellow color, odor, and nauseating bitter taste. [1,2,3,4,5]

HISTORY: Guduchi is an Indian medicinal plant and has been used in Ayurvedic preparations for the treatment of various ailments throughout the centuries. Ancient Hindu physicians prescribed it for gonorrhea. European medical men in India became interested in the tonic, antiperiodic, and diuretic properties of *T. cordifolia*. Today, the drug and a tincture prepared from it are official in the *Indian Pharmacopoeia*.[1,6] They are used for the treatment of general weakness, fever, dyspepsia, dysentery, gonorrhea, secondary syphilis, urinary diseases, impotency, gout, viral hepatitis, skin diseases, and anemia. In compound formulations, guduchi is clinically used to treat jaundice, rheumatoid arthritis, and diabetes. The root is considered to be a powerful emetic and is used for bowel obstruction. [7,8,9,10]

CHEMISTRY: A large number of compounds have been isolated from the aerial parts and roots of *T. cordifolia*. In the early 1900s, giloin, gilenin, and gilosterol were found in the plant together with the following bitter principles: Columbin, chasmanthin, and palmarin. [1] More recently, a wide variety of sesquiterpenes and diterpenes have been isolated from the stems of the plant. The major isolated compounds include the following: Cordiofolisides A, B, and C (new norditerpene furan glycosides);[11] tinocordifolin and tinocordifolioside (daucane-type sesquiterpenes); [8,12] palmatosides C and F (furanoid diterpene glucosides); [13] cordioside, tinosponone, and tinocordioside (clerodane diterpenoids); [14,15] tinosporaside (a novel 18-norclerodane diterpene glucoside), [16] and tinocordiside (a new cadinane sesquiterpene glycoside).[17] In addition, syringin, cordiol, cordioside, cordifoliosides A and B (new phenylpropene disaccharides) were identified as the active principles with anticomplement and immunomodulatory activities.[9,18] It has been shown that the stems of the plant contain an alkaloid berberine, and cultures of stem callus from this plant have been shown to have the capability of synthesizing this compound. [19] Ecdysterone, makisterone A, and 20ß-hydroxyecdysone are the phytoecdysones isolated from the aerial parts of the plant. [20,21,22]

Other constituents reported from *T. cordifolia*include a new phenolic lignan and the following compounds: Octacosanol, nonacosan-15-one, heptacosanol, ß-sitosterol, tinosporidine, cordifol, cordifolone, [23,24] magnoflorine, tembetarine,[25] syringine, and syringine apiosylglycoside. [26]

The roots of *T. cordifolia* contain isocolumbin, palmatine, tetrahydropalmatine, magnoflorine, and jatrorrhizine. [27,28]

PHARMACOLOGY: Even though much work has been performed on the chemistry of *T. cordifolia*, there is not much information on which compounds are responsible for the various activities of the plant. Many authors have ascribed the medicinal properties of *T. cordifolia*to the presence of berberine or bitter substances, without any isolation or identification of the active principles. [1]

Adaptogenic effects: *T. cordifolia* has been proposed to possess tonic and antistress properties. [2] The adaptogenic activity of the plant was investigated using a model of cisplatin-induced alterations in GI motility. The aqueous extract not only reversed the effects of cisplatin on gastric emptying, but also normalized cisplatin-induced intestinal hypermotility. The plant was also found to normalize the phagocytic function of peritoneal macrophages after exposure of rats to either carbon tetrachloride or horse serum, and thus it satisfied the definition of an adaptogen. [29]

Antineoplastic effects: *T. cordifolia* may be active against throat cancer in humans. The stem extracts (aqueous, methanol, and methylene chloride extracts) were evaluated in vitro for their cell-killing effects. When HeLa cells were exposed to various doses of the extracts, a dose-dependent increase in cell killing was observed, as compared with nondrug-treated controls. The methylene chloride extract was the most potent. The effect of guduchi extracts was comparable or better than doxorubicin treatment and thus the plant warrants a future study as an antineoplastic agent. [10]

Immunologic effects: *T. cordifolia* has been shown to be effective in the treatment of chronic infections and immunological disorders. It appeared to be immunotherapeutic in *Escherichia coli*peritonitis and bacteremia. It also improved the surgical outcome in extrahepatic obstructive jaundice by strengthening host defenses.[33,34,35,36,37] Syringin, cordiol, cordioside, and cordifoliosides A and B were identified as the active principles responsible for anticomplement and immunomodulatory activities.[9] An arabinogalactan polysaccharide, isolated from the dried stems of *T. cordifolia*showed polyclonal mitogenic activity against B-cells. [6]

Antidiabetic effects: The stems of *T. cordifolia* have long been used in Indian Ayurvedic medicine for the treatment of diabetes mellitus. [30] Studies have shown that aqueous, alcoholic, and chloroform extracts of the leaves exhibited an insulin-like action and significantly reduced the blood glucose levels in normal and alloxan-induced diabetic rabbits. The chloroform extract was more potent than the aqueous and alcoholic extracts. [7] An aqueous *T. cordifolia* root extract administered to alloxan-induced diabetic rats also caused a reduction in blood glucose levels. [2]

Antioxidant effects: The antioxidant properties of *T. cordifolia*roots were studied by administering the aqueous extract to alloxan-induced diabetic rats. After 6 weeks, the levels of plasma thiobarbituric acid reactive substances, ceruloplasmin, and alpha-tocopherol were reduced. In addition, the levels of glutathione and vitamin C were increased. The root extract at a dose of 5 g/kg was the most effective.[3] In another study, a guduchi extract was shown to inhibit the lipid peroxidation and superoxide and hydroxyl radicals in vitro at mg/mL concentrations.[31]

Hypolipidemic effects: Since diabetes is often associated with hyperlipidemia and *T. cordifolia* has been shown to have hypoglycemic properties, the plant was evaluated for its hypolipidemic activity. An aqueous extract of *T. cordifolia* root was administered to alloxan-induced diabetic rats (2.5 and 5 g/kg body weight for 6 weeks) and it reduced serum and tissue cholesterol, phospholipids, and free fatty acids levels. [32] In another study in rats, the aqueous extract also reduced levels of brain lipids.[2]

Other effects: Guduchi also is reported to have anti-inflammatory activity. The activity resembles that of nonsteroidal anti-inflammatory agents. Other reported properties of the plant include antimalarial, antipyretic, and hepatoprotective properties. [3,10,28,38]

TOXICOLOGY: There is relatively little known about the toxicology of *T. cordifolia*. In limited acute toxicity studies, guduchi has been reported to be nontoxic with almost no side effects. When *T. cordifolia* stem extract was administered to rabbits up to the highest oral doses of 1.6 g/kg, there were no noteworthy adverse effects.[10,39]

SUMMARY: *T. cordifolia* has a long history of use as a medicinal plant in the Indian system of medicine. It is clinically used for the treatment of jaundice, diabetes, and rheumatoid arthritis. The plant is also known to possess adaptogenic, anti-inflammatory, antineoplastic, antioxidant, hepatoprotective, hypolipidemic, and

immunologic properties. However, there are limited in vitro or human studies to support these uses. Even though many compounds have been isolated from the plant, in particular a large number of sesquiterpenes and diterpenes, it is not well known which of these compounds are responsible for the various activities of the plant. Limited toxicity studies revealed no significant toxic or adverse side effects of *T. cordifolia* or its extracts.

PATIENT INFORMATION— Tinospora cordifolia

Uses: Although *T. cordifolia* is used clinically in the Indian system of medicine for the treatment of jaundice, diabetes, and rheumatoid arthritis, it has also been found to possess adaptogenic, anti-inflammatory, antineoplastic, antioxidant, hepatoprotective, hypolipidemic, and immunologic properties. There are limited human studies to support these uses.

Side Effects: Limited toxicity studies revealed no adverse side effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TINOSPORA CORDIFOLIA

TOLU BALSAM

DATE OF ISSUE: JUN 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Derived from *Toluifera balsamum* L. which is synonymous with *Myroxylon toluiferum* HBK and *M. balsamamum* (L.) Harms. Family: Leguminosae[1,2,3]

COMMON NAME(S): Opobalsam, resin tolu, Thomas balsam, tolu balsam,[3] balsamum tolutanum, balsam of Tolu, resina tolutana

BOTANY: *T. balsamum* is a tall tree native to South America and grows abundantly on the high plains and mountains of Venezuela, Columbia, and Peru. It is also cultivated in the West Indies. The balsam is collected from incisions made in the tree trunk. The tree differs little from that yielding Balsam of Peru. [4]

HISTORY: Tolu balsam has been used for centuries as a fragrance in perfumes, candies, and chewing gums. Today, it remains in use in pharmaceutical preparations, in the form of a syrup, as an expectorant and as a fragrant vehicle for other compounds. [1,2] It is an ingredient in compound benzoin tincture [2] that is used for the treatment of bedsores, cracked skin, and minor cuts. It has been reported to have been used in the folk treatment of cancer. [3]

CHEMISTRY: Tolu balsam is a yellow-brown semifluid or near solid material with an aromatic vanilla-like odor and taste. On drying it becomes hard and brittle. It is insoluble in water but soluble in pharmaceutical solvents such as alcohol, ether, sodium hydroxide solution, and chloroform. The balsam contains up to 80% resin, approximately 15% free cinnamic acid and benzoic acid, and about 40% of the benzyl and related esters of these free acids. A volatile oil is present in small amounts (from 1.5% to 7%)[1,2] as is a small amount of vanillin (0.05%).[2] A wide variety of additional minor components have been identified in the balsam. [5] The concentrations of these components vary widely in commercial products because of a lack of international standards for tolu balsam. [3]

PHARMACOLOGY: Tolu balsam has mild antiseptic and expectorant properties.[3]

TOXICOLOGY: Allergic reactions to tolu balsam have been reported to occur in some individuals. [3]

SUMMARY: Tolu balsam is an aromatic plant extract that finds widespread use as a fragrance and in flavoring pharmaceutical products. It is not generally used for any unique pharmacologic action, although it is a component of compound tincture of benzoin, which is used to speed wound healing.

PATIENT INFORMATION — Tolu Balsam

Uses: Tolu balsam is most known for its fragrance and flavoring in pharmaceutical products, although it does have mild antiseptic and expectorant properties.

Side Effects: Allergic reactions have been reported in conjunction with tolu balsam.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TOLU BALSAM

TONKA BEAN

DATE OF ISSUE: NOV 1995

REPLACES MONOGRAPH DATED: SEP 1994

SCIENTIFIC NAME(S): *Dipteryx odorata* (Aubl.) Willd. Also *D. oppositifolia* may be used. Family: Fabaceae (Leguminosae)

COMMON NAME(S): Tonka bean, tonga bean, tongo bean, tonco seed, tonquin bean, torquin bean, cumaru, tonco bean

BOTANY: Members of the genus *Dipteryx* are native to South America (Venezuela, Guyana, and Brazil), and are typically large trees bearing single-seeded fruits about 3 to 5 cm in length. The fruit is dried with the seed removed. If not processed further, the fruit is known as "black beans." The beans are macerated in rum and then air-dried. This treatment results in the formation of a crystalline deposit of coumarin and the seeds appear to be frosted.

Tonka beans are rounded at one end and bluntly pointed at the other. The bean is black and deeply wrinkled longitudinally. The bean has a very fragrant odor and an aromatic, bitter taste.[1]

HISTORY: Tonka beans contain the chemical coumarin. Coumarin is used in the food, cosmetic and related industries to impart a pleasant fragrance to cakes, preserves, tobacco, soaps and liqueurs.[2,3] The seeds are sometimes cured in rum.[4] However, according to the FDA Code of Federal Regulations Section 189.130, food containing any coumarin as a constituent of tonka beans or tonka extracts is deemed to be impure.[5] Synthetic coumarin has, to some extent, replaced the natural product.

South American natives mix the seed paste with milk to make a thick nutty flavored beverage. Extracts of the plant have been used in traditional medicine to treat cramps and nausea, as well as a tonic. Seed extracts are administered rectally for schistosomiasis in China. The fruit has been said to have aphrodisiac properties.

CHEMISTRY: Coumarin is present in 1% to 3% (by weight) of the fermented seed, but some strains may contain up to 10%.[2,3,6] Tonka beans also contain 25% fat (containing unsaponifiable sitosterin and stigmasterin) and a larger amount of starch.[1] Coumarin has an odor reminiscent of vanillin. Umbelliferone (7-hydroxycoumarin) has been isolated from the seed. A number of related isoflavones have been isolated from the heartwood, including odoratin and dipteryxin. The bark exudes a resin that contains lupeol, betulin, and other minor components.

PHARMACOLOGY: There are no well-controlled studies describing the pharmacologic effects of Tonka beans or their components. As noted below, coumarin is toxic when ingested in high doses.

Synthetic coumarin has been developed to replace the natural product in some cases. A related compound, warfarin (eg, *Coumadin*) is a potent anticoagulant used in human therapeutics as well as rodenticides.[7,8] Further literature reviews from 1966 to 1995 yielded no new studies on Tonka bean.

TOXICOLOGY: Dietary feeding of coumarin to rats and dogs has been associated with extensive hepatic damage, growth retardation, and testicular atrophy.[2] It is said that large oral doses of the fluid extract can result in cardiac paralysis.[2] The LD50 (Oral) is 680 mg/kg in rats and 202 mg/kg in guinea pigs.[9]

SUMMARY: Tonka beans contain the chemical coumarin. Coumarin is used as a flavoring in foods and tobacco, as well as a fragrance in cosmetics. Coumarin is safe when ingested in normal food-level amounts, but may cause severe hepatic damage when ingested in large amounts. According to the FDA Code of Federal Regulations Section 189.130, food containing any coumarin as a constituent of tonka beans or tonka extracts is deemed to be impure.[5]

PATIENT INFORMATION— Tonka Bean

Uses: Tonka bean contains the element coumarin that is used as a flavoring in foods and tobacco, as well as a fragrance in cosmetics. Otherwise, tonka beans have no proven pharmacological effects.

Side Effects: If ingested in safe amounts, tonka beans do not have any potent side effects. When ingested in animals, ingredients in the tonka bean have caused severe hepatic damage, growth retardation, and testicular atrophy. Large doses of the fluid extract can result in cardiac paralysis.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TONKA BEAN

TRAGACANTH

DATE OF ISSUE: MAY 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): A wide variety of *Astragalus* species, but most commonly *A. gummifera*, are used in commerce. Family: Leguminosae or Fabaceae.

COMMON NAME(S): Goat's thorn, green dragon, gum dragon, gum tragacanth, gummi tragacanthae, hog gum, Syrian tragacanth, tragacanth [1,2,10]

BOTANY: The tragacanth species are generally characterized as low-growing, thorny shrubs that are native to the mountainous regions of the Middle East. [1] Gum tragacanth is obtained by tapping the branches and tap roots. The gum dries as it exudes and is collected rapidly. The word tragacanth is said to derive from the Greek meaning "goat's horn," which may describe the appearance and texture of the crude gum. [1]

HISTORY: Tragacanth has been used since ancient times as an emulsifier, thickening agent, and suspending agent. [1,3] Today it is used extensively in foods and dressings and to thicken ice cream.

CHEMISTRY: Tragacanth contains from 20% to 30% of a water-soluble fraction called tragacanthin (composed of tragacanthic acid and arabinogalactan). It also contains from 60% to 70% of a water-insoluble fraction called bassorin. Tragacanthic acid is composed of D-galacturonic acid, D-xylose, L-fructose, D-galactose, and other sugars. Tragacanthin is composed of uronic acid and arabinose and dissolves in water to form a viscous colloidal solution (sol), while bassorin swells to form a thick gel. [1,2]

Tragacanthin partially dissolves and partially swells in water yielding a viscous colloid. The maximal viscosity is attained only after 24 hours at room temperature or after heating for 8 hours at high temperatures. The viscosity of these solutions is generally considered to be the highest among the plant gums. [1] The solutions are heat stable and stable under a wide range of pH levels.

PHARMACOLOGY: Tragacanth has been used as a demulcent in cough and cold preparations and to manage diarrhea. [2] As with other water-soluble gums, there is some preliminary evidence that concomitant ingestion of tragacanth with a high sugar load can moderate the blood sugar levels in patients with diabetes, [4] although this effect has not been demonstrated consistently [5] and requires much more detailed investigation. Although gum tragacanth swells to increase stool weight and decrease GI transit time, it appears to have no effect on serum cholesterol, triglyceride or phospholipid levels after a 21-day supplementation period as do other soluble fibers. [5,6]

Tragacanth has been reported to inhibit the growth of cancer cells in vitro and in vivo. [1,2]

Because of its mucilaginous adhesive properties, tragacanth is used as a component of some denture adhesives. [7]

TOXICOLOGY: Tragacanth is Generally Recognized as Safe (GRAS) in the US for food use. [8] There is no indication that dietary supplementation for up to 21 days has any significant adverse effects in man. [5]

Tragacanth is highly susceptible to bacterial degradation, and preparations contaminated with enterobacteria have been reported to have caused fetal deaths when administered intraperitoneally to pregnant mice. [1] A cross-sensitivity to the asthma-induced effects of quillaja bark has been observed for gum tragacanth. [9]

SUMMARY: Gum tragacanth is widely used throughout the world as a thickener and suspending agent in foods and pharmaceuticals. It is characterized by a very safe use profile. It does not appear to have any beneficial influence on serum lipid or glucose levels as do other soluble gums.

PATIENT INFORMATION — Tragacanth

Uses: Tragacanth has been used as a demulcent in cough and cold preparations and to manage diarrhea. It also has been shown to moderate the blood sugar level, but this has not been demonstrated consistently.

Side Effects: Presently, tragacanth is not recognized as having any adverse effects.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TRAGACANTH

TRILLIUM

DATE OF ISSUE: JUL 1992

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Trillium erectum* L. Family: Liliaceae (Trilliaceae). *T. grandiflorum* (Michaux) Salisb. has also been used medicinally in American traditional medicine.

COMMON NAME(S): Trillium, birthroot, bethroot, Indian balm, purple trillium, stinking Benjamin, wake-robin, trillium pendulum, ground lily, cough root, jewsharp, snake bite[1,2]

BOTANY: Trillium grows abundantly in the southern Appalachians. *T. erectum* is a low-growing perennial that reaches a height of about 18 inches. It has 3 dark green diamond-shaped leaves, each about 7 inches long. From April to June it produces a solitary odiferous, reddish brown flower. The smell is the reason for the name stinking Benjamin. The flower produces an oval reddish berry.

HISTORY: Birthroot is a popular folk remedy for bleeding, snakebites, and skin irritations. Teas made from the plant had been used traditionally to stop bleeding following childbirth, hence the name birthroot. The Indians applied topical preparations to relieve insect bites and skin irritations. The leaves have been used as a potherb or salad green.

CHEMISTRY: Little is known about the chemistry of this plant. *Trillium* species have been reported to contain a fixed and volatile oil, a saponin (trillarin, which is a diglycoside of diosgenin), a glycoside resembling convallamarin, tannic acid, and considerable starch. [3]

PHARMACOLOGY: Although trillium has been used for many years as an herbal means of controlling postpartum bleeding as well as other uterine bleeding problems, a clear mechanism for this systemic effect has not been identified.[1,4] The plant may have astringent properties that account for its ability to limit topical bleeding and irritation. This action was also the basis for its historic use in diarrhea. [2,4] The plant has been used traditionally as an expectorant, but no chemical basis has been identified for this action. There is not evidence to support the use of trillium for the treatment of snoring. Extracts of trillium have been used as molecular probes in chromosome studies.[5] The saponin glycosides have been shown to have significant antifungal activity. [6]

TOXICOLOGY: Although the leaves of the plant have been considered to be edible by some, there remains the possibility of toxicity from the plant. The saponin could have potential membrane-irritating effects and the convallamarin-like glycoside could induce some cardiac activity, although neither of these events have been observed clinically.[3]

SUMMARY: Trillium has a long history of use in traditional medicine for the management of bleeding particularly following childbirth. There are no studies to support this use. The chemistry of trillium is not well defined, but the tannin content may play a role in the topical control of bleeding and the relief from insect bites that the plant is said to afford.

PATIENT INFORMATION — Trillium

Uses: Trillium has been used to stop postpartum bleeding, although there are no studies to support this use. It may also play a role in the topical control of bleeding and relief from insect bites.

Side Effects: Although not yet clinically observed, trillium could have potential membrane-irritating effects and induce some cardiac activity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TRILLIUM

TUNG SEED

DATE OF ISSUE: SEP 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Aleurites moluccana*(L.) Willd or *A. cordata* Steud. Family: Euphorbiaceae

COMMON NAME(S): Tung, candlenut, candleberry, varnish tree, balucanat, otaheite walnut, China-wood oil

BOTANY: The tung is indigenous to China and Japan but now grows in many warm regions, including Florida.

HISTORY: The seed is the source of an oil that has been widely used as a wood preservative. It dries faster than linseed oil, making it a near perfect drying oil. The oil is incorporated into paints and varnishes, soaps, rubber substitutes, linoleum, and insulation. [1] The seed cake is used as a fertilizer, but the seeds can be poisonous. The roasted kernels, however, are said to be edible. [1] An extract of the bark is used to treat tumors in Japanese traditional medicine. The oil is a purgative. Tung seed is used in Hawaiian traditional medicine for the treatment of asthma. [2]

CHEMISTRY: The seed is the source of an inedible, semi-drying oil. The pale yellow oil contains eleostearic acid, linolenic, linoleic, and oleic acids. It is high in protein. The presence of a toxalbumin and HCN have been suggested. [1]

PHARMACOLOGY: There are no good studies to assess the human pharmacology of tung seed.

TOXICOLOGY: The various species of *Aleurites* vary in their potential toxicity. *A. fordii* is said to be about twice as toxic as *A. trisperma*, with *A. montana* and *A. moluccana* demonstrating intermediate toxicity. Ingesting the seeds can result in severe stomach pain, vomiting, diarrhea, slowed reflexes, and possibly death. The seeds are thrown into fishing areas to stupefy fish in some remote regions, which reflects the potential human toxicity of this plant. [1] Contact with the latex can result in dermatitis; this appears to be related to the presence of a saponin and phytotoxin.

SUMMARY: The tung plant is the source of commercially important tung oil, which is used as a wood finish and a component of paints and varnishes. The tung seed is generally considered to be toxic.

PATIENT INFORMATION— Tung Seed

Uses: Tung seed is commonly used as a wood finish and a component of paints and varnishes. No studies assess the human pharmacology of tung seed.

Side Effects: The tung seed is considered to be toxic, resulting in stomach pain, vomiting, diarrhea, slowed reflexes, and possibly death.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TUNG SEED

TURKEY TAIL

DATE OF ISSUE: MAR 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Coriolus versicolor* (L. ex Fr.) Family: Polyporaceae

COMMON NAME(S): Cloud mushroom, PSK, PSP, yun zhi, polysaccharide krestin, turkey tail[1]

BOTANY: The turkey tail fungus is commonly found throughout North America, Asia, and Europe. Its fruiting bodies overlap one another, forming a dense mass that grows on tree trunks, stumps, and fallen trees. The colors of the distinctive layers created by these bodies may be light to dark brown or gray. The polysaccharides of the fruiting bodies are commercially marketed as a tea that is commonly used in Asian and European traditional medicine. [1]

HISTORY: Folklore remedies of turkey tail include the treatment of lung and liver infections. In China, turkey tail has been used as a preventive and curative agent for liver infections and liver cancer. In Japan, it is considered a panacea for a variety of cancers. Overall, the mycelium and fruiting body of the mushroom is considered an immune stimulant and is believed to have anticarcinogenic activity. [1,2,3]

CHEMISTRY: The water-extracted protein-bound polysaccharide krestin (PSK) and polysaccharide peptide (PSP) polysaccharides of *C. versicolor* have immunomodulating and antitumor activity. The peptides are chemically similar but distinguished by fucose in PSK and rhamnose and arabinose in PSP. PSP has a molecular weight of 100 kDa. The polypeptide component contains mostly glutamic and aspartic acids and the polysaccharides are mostly composed of monosaccharides with alpha-1,4 and beta-1,3 glucosidic linkages. [2,3,4]

PHARMACOLOGY: Clinical research with PSK began around 1970 and has focused on its immunotherapeutic efficacy in stomach, colorectal, esophageal, nasopharyngeal, lung, and breast cancers. Overall, the polysaccharides in PSK reportedly increase gamma-interferon production, interleukin-2 production, and T-cell proliferation, therefore improving immune system functioning. Other studies have focused on the antimicrobial, antiviral, and antioxidant properties of PSK. [1]

A multicentered, randomized clinical trial of 262 patients in Japan resulted in PSK improving the 5-year disease-free rate ($p = 0.047$) and 5-year survival rate ($p = 0.044$) when combined as an adjuvant treatment with standard chemotherapy in patients after curative gastrectomy.[5,6] Another clinical study of 579 patients followed for 5 years also supports the use of PSK as an adjuvant immunochemotherapeutic agent for patients who have had curative gastric resection. [7,8] Meta-analysis of clinical trials provide evidence of a survival benefit for stage I gastric cancer with PSK. [9,10]

A retrospective study of 185 patients with non-small cell lung cancer at stages I through III supports the use of PSK as adjuvant treatment after radiotherapy. The 5-year survival rates of patients were statistically significant. [11]

Two randomized clinical trials found PSK useful as a maintenance therapy for patients following curative surgical operations for colorectal cancer. In both trials, the survival rate of patients was significant ($P < 0.05$) probably because of increased immune system response induced by PSK.[12,13]

An in vitro study with PSP demonstrated antiviral activity against human immunodeficiency virus type 1 infection (HIV-1). The mechanism of action is postulated to include PSK interfering with the binding of HIV-1 to its cellular target. [14] Other in vitro studies in mice suggest a protective effect of PSK against *Candida* infection mainly through TNF-alpha activity.[15]

There are several review articles on PSK as an anticancer agent that inhibits acting cancer cells. The therapeutic effect is postulated to include induction of immunomodulatory cytokines and cytokine receptors as well as antioxidant activity. [16,17,18,19]

TOXICOLOGY: Adverse effects observed in patients include diarrhea, darkened stools, and darkened nail pigmentation. PSK is considered to be very well tolerated by patients.[1] Additional scientific studies are needed to attain a profile of any potential serious side effects.

SUMMARY: Various clinical trials demonstrate the immunotherapeutic efficacy of turkey tail as an adjuvant treatment in cancer patients, particularly in those with GI cancers. Other in vitro studies also support the antiviral and immune-stimulating effects of turkey tail.

PATIENT INFORMATION— Turkey Tail

Uses: Turkey tail has antioxidant activity, boosts immune response, and is considered an adjunctive treatment in cancer chemotherapy. Several clinical trials have supported these uses.

Side Effects: Patients have reported diarrhea, darkened stools, and darkened nail pigmentation.

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TURKEY TAIL

TURMERIC

DATE OF ISSUE: FEB 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Curcuma longa* L. Synonymous with *C. domestica* Val. Family: Zingiberaceae

COMMON NAME(S): Turmeric, curcuma, Indian saffron

BOTANY: Turmeric is a perennial member of the ginger family characterized by a thick rhizome. The plant grows to a height of 3 to 5 feet and has large (1.5' x 8") oblong leaves. It bears funnel-shaped yellow flowers.[1] The plant is cultivated widely throughout Asia, India, China, and tropical countries. The primary (bulb) and secondary (lateral) rhizomes are collected, cleaned, boiled, and dried; and lateral rhizomes contain more yellow coloring material than the bulb. [2] The dried rhizome forms the basis for the culinary spice.

HISTORY: Turmeric has a warm, bitter taste and is a primary component of curry powders and some mustards. The powder and its oleoresins are also used extensively as food flavorings in the culinary industry. The spice has a long history of traditional use in Asian medicine. In Chinese medicine, it has been used to treat problems as diverse as flatulence and hemorrhage. It also has been used topically as a poultice, as an analgesic and to treat ringworms. [3] The spice has been used for the management of jaundice and hepatitis.[2] The oil is sometimes used as a perfume component.

CHEMISTRY: Turmeric rhizome contains up to 7% of an orange-yellow volatile oil composed primarily of tumerone (60%), isomers of atlantone and zingiberene (25%). More than a half-dozen minor components have been identified in the oil.

Turmeric contains about 5% diaryl heptanoids known as curcuminoids (curcumin and related compounds) that impart the yellow color. [2]

PHARMACOLOGY: A number of soluble fractions of turmeric, including curcumin, have been reported to have antioxidant properties. Turmeric inhibits the degradation of polyunsaturated fatty acids.[4] Dietary administration of this compound at a level of 2% to mice reduced the incidence of experimentally-induced colonic hyperplasia, indicating that the antioxidant effects are active in vivo. [5] The curcumins inhibit cancer at initiation, promotion, and progression stages of development. [6]

Tumor-preventing activity has been reported in hamsters given turmeric, and the effect was additive to that observed during treatment with betel leaf extract. [7] In smokers, turmeric given at a daily dose of 1.5 g for 30 days significantly reduced the urinary excretion of mutagens compared with controls; turmeric had no effect on hepatic enzyme levels or lipid profiles suggesting that the spice may be an effective antimutagen useful in chemoprevention. [8]

Ukonan-A, a polysaccharide with phagocytosis-activating activity has been isolated from *C. longa*[9] and Ukonan-D has demonostrated strong reticuloendothelial system-potentiating activity.[10] Aqueous extract of *C. longa* has recently been shown to have cytoprotective effects that inhibit chemically-induced carcinogenesis, and this activity may form a basis for the traditional use of turmeric as an anticancer treatment. [11]

A fraction of curcuma oil has been shown to have anti-inflammatory and antiarthritic activity in a rat model. [3] A combination of turmeric and neem (*Azadirachta indica*) applied topically has been shown to effectively eradicate scabies in 97% of 814 people treated within 3 to 15 days. [12] Curcumin has a slight antiedemic effect in rats; other pharmacologic properties of turmeric include choleretic, hypotensive, antibacterial, and insecticidal activity.

The choleretic (bile stimulating) activity of curcumin has been recognized for almost 40 years, and these compounds have been shown to possess strong antihepatotoxic properties.[13]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Acute and chronic (100 mg/kg/day for 90 days) evaluation of *C. longa* ethanolic extracts in mice found the material to be relatively devoid of serious side effects. No reports of significant toxicity have been reported following the ingestion of turmeric. No significant change in weight was observed following chronic treatment, although significant changes in heart and lung weights were observed; a significant decrease in white and red blood cell levels were observed. Although a gain in weight of sexual organs and an increase in sperm motility was observed, no spermatotoxic effects were found. [14]

SUMMARY: Turmeric is a widely used spice that is a major component of curry powder. The spice has a long history of use in traditional Asian medicine. Recent investigations indicate that the strong antioxidant effects of several components of turmeric result in an inhibition of carcinogenesis, and extracts of the spice may play a role as chemoprotectants, which limit the development of cancers.

PATIENT INFORMATION — Turmeric

Uses: Turmeric is used as a spice. Recent investigations indicate that the strong antioxidant effects of several components of turmeric result in an inhibiton of carcinogenesis and may play a role in limiting the development of cancers.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: There are no known side effects.

Dosing: Powdered turmeric root has been used as a stimulant and carminative at doses of 0.5 to 3 g/day. Higher doses of 6 g/day were investigated for protective effects against ulcer.[15]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
    TURMERIC

TURPENTINE

DATE OF ISSUE: APR 1993

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Pinus palustris* Mill. and several other species and varieties of *Pinus*. Family: Pinaceae

COMMON NAME(S): Turpentine, gum turpentine, gum thus, turpentine oil, turpentine balsam

HISTORY: The primary use of turpentine has been as a solvent in paints. During the last century, it became an important starting material for the commercial synthesis of many widely used compounds, including camphor and menthol. Various products derived from turpentine have been used in chewing gums, and steam-distilled turpentine oil has been used as a food and beverage flavoring in very small quantities (typically about 20 ppm). Turpentine and its related products have a long history of medicinal use, where they have been employed primarily as topical counterirritants for the treatment of rheumatic disorders and muscle pain. A gum derived from turpentine was used in traditional Chinese medicine to relieve the pain of toothaches.

Other extracts (including the semi-synthetic derivative terpin hydrate) have been used for the treatment of cough and cold symptoms; [1] the cis-form of terpin hydrate is used as an expectorant.[2]

A variety of gum and resin products had been derived from pines for use in the early naval industry as tars and pitches. Consequently the terms "wood naval stores" and "gum naval stores" came to be associated with these pine-derived products. [3]

SOURCE AND COMPOSITION: Research suggests that the term "turpentine" is used imprecisely to describe either the oleoresin obtained from the longleaf pine (*Pinus palustris* Mill.) or the slash pine (*P. elliottii* Engelm.) along with other *Pinus* species that yield exclusively terpene oils, or the essential oil obtained from the above oleoresin.[4] More than a half-dozen additional *Pinus* species have been used in the production of turpentine.[3] The oleoresin is sometimes referred to as "gum turpentine" while turpentine or its oil (also known as spirits of turpentine) are terms for the essential oil. Following steam distillation, gum turpentine yields turpentine oil and a resin called colophony (also known as rosin). Alternately, rosin is collected by scarring the tree trunk, and various grades of material are then refined. [3] Turpentine and rosin also are obtained by the steam distillation of wood chips of pine that are by-products of the lumber and paper industries, and these sources account for the bulk of the production of these compounds. In terms of volume, turpentine is the largest volume essential oil product in the world, with the bulk of production occurring in the United States. The labor-intensive production of rosin, however, occurs to a greater extent in Spain, Greece, India, and Morocco.

Turpentine is composed primarily of monoterpene hydrocarbons, the most prevalent of which are the pinenes, camphene, and 3-carene. Rosin contains mostly diterpene resin acids such as abietic acid, dehydroabietic acid, palustric acid and isopimaric acid. Numerous other compounds are present in small quantities in all turpentine products.

Canada turpentine or Canada balsam is an oleoresin obtained from the stems of the balsam fir, *Abies balsamae* (Family Pinaceae).

PHARMACOLOGY: When applied topically, turpentine causes skin irritation and, therefore, has been shown to exert rubefacient and counterirritant actions.

Turpentine possesses antibacterial activity in vitro [4] and has been applied topically to debride severe wounds infested with fly larvae. [5] Preliminary reports from Russia suggest that turpentine baths may assist in the treatment of disseminated sclerosis, [6] but the safety of this treatment has not been established.

Turpentine is now being injected in animals as part of experimental models of inflammation to induce a systemic inflammatory immune response. [7]

TOXICOLOGY: The contact allergenic activity of turpentine is believed to be due primarily to the pinenes, 3-carene, and dipentene. [4,8] The resin also has irritant potential. In one survey of persons involved in the manufacture of tires, patch testing indicated that 2.6% of those tested developed hypersensitivity reactions to turpentine. Benign skin tumors have been observed in animal models following chronic topical application of turpentine.

Turpentine has been used for traditional self-medication in the United States, and fatal poisonings have been reported in children who have ingested as little as 15 ml of the material.[9] Turpentine is among the most commonly ingested poisons among childhood cases reported to poison control centers. [10] Toxic effects of turpentine ingestion include headache, insomnia, coughing, vomiting, hematuria, albuminuria, and coma. [4]

SUMMARY: Turpentine and its related products (the oil and rosin) are important in commerce and traditional medicine. These products can pose a toxicity problem, and should be handled and stored carefully.

PATIENT INFORMATION— Turpentine

Uses: Turpentine has been used experimentally in a bath for the treatment of disseminated sclerosis, and is presently being injected into animals as experiemental models of inflammation to induce a systemic inflammatory immune response.

Side Effects: If ingested, turpentine is highly toxic.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "T" MONOGRAPHS
      TURPENTINE

"U" MONOGRAPHS

UBIQUINONE

DATE OF ISSUE: AUG 1997

REPLACES MONOGRAPH DATED: MAY 1988

SCIENTIFIC NAME(S): *Coenzyme Q-10*, *Ubidecarenone*, *mitoquinone*

COMMON NAME(S): Adelir, Heartcin, Inokiton, Neuquinone, Taidecanone, Udekinon, Ubiquinone

HISTORY: The first ubiquinone was isolated in 1957. Since that time, ubiquinones have been extensively studied in Japan, Russia, and Europe with research in the US having begun more recently. Lay press accounts claim that roughly 12 million Japanese now use ubiquinones as the medication of choice for management of cardiovascular diseases supplying the demand for more than 250 commercially available preparations. Ubiquinone is touted as an effective treatment of congestive heart failure (CHF), cardiac arrhythmias and hypertension, and in the reduction of hypoxic injury to the myocardium. Other claimed effects include the increase of exercise tolerance, stimulation of the immune system, and counteracting of the aging process. Clinical uses have included the treatment of diabetes, obesity, and periodontal disease. Ubiquinone has not been approved for therapeutic use in the US, but it is available as a food supplement. [1]

CHEMISTRY: Ubiquinones are a class of lipid-soluble benzoquinones that are involved in mitochondrial electron transport. They are found in the majority of aerobic organisms, from bacteria to mammals, hence the name "ubiquinone" ("quinone found everywhere"). Studies in rats have shown that levels of ubiquinone and cytochrome C reductase increase adaptively during endurance exercise training. This increase occurs in red quadriceps and soleus muscle but not in white cardiac or quadriceps muscle. The increase in red muscle levels represents a positive adaptation to training. [2] Experiments have shown that ubiquinones participate in oxidation-reduction reactions in the mitochondrial respiratory chain. They also have properties of hydrogen carriers, thus providing a coupling of proton translocation to respiration by means of a chemiosmotic mechanism.[3]

Structurally ubiquinones are analogous to vitamin K. The basic molecule is 2,3-dimethoxy-5-methylbenzoquinone, to which are attached variable terpenoid side chains containing 1 to 10 monounsaturated trans-isoprenoid units. The 6- to 10-unit chain forms (Q-6 to Q-10) are found in animals, with Q-10 being exclusive to humans. All of the ubiquinones have been synthesized in the laboratory. [4] Studies with deuterated analogs of Q-10 have demonstrated that Q-10 occurs in a mobile environment within the cell, physically separate from the orientational constraints of bilayer lipid chains. This suggests that the bulk of the long-chain ubiquinones are not directly involved functionally in electron transport. Q-10 may represent only a small fraction of total ubiquinone. [5]

HPLC of ubiquinone-10 has been performed,[6] as has sodium lauryl sulfate use in hexane extraction of ubiquinone-10 from plasma samples.[7]

PHARMACOLOGY: Biomedical evidence provides the rationale for the use of ubiquinone in cardiovascular diseases. Endogenous forms function as essential cofactors in several metabolic pathways, especially in oxidative respiration. Supraphysiologic doses of ubiquinone may benefit tissues that have been rendered ischemic and then reperfused. Ubiquinone appears to function in such tissues as a free-radical scavenger, membrane stabilizer, or both. [8] Ubiquinone as a mobile component in mitochondrial membrane and its role in electron transfer has been reported. [9] It may have applications in treating ischemic heart disease, CHF, toxin-induced cardiopathy and possibly hypertension. It protects ischemic myocardium during surgery. [8]

Experiments with rabbit hearts measured the effects of Q-10 during hypoxia and following reoxygenation. In untreated hearts, reoxygenation was followed by a release of ATP metabolites and creatine phosphokinase. Pretreatment of the hearts with Q-10 eliminated these releases. This suggests that Q-10 retards the breakdown of ATP metabolites, providing a pool from which ATP can be constructed by a salvage process during reoxygenation. [10,11] Coenzyme Q-10 also provides a protective effect when used on rat mitochondria.[12]

Q-10 has also been shown to eliminate biochemical derangements (reductions of norepinephrine and ATP) in thyrotoxic rabbit hearts. [13] In beef hearts, Q-10 protected mitochondria from oxidative damage to lipid membranes induced by treatment with an adriamycin-iron complex. In these experiments, it reduced the inactivation of NADPH and succinate oxidases.[14] In transplantation experiments, rats receiving livers subjected to prior warm ischemic damage did not survive more than 2 days. Pretreatment of the donors with Q-10 significantly increased the duration of survival, decreased AST and ALT levels and increased total protein to the normal range without affecting total bilirubin or hepatic histology. Thus, ubiquinone had a protective effect on donated livers subjected to heat-induced ischemia before transplantation.[15]

Ubiquinone's role in cardiac treatment using human subjects is promising. In geriatric patients, Q-10 treatment improved both symptoms and clinical conditions of all 34 patients with CHF.[16] It was also effective for symptomatic mitral valve prolapse and improved stress-induced cardiac dysfunction in 400 pediatric patients. [17] Activity tolerance improvements were observed in a double-blind study of 19 patients with chronic myocardial disease given oral ubiquinone-10. [18] In advanced heart failure, 12 patients given 100 mg daily of the drug showed marked clinical improvement. [19] Immune system effects were enhanced in myocardial failure in another report, when Q-10 was used in conjunction with other drugs.[20] Aiding defective myocardial supply, ubiquinone's role in oxidative phosphorylation offers positive results in adjunctive treatment, clinical outcomes, symptoms, and quality of life in these cardiac patients. [21]

Q-10 actions on lipids have also been reported. The mechanism may be membrane phospholipid protection against phospholipase attack. [22] In its reduced form, ubiquinone's presence in all cellular membrane, blood serum, and serum lipoproteins, allows protection from lipid peroxidation. [23] Its ability to remain stable in hypercholesterolemia patients has been studied.[24,25] Ubiquinol can also sustain vitamin E's antioxidant effects by regenerating the vitamin from its oxidized form. [23,26]

One report describes ubiquinone and its role in human nutrition.[27] A case report uses ubiquinone to treat drug-induced rhabdomyolysis and hepatotoxicity. [28]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: No serious side effects have been associated with the use of ubiquinone. Use of the substance is contraindicated in people with demonstrated hypersensitivity. Use during pregnancy or lactation is not recommended, because studies have not demonstrated the safety of ubiquinone for fetuses and infants. Rare side effects have included epigastric discomfort, loss of appetite, nausea and diarrhea, affecting fewer than 1% of more than 5000 individuals in one study. [1]

SUMMARY: Ubiquinones, particularly Q-10, are naturally occurring compounds found in aerobic organisms. Q-10 has been widely used in Japan, Russia, and Europe for a variety of indications, notably cardiovascular diseases. Studies using ubiquinone offer mainly positive outcomes in CHF therapy. Reports on ubiquinone's effects on lipid disorders and antioxidant effects have also been promising. This research indicates that Q-10 may have value for some of the purposes claimed by proponents, and toxicity appears to be minimal. No doses have been established for the treatment of any human disorder and no RDA has been established for this compound. This compound appears to possess important pharmacologic activity and warrants further investigation in disease states.

PATIENT INFORMATION — Ubiquinone

Uses: Ubiquinone may have applications in treating ischemic heart disease, congestive heart failure, toxin-induced cardiopathy and hypertension, and protects ischemic myocardium during surgery.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Rare side effects include epigastric discomfort, loss of appetite, nausea and diarrhea. Use is not recommended in pregnancy and lactation and in people with demonstrated hypersensitivity.

Dosing: Ubiquinone has been studied in clinical trials at doses of 90 to 200 mg/day for heart failure, cirrhosis, and antioxidant properties. [29,30,31,32,33,34,35,36]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "U" MONOGRAPHS
    UBIQUINONE

UVA URSI

DATE OF ISSUE: JUL 1997

REPLACES MONOGRAPH DATED: SEP 1987

SCIENTIFIC NAME(S): *Arctostaphylos uva ursi* L. Sprengel. (Also referred to as *Arbutus uva ursi*L.). The related plants *A. adenotricha*and *A. coactylis* Fern et Macbr. have also been termed uva ursi by some authors. Family: Ericaceae

COMMON NAME(S): Uva ursi, bearberry, kinnikinnik, hogberry, rockberry, beargrape, manzanita.

BOTANY: Uva ursi is a low-growing evergreen shrub with creeping stems that form a dark green carpet of leaves. It can grow to 20 inches in height. The plant has small, dark, fleshy, leathery leaves and clusters of small white or pink bell-shaped flowers. It blooms from April to May and produces a dull orange berry. The plant grows abundantly throughout the northern hemisphere from Asia to the United States. [1,2]

HISTORY: "Uva ursi" means "bear's grape" in Latin, probably because bears are fond of the fruit. Uva ursi was first documented in a 13th century Welsh herbal. [2] Teas and extracts of the leaves have been used as urinary tract antiseptics and diuretics for centuries. The plant has been used as a laxative and the leaves have been smoked.[3] Bearberry teas and extracts have been used as vehicles for pharmaceutical preparations. In homeopathy, a tincture of the leaves is believed to be effective in the treatment of cystitis, urethritis, and urinary tract inflammations. The berries are not used medicinally. They are juicy but have an insipid flavor that improves upon cooking.[4]

CHEMISTRY: The leaves contain hydroquinone derivatives, mainly arbutin and methyl-arbutin in concentrations ranging from 5% to 15%. HPLC determination of these substances has been evaluated.[5] Tannins are also present (6% to 40%) including hydrolysable types, ellagic and gallic acid tannins. Because of this high concentration of tannin, teas prepared from this plant are generally made by soaking the leaves in cold water overnight. This minimizes extraction of the bitter tannins. A report on tannin isolation from uva ursi leaves is available. [6]

Flavonoids including hyperoside, myricetin, quercetin, and glycosides such as hyperin, isoquercitrin, myricitrin, and quercitrin are also found.

Triterpenes, monotropein, piceoside, phenol-carboxylic acids such as gallic and p-coumaric, and syringic acids can be found. Terpenoids such as alpha-amyrin and ursolic acids are present in the plant, as well as other constituents, including malic acid, allantoin, resin, volatile oil, and wax. [1,2,7]

Reports are available, including: Isolation of 14 phenolic acids from uva ursi leaves using GLC; [8] isolation of 8 triterpenoids from uva ursi roots; [9] isolation and identification of free and bonded saccharides in the plant leaves; [10] and differentiation of adulterated uva ursi leaf samples. [11]

PHARMACOLOGY

Antimicrobial effects: Arbutin is hydrolyzed in gastric fluid to hydroquinone. In alkaline urine, hydroquinone is mildly astringent and is an effective antimicrobial agent. Despite this activity, in practice, large amounts of uva ursi must be consumed for any significant effect to occur and the urine must be alkalinized. [12] Evidence suggests that arbutin itself may contribute to the antiseptic activity of the plant, because both arbutin and crude leaf extracts have been shown to possess mild antimicrobial activity in vitro.[13] A report discusses liquid concentration of uva ursi possessing antiseptic and diuretic properties. [14] Uva ursi aerial part extracts were found to be most active against *Escherichia coli* and *Proteus vulgaris*.[15]

Urinary tract effects: Antibacterial activity of arbutin causing urinary tract infection is caused by beta-glucosidase activity of the infective organism. [13] Uva ursi is one of the best natural urinary antiseptics and has been extensively used in herbal medicine. [2] The German Commission E monograph lists its use as "for inflammatory disorders of the lower urinary tract." An herbal remedy including uva ursi is used to treat "compulsive strangury, enuresis, and painful micturition." [1] One report discusses metabolite production of uva ursi,[16] other reports discuss bile expelling/lowering effects of the plant [17] and its beneficial effects on treatment of kidney stone formation.[18]

Several plant compounds (ursolic acid and isoquercetin) are mild diuretics and contribute to the plant's diuretic effect. Uva ursi is a constituent in many over-the-counter herbal diuretic preparations. A report on bearberry reviews diuretic effects and other plant properties. [19]

Other effects: Arbutin may increase inhibitory action of prednisolone and dexamethasone on induced contact dermatitis, allergic reaction-type hypersensitivity, and arthritis, suggesting uva ursi's therapeutic effects against immuno-inflammation. [20,21,22,23] Another study reports reduced hyperphagia, reduced polydipsia and reduced loss of weight in diabetes-induced mice given bearberry. There was no effect on glucose or insulin plasma concentrations, but it may be of some benefit in these diabetes symptoms.[24] Therapy of experimentally induced hepatitis in rats with extract of *A. uva ursi* has been reported.[18,25] Bearberry leaf was also found to be effective in inhibiting melanin production in vitro. [26]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Hydroquinone is toxic in large doses (oral LD-50 in rats is 320 mg/kg). [27] Ingestion of 1 g of the compound resulted in ringing of the ears, nausea, vomiting, cyanosis, convulsions and collapse. Death followed the ingestion of 5 g of hydroquinone. [7] These symptoms are rare; most commercial products have less than 1 g of crude uva ursi per dose. Doses up to 20 g of uva ursi have not caused pharmacologic responses in healthy individuals. [28] Products containing uva ursi may turn urine green. The plant's astringent tannin content may cause gastric discomfort and usually limits the dose ingested.

The published report of the Expert Advisory Committee in Herbs and Botanical Preparations to the Canadian Health Protection Branch (January 1986) recommended that food preparations containing uva ursi provide labeling contraindicating their use during pregnancy and lactation because large doses of uva ursi are oxytocic. [7]

Do not use uva ursi if suffering from kidney disease. Do not take the plant for more than 7 to 10 days at a time. [2]

SUMMARY: Uva ursi has been used for urinary tract ailments; however, the urine must be alkaline for its antimicrobial effects. Studies have been done on the plant's effects against inflammation, diabetes symptoms and other effects. Hydroquinone, a plant constituent, is toxic in large doses. Use is contraindicated in pregnancy.

PATIENT INFORMATION— Uva Ursi

Uses: Uva ursi is useful in treating urinary tract infections; as a diuretic; to treat induced contact dermatitis, allergic reaction-type hypersensitivity, and arthritis in conjuction with prednisolone and dexamethasone.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Ingestion of uva ursi in large doses has resulted in ringing of the ears, nausea, vomiting, cyanosis, convulsions, collapse, and death. The product may also impart a green color to the urine and cause gastric discomfort.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "U" MONOGRAPHS
    UVA URSI

"V" MONOGRAPHS

VALERIAN

DATE OF ISSUE: OCT 1999

REPLACES MONOGRAPH DATED: OCT 1991

SCIENTIFIC NAME(S): *Valeriana officinalis* L. Family: Valerianaceae. A number of other species have been used medicinally, including *V. wallichi* DC, *V. sambucifolia* Mik., and the related *Centranthus ruber* L.

COMMON NAME(S): Valerian, baldrian, radix valerianae, Indian valerian(*V. wallichii*), red valerian (*C. ruber*)

BOTANY: Members of the genus *Valeriana* are herbaceous perennials widely distributed in the temperate regions of North America, Europe, and Asia. Of the approximately 200 known species, the Eurasian *V. officinalis* is the species most often cultivated for medicinal use. The dried rhizome contains a volatile oil with a distinctive, unpleasant odor.[1] The fresh drug has no appreciable smell; however, drying liberates the odiferous constituent isovaleric acid. [2]

HISTORY: Despite its odor, valerian was considered a perfume in 16th century Europe. The tincture has been used for its sedative properties for centuries; it is still widely used in France, Germany, and Switzerland as a sleep aid. About 50 tons of valerian are sold each year in France. [2]

CHEMISTRY: Three distinct classes of compounds have been associated with the sedative properties of valerian: 1) mono- and sesquiterpenes, 2) iridoid triesters (valepotriates), and 3) pyridine alkaloids. The composition of the volatile oil varies markedly between cultivars and species, as does the amount and relative proportion of valepotriates, making chemical standardization difficult but highly desirable.

The most important sesquiterpenes include valerenic acid and its congeners, although in the Japanese *V. officinalis* var. latifolia, kessyl alcohols and esters predominate. Valtrate, acevaltrate, and didrovaltrate are the most important iridoids; European valerian extracts were formerly standardized on these rather unstable compounds, which have a short shelf-life in the tincture. The alkaloid concentration in roots and rhizomes is low, usually less than 0.2%. The aqueous extract of valerian has been found to contain substantial quantities of GABA; however, it is doubtful whether GABA penetrates the blood-brain barrier with oral administration. [3]

Many analytical high performance liquid chromatographic (HPLC) methods have been developed for the sesquiterpenes and valepotriates. [4] The seasonal variation in valerenic acids and valepotriates has been studied. [5] Tissue culture of valerian species has focused on production of valepotriates. [6]

PHARMACOLOGY: While there is substantial debate over the constituents responsible for valerian's sedative activity, it is undeniable that valerian preparations have sedative effects. Human studies have documented valerian's effectiveness as a sleep aid.

Aqueous and hydroalcoholic extracts of valerian induced release of [3H]GABA from synaptosomal preparations, which was interpreted as an effect on the GABA transporter. The in vitro effect was correlated with the content of GABA itself in the extract. Thus GABA may be responsible for some of the peripheral effects of valerian, while glutamine, another free amino acid in the extract, can cross the blood-brain barrier and be metabolized to GABA in situ, thereby producing central sedation.[3]

An ethanol extract containing no valepotriates antagonized picrotoxin convulsions in mice but had no effect on metrazol- or harman-induced convulsions. The same extract prolonged barbiturate sleeping time, but did not affect spontaneous motility, pain perception, or body temperature. The effects were traced to valerenic acid. [7]

A commercial aqueous alkaline extract of valerian (*Valdispert*), standardized on valerenic acid given orally to mice, reduced spontaneous motility and increased barbiturate sleeping time, but had no effect on metrazol-induced convulsions. [8] Cerebral metabolism was examined in rats with PET scanning, and an effect consistent with a GABAergic mechanism was reported with the methylene chloride extract of valerian; however, valepotriates and valerenic acids were not responsible for the effect. The active compounds were not identified.[9]

Valerenic acid has been found to inhibit GABA transaminase, the principle enzyme that catabolizes GABA. GABA-T inhibition increases the inhibitory effect of GABA in the CNS, and can therefore contribute to valerian's sedative properties. [10] Valerenic acid given intraperitoneally had CNS depressant effects in mice, including potentiating barbiturate sleeping time and decreasing spontaneous motor activity and rotorod performance. [11,12] The valepotriates isovaltrate and valtrate, along with valerenone, were found to have antispasmodic effects in isolated guinea pig ileum, as well as other smooth muscle preparations. [13]

Clinical trials: There is abundant evidence that valerian is effective as a sleep aid and as a mild antianxiety agent, although the effect appears to be weaker in healthy subjects than in poor sleepers. An aqueous extract of the root (400 mg extract) improved sleep quality in a number of subjective parameters in 128 healthy volunteers using a crossover design.[2] Elderly patients with nervous disorders responded positively to a commercial valerian preparation in a placebo-controlled study, as measured by both subjective and objective parameters.[14] Sleep latency was decreased in a group of 8 poor sleepers given an aqueous extract of valerian in a double-blind, placebo-controlled study. [15] A sleep laboratory study found minor sedative effects in healthy volunteers. [16] An uncontrolled multicenter study of > 11,000 patients suffering from sleep-related disorders found subjective improvements in 94% of those treated. [17] Another multicenter trial of the same preparation in a younger study population found progressive symptomatic improvement over 10 days of treatment. [18] Valerian was found to increase slow-wave sleep in a pilot study of poor sleepers.[19] In contrast to previous studies that demonstrated a prompt decrease in symptoms, one study found that 2 to 4 weeks was required to see improvement in 121 patients with serious insomnia.[20] These studies have been reviewed.[21]

Combination studies: Valerian is often combined with other herbs such as hops, St. John's wort, or balm in commercial products. A number of these combinations have been evaluated in clinical studies. A combination of Hyperion and valerian was evaluated for antidepressant activity in a double-blind study of 93 patients treated for 6 weeks. All psychometric scales showed statistically significant improvement. [22] A second study of the same combination in the treatment of anxiety reached similar positive conclusions. [23] A combination of valerian and *Hibiscus syriacus* (rose of sharron) was active in 130 depressed patients over 6 weeks. [24] A valerian combination preparation containing valerenic acid sesquiterpenes, but not valepotriates, improved sleep quality in a small crossover study of poor sleepers. [25] Valerian and *Melissa officinalis* (balm) were effective in combination in a study (20 patients) of poor sleepers. [26] The same combination was found to be tolerated in healthy volunteers, and increased the quality of sleep. [27] A complex product made up of 6 herbs (*Crataegus*, *Ballota*, *Passiflora*, *Valeriana*, *Cola*, and *Paullinia*) was used to treat generalized anxiety (n = 91), producing progressive decreases in the Hamilton Anxiety Scale that were significantly greater than with placebo. [28]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Concern was raised over the discovery that valepotriates are mutagenic in the Ames assay; however, their poor bioavailability makes them a dubious source of toxicity for patients.[29] Mice have tolerated > 1 g/kg doses of valerian by oral and intraperitoneal routes, showing ataxia, muscle relaxation, and hypothermia.[30]

Clinical studies have generally found valerian to have fewer side effects than positive control drugs such as diazepam, producing little hangover effect when used as a sleep aid. An intentional overdose has been reported in which 20 times the recommended dose was ingested; the patient experienced mild symptoms that resolved within 24 hours.[31] A case of withdrawal after chronic use of valerian has been reported; however, the complex nature of the patient's medical history provides weak support for valerian's role.[32]

Valerian has been classified as GRAS (generally recognized as safe) in the US for food use; extracts and the root oil are used as flavorings in foods and beverages.

SUMMARY: Valerian root was approved by the German Commission E for restlessness and sleep disorders based on nervous conditions, and is official in the European Pharmacopoeia. A USP supplemental monograph on valerian was completed. ESCOP (F-4), BHP (vol.1) and WHO (vol.1) have also produced valerian monographs. While it appears to be safe and efficacious as a sleep aid, further research is required to elucidate the compounds responsible for its activity.

PATIENT INFORMATION — Valerian

Uses: Valerian has been used for the treatment of restlessness and sleep disorders. Valerian is classified as GRAS in the US for food use.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Studies have generally found valerian to have fewer side effects than other positive control drugs.

Dosing: Valerian root (fresh or dried) has been used at doses of 2 to 3 g given 1 to 3 times/day for nervousness or as an antispasmodic, and at bedtime for insomnia. Several types of extracts have been tested; an aqueous extract has shown activity in sleep studies at doses of 270 to 900 mg, while an ethanolic extract has been recommended at 600 mg for sleep. Combinations with extracts of hops (eg, *ReDormin*, *Ze 91019*) or with lemon balm (*EuVegal Forte*) are quite common as sleep aids and the valerian extract dose in combinations is 320 to 500 mg. Lipophilic extracts such as *Baldrian-Dispert*have fallen out of favor because of toxicity concerns and the failure to identify active principles in them. [2,15,16,17,25,27,33,34,35]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "V" MONOGRAPHS
    VALERIAN

VANILLA

DATE OF ISSUE: NOV 1994

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Vanilla planifolia* Andr. (synonymous with *V. fragrans* and *V. tahitensis*). Family: Orchidaceae

COMMON NAME(S): Vanilla, Bourbon vanilla, Mexican vanilla, Tahiti vanilla.

BOTANY: The vanilla plant is a perennial herbaceous vine that grows to heights of 25 m in the wild and can produce fruit for 30 to 40 years. [3] It is native to tropical America and grows abundantly in Mexico. It is now cultivated throughout the tropics, including Reunion (Bourbon); [3] Madagascar produces approximately 80% of the world's supply.[4] The fully-grown unripe fruit (called the bean or pod) is collected and subjected to a complicated and labor-intensive fermentation process; together with the drying stage, this curing process requires from 5 to 6 months to complete. [1] During this time, vanillin is produced by the enzymatic conversion of glucovanillin [3] within the bean and vanillin may accumulate as white crystal on the bean surface giving it a frosted appearance.

HISTORY: Vanilla has a long history of use as a food flavoring and fragrance. Westerners were likely introduced to vanilla by the Aztec emperor Montezuma II, who prepared a vanilla-flavored chocolate drink for Hernando Cortez in the early 1500s. [4] Although vanillin is often used in bulk food preparation, it cannot be readily substituted for the natural extract where the delicate fragrance of the pure extractive is desired. Traditional uses of vanilla have included its use as an aphrodisiac, carminative, antipyretic, and stimulant. It has been added to foods to reduce the amount of sugar needed for sweetening and has been said to curb the development of dental caries.[2]

CHEMISTRY: The quality of the vanilla bean is not dependent on the vanillin content even though vanillin is associated with the characteristic fragrance of the plant. Numerous other constituents characterize the flavor and quality of vanilla and its extracts. [1]

Vanilla extracts are prepared by percolating ground vanilla bean with an alcohol/water mixture. Vanilla has been reported to contain up to approximately 3% vanillin, the major flavoring component. However, more than 150 other minor components contribute to the full-bodied fragrance of natural vanilla. The vanillin content differs with the variety of the bean, with Bourbon beans containing generally higher amounts than Mexican and Tahiti beans. [1]

Because synthetically-produced vanillin can be obtained inexpensively, it is often used as a substitute or adulterant for natural vanilla extract. Extracts of Mexican origin have been adulterated with coumarin, presumably arising from the use of tonka beans. [3] These products do not meet FDA food safety standards. The FDA has prohibited use of coumarin in food since 1954, due to its potential hazards. Unfortunately, there is no simple method to distinguish if a vanilla extract is authentic, although more sophisticated chromatographic methods can assist in defining the quality of an extract. [3] Only about 6% of the market for vanilla flavoring is held by pure vanilla extract.[4] Vanilla extract produced by biotechnological methods of plant culturing have yielded good grades of natural vanilla. [4]

PHARMACOLOGY: The anti-caries effects of vanilla have not been well documented but are believed to be related to the catechin content of the plant. [2]

Meals flavored with vanilla have been shown in controlled studies to provide a greater degree of satiety relative to nutritionally-identical unflavored meals. [6]

TOXICOLOGY: Although allergenic properties have been associated with vanilla, they do not appear to be related to the vanillin component of the plant. [1] Rather, the dermatitis may be caused by the calcium oxalate crystal in the plant.[2] Workers preparing vanilla have reported headache, dermatitis, and insomnia, which together have been characterized as a syndrome known as "vanillism."[2]

In a recent survey of ingredients of prescription and OTC health care products, vanilla was the second most common flavoring, superseded only by cherry, suggesting that persons with a known hypersensitivity to vanilla extract should be vigilant to the wide-spread use of this flavoring in pharmaceuticals. [5]

SUMMARY: Vanilla and its extract are widely used as food and perfume components. The fragrance of vanilla is the result of the combined characteristics of more than 150 volatile components, although vanillin accounts for the majority of the flavor.

PATIENT INFORMATION— Vanilla

Uses: Vanilla has been used widely as a food, flavoring, and in perfume components.

Side Effects: Some allergenic properties have been associated with vanilla.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "V" MONOGRAPHS
    VANILLA

VERATRUM

DATE OF ISSUE: JAN 1999

REPLACES MONOGRAPH DATED: FEB 1987*

* Replaces the White Hellebore Monograph.

SCIENTIFIC NAME(S): *Veratrum* species Family: Liliaceae

BOTANY: Included among its approximately 30 species are the following:

Scientific Name	Common Names	Distribution
V. album L.	White hellebore, langwort	Europe and Northern Asia
V. viride A.	Green hellebore, false hellebore, itchweed, Indian poke	Eastern US and Canada
V. californicum Dur	California false hellebore, Western hellebore	Western US
V. nigrum L.	Black false hellebore	Central Europe
V. fimbriatum	Fringed false hellebore	North America
V. frigidum[1,2]		Mexico

Veratrum album or white hellebore (WH) is a perennial that has a wide distribution throughout Europe, northern Asia, and North America. It grows to 5 feet and is characterized by a hairy stem. Its large, oval, yellow-green leaves alternate around the stem and have a slightly hairy undersurface. The lower leaves can reach a foot in length. Its greenish flowers bloom in June and July. The rhizome has an acrid taste and onion-like odor. The fruit is a capsule. [3]

Veratrum viride or green hellebore (GH) can grow to 8 feet in height and is found in damp areas such as marshes and swamps. It has oval to linear leaves, with green flowers on short stalks. Its habitat is northern North America, west of the Rockies. [4] The dried rhizome is the part of the plant used. [5] The plant's flowers are greenish yellow in color. [2]

WH resembles GH in structure and appearance (ie, similar leaves), [2] although its external color is much lighter. [5] The rhizomes of the 2 species are histologically, chemically, and toxicologically similar. WH may be more poisonous and contain more alkaloids than GH. [2]

HISTORY: *Veratrum* comes from the Latin *vere* meaning "truly," and *ater* meaning "black." In 1900, both species (*V. album* and *V. viride*) were recognized.[2]

The use of *V. album* centers around its toxic potential. It had been used as a poison during Roman times and an extract of the plant was used as an arrow tip poison. Small doses had been used to treat symptoms of cholera, often with less than desirable effects. White hellebore had been used in place of *Colchicum* for the treatment of gout, to aid in the treatment of hypertension, and externally to treat herpetic lesions, but its use has always been limited by its toxicity.

Green hellebore derives its name from the Latin viride meaning "green." This species was used by certain Indian tribes to treat congestion and arthritic pain. European settlers used the plant as a delousing agent. Like WH, GH is also highly toxic and rarely used in herbal medicines today except homeopathy in some cases.[4]

CHEMISTRY: Important alkaloids of both species in general include esters of highly hydroxylated parent alkanolamine bases, mainly cervine, germine, and protoverine. Other alkanolamines include jervine, rubijervine, pseudojervine, and isorubijervine. Alkaloids present in both species include veratrobasine and geralbine.[2] Veratrum alkaloids (cyclopamine, cycloposine, jervine, and veratramine) have been evaluated by carbon-13 and proton nuclear magnetic resonance spectra analyses.[6] Analysis of jervine from Veratrum species has also been performed using densitometry, thin layer, and liquid chromatography methods. [7] In addition, alkaloids from 17 species of veratrum have been identified and reviewed. [8,9]

White hellebore has been found to contain 2 related alkaloids, protoveratrine A and B. The rhizome contains about 1.5% total alkaloids, which also include germerine, jervine, pseudojervine, and veratrosine.[10] Minor and other alkaloids have been described. [11,12] Non-alkaloidal compounds have also been isolated from WH "above ground" parts and include cinnamic, isoferulic, caffeic, chlorogenic, fumaric, and succinic acids, and tectochrysin. [13] Organic acids veratric and vanillic are also present.[14] Other reports concerning WH-specific chemistry include: Phenolic compounds from aerial plant parts, [15] isolation of flavonoids chrysoeriol and apigenin, [16] determination of beta-adrenoceptor agonist, "o-acetyljervine," [17] and identification of glycoside veratramarine. [18]

Three alkaloid groups are present in:

1.) Esters of steroidal bases (alkamines) with organic acids, including cevadine, germidine, germitrine, neogermitrine, neoprotoveratrine, protoveratrine, and veratridine;

2.) The glucosides of the alkamines pseudojervine and veratrosine;

3.) The alkamines themselves including germine, jervine, rabijervine, and veratramine. [5,19] Alkaloid mixtures alkavervir and cryptenamine are also specifically mentioned as being constituents in WH. [20]

Other *Veratrum* species chemistry is available, including vertaline B structure from *V. taliense*,[21] steroidal alkaloid isolation from *V. californicum*,[22] isolation of alkaloids verazine and angeloylzygadenine from *V. maacki*,[23] and isolation of a new indole alkaloid echinuline from *V. nigrum*.[24]

PHARMACOLOGY: The white and green varieties of veratrum have been used for their antihypertensive properties. [5,25,26,27] When administered intravenously, protoveratrine A and B cause a rapid reduction in blood pressure. Protoveratrine A is more active orally than B. Extracts of this plant have sometimes been combined with rauwolfia alkaloids in the treatment of hypertension.[28] Some alkaloids of *Veratrum* species exhibit a cardiotonic, digitalis-like effect. [9] Other sources report the ester alkaloids to reduce systolic and diastolic pressure, slow the heart rate, and stimulate peripheral blood flow. [2,19] (Large doses of plant extracts may cause respiratory depression.) Neurophysiological studies show certain alkaloids of GH work on the pacemaker area of the heart, and are of possible use in management of tachycardia or fibrillations. [2] In another report, protoveratrines caused prompt improvement of cardiac and respiratory functions in rats suffering from severe hypotension and respiratory depression, warranting further experimentation in the area of such crisis management as massive blood loss, etc. The mechanism could be attributable to an increase in total peripheral resistance and cardiac output. [29] However, the use of veratrum derivatives in the 1950s for hypertension therapy diminished with the discovery of more effective agents in the 1960s. [30]

Other actions of veratrum include stimulation of cardiac receptors, inhibiting ADH secretion in dogs, [31] and possible serotonin-agonist actions of constituent veratramine.[32]

Certain veratrum alkaloids exhibit in vitro cytotoxic effects on leukemia cells. [33] A later report discusses the demonstration of hemolytic and cytotoxic effects of the alkaloids.[34]

At least 1 report is available discussing a synthetic veratrum derivative and how it may be of use in myasthenia gravis treatment. [35]

Veratrum species have also been used as insecticides.[5,19] One report on *V. album* discusses its insecticidal activity against *Drosophila*, *Tribolium*, and *Aedes* species.[36]

Other uses for veratrum include treatments for cancers, respiratory problems, convulsions, mania, neuralgia, headaches, analgesia, inflammations, fluid retention, vomiting, toothache, amenorrhea, hiccoughs, measles, and sunstroke.[19]

Other *Veratrum* species literature is available concerning antiplatelet principles of *V. formosanum*,[37] absorption studies of *V. nigrum*,[38] and hemodynamic effects of *V. nigrum*.[39]

TOXICOLOGY: All *Veratrum* species are irritating;[19] however, *V. album*-specific poisonings have been the most often observed. For example, 7 cases have been reported to the Austrian Poison Information Center from 1977 to 1981. [40] Usual symptoms include hypotension, bradycardia, and gastrointestinal distress. [19,20,41] One source suggests ingestion of the alkaloids causes a burning sensation in the upper abdominal area followed by salivation, vomiting, and gastric erosion. Symptoms have been described as "having a heart attack." However, symptoms often disappear within 24 hours. [42]

Stereochemical configuration of veratrum alkaloids offer reason for the plant's teratogenicity. [43] Parasympathetic stimulation and increase in the permeability of sodium channels also contribute to its toxic mechanisms.[3]

Inhalation of the powdered rhizome induces a runny nose and violent sneezing. [44] Seven cases of intoxications have been reported from *V. album* alkaloids present in sneezing powder.[45] The fatal human dose of powdered rhizome is 1 to 2 g.[18]

Five cases of *V. album* poisoning have been reported, all having occurred shortly after ingestion of what was believed to be gentian wine (homemade; *V. album* was mistaken for *Gentiana lutea* when harvested because of similarities in appearance and habitat). Clinical effects included nausea, vomiting, abdominal pain, hypotension, and bradycardia. Therapy with atropine led to recovery within a few hours. [46] Another case of "mistaken identity" of *V. album* with *G. lutea* describes similar gastrointestinal and cardiac symptoms.[47]

Two additional *V. album* poisonings have occurred within 30 minutes of ingestion. Symptoms included vomiting, decrease in blood pressure, and bradycardia. Both cases had favorable outcomes.[48]

Six cases of *V. viride* poisonings have been reported, the symptoms being similar to those of *V. album* toxicity.[49]

Congenital tracheal stenosis occurred in 7 of 9 lambs born to 6 ewes who ingested the related species *V. californicum*. All 7 died from asphyxia within 5 minutes after birth.[50] Poisoning by this species is a veterinary problem in the US.

SUMMARY: Veratrum includes many species, most notably *V. album* and *V. viride*, which are similar. Their chemistry includes numerous alkaloids, some of which are toxic. Both species have been used for their antihypertensive properties. Different constituents may cause bradycardia, respiratory depression, or stimulation of peripheral blood flow. Other actions of veratrum include use as an insecticide and as a cytotoxic agent. *V. album* is considered toxic, with many reports of hypotension, bradycardia, and gastrointestinal distress. The toxicity of veratrum is so high that its use is not recommended.

PATIENT INFORMATION — Veratrum

Uses: Veratrum has been used to treat high blood pressure.

Side Effects: Veratrum is irritating and ingestion can result in a burning sensation in the upper abdominal area followed by salivation, vomiting, gastric erosion, hypotension, and bradycardia. There have been several poisonings reported in humans with the different species, but all had favorable outcomes.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "V" MONOGRAPHS
    VERATRUM

VERVAIN

DATE OF ISSUE: AUG 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Verbena officinalis* (L.) Wettst. Family: Verbenaceae

COMMON NAME(S): Vervain, verbena, yerba de Santa Ana, enchanter's plant, herb of the cross, Juno's tears, pigeon's grass, pigeonweed, herb of grace

BOTANY: Vervain is a slender perennial plant with small, pale lilac flowers borne on leafless spikes. It is indigenous to the Mediterranean but has been widely cultivated throughout eastern Europe and in China. The related American species *V. hastata* L. is known as blue vervain, simpler's joy, or wild hyssop. A different species in the same family, *Lippia citriodora* (Lam.) Kunth., known as lemon verbena, is used to produce the essential oil of verbena, or vervaine.

HISTORY: The name "verbenae" was originally used in Roman times to describe all plants used on altars for their aromatic qualities. The above-ground parts have been used medicinally for many conditions, including stimulation of lactation and treatment of dysmenorrhea, jaundice, gout, kidney stones, and headache. Vervain is also an astringent, a bitter digestive tonic, and a diuretic. [1]

CHEMISTRY: The most characteristic chemical constituents of vervain are the iridoid glycosides verbenalin [2] and hastatoside.[3] Also prominent is the caffeic acid glycoside verbascoside, which is found in a number of other medicinal plants. [4] Flavonoids such as luteolin 7-diglucuronide also have been found in vervain. [5] Ursolic acid and several related triterpenes have been isolated as well. [6]

The biosynthesis of the iridoid glycosides has been studied in detail. [7] Several methods have been published for the analysis of vervain constituents. High pressure liquid chromatography (HPLC) with post-column derivatization was used to quantify iridoids, flavonoids, and phenolics. [8] An HPLC separation with diode array detection was used to assay the same compounds in another study.[9] Micellar electrokinetic capillary chromatography (MEKC) with mass spectrometry was used to achieve a separation and characterization of several iridoids, including verbenalin. [10]

PHARMACOLOGY: Vervain extracts were found to lack pharmacologic activity in thyroid hormone models. [11,12] Modest inhibition of progesterone and estrogen receptor binding activity by a vervain extract was detected; however, no effects in more complex cellular models were reported. [13] Anti-inflammatory activity of a vervain extract and several fractions in a carrageenan paw edema model was reported; however, the specific triterpenes, iridoids, and phenolics isolated were not bioassayed to identify which of them were active.[14] Other reports have shown that verbenalin was active in blocking both 12- *O*-tetradecanoylphorbol acetate-induced mouse ear edema and carrageenan-induced paw edema.[15]

Verbascoside has been isolated from a wide variety of plants and has been studied in many pharmacologic and biochemical models. It has been reported to inhibit protein kinase C by competing at the ATP binding site. [16] The differentiation of a human adenocarcinoma cell line was found to be induced by verbascoside, reducing the malignant phenotype.[17] The same group found that verbascoside affected telomerase activity and telomere length, and induced apoptosis in a gastric cancer cell line.[18] A further study by this group found that verbascoside counteracted muscle fatigue in an isolated tissue preparation. [19] In the isolated rat heart, verbascoside was found to increase heart rate, force, and coronary perfusion, with a marked increase in cyclic AMP levels. [20] A later publication found a significant increase in prostacyclin levels, which may be responsible for the observed effects. [21] Antioxidant effects of verbascoside also have been demonstrated in several models, including radical scavenging [22] and pulse radiolysis methods.[23] Vervain essential oil also was active in an antioxidant screen, although the oil would not be expected to contain verbascoside.[24] Modest antiviral activity against vesicular stomatitis virus (but not herpes simplex) at a high dose of verbascoside was observed. [25] Antibiotic activity caused by an effect on protein synthesis and leucine incorporation also was found with verbascoside. [26]

Vervain flavonoids have been infrequently studied; however, a flavonoid fraction of vervain was shown to inhibit growth of several bacterial species at relatively high concentrations.[27]

There are no clinical trials of vervain or its components reported in the literature.

TOXICOLOGY: No toxicology studies have been reported on vervain.

SUMMARY: Vervain has been used for many indications; however, there are no reports documenting clinical efficacy or toxicity.

Vervain is monographed in the *Chinese Pharmacopeia* and the *British Herbal Pharmacopeia*, Vol. 2. It was listed as unapproved in the *Complete German Commission E Monographs* because of the absence of proof of efficacy.

PATIENT INFORMATION — Vervain

Uses: Vervain has been used for many conditions including stimulation of lactation and treatment of dysmenorrhea, jaundice, gout, kidney stones, and headache; however, there are no clinical trials of vervain or its components reported in the literature. Vervain is an astringent, a bitter digestive tonic, and a diuretic.

Side Effects: None known.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "V" MONOGRAPHS
    VERVAIN

VITAMIN E

DATE OF ISSUE: JUN 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Alpha-tocopherol*

COMMON NAME(S): Vitamin E

HISTORY: Vitamin E was first discovered in 1922, when it was found that reproductive abnormalities in rats reared on a basic diet were cured by a substance isolated from vegetable oils. A pure fraction was chemically identified in 1938 and named tocopherol after the Greek words tokos, which means childbirth, and phero, which means to bring forth.[1]

CHEMISTRY: Vitamin E is a generic term for a group of tocol and tocotrienol derivatives. It is a fat-soluble vitamin that exists in a variety of forms in many foods (eg, spinach, nuts, sunflower seeds, olives, asparagus, vegetable oils, mangoes, wheat germ, whole-wheat breads). Its most common form in a Western diet is a-tocopherol.[2] The most important chemical characteristic is its antioxidant property.

Vitamin E is fairly stable to heat and acids and unstable to alkalis, ultraviolet light, and oxygen. It is destroyed when in contact with rancid fats, lead, and iron. Esters of tocopherol such as tocopherol acetate, the most naturally occurring form, are more stable. [1]

One IU of vitamin E activity is equivalent to 1 mg of tocopheryl acetate.

PHARMACOLOGY: Vitamin E has been extensively studied over a number of decades. A role for its use in atherosclerosis, coronary artery disease, cancer, diabetes, and rheumatoid arthritis as well as a number of neurologic diseases has been reported. Positive outcomes have been suggested for prevention of stretch marks in pregnancy,[3] nitrate tolerance in patients with coronary heart disease, [4] and pre-eclampsia in women at increased risk of the disease.[5] Vitamin E also may be effective in the treatment of chronic hepatitis B, [6] delaying the onset of Parkinson's disease, [7] enhancing T-cell function, [8] and improving immune responses.[9]

Atherosclerosis: Over the past 2 decades, considerable evidence has been gathered in support of the hypothesis that free-radical-mediated oxidative processes and specific products arising from this play a key role in atherogenesis. Low-density lipoproteins (LDLs) undergo multiple changes upon oxidation that are thought to be pro-atherogenic.[10] Laboratory evidence is available illustrating that vitamin E is carried within LDL particles and prevents LDL oxidation. [10]

A double-blind study has proposed that doses of vitamin E as low as 500 mg daily can prevent LDL oxidation. This preventative effect has been measured ex vivo [11] and observed in studies in postmenopausal women.[12]

Coronary artery disease: Epidemiological studies report strong inverse associations between intake of antioxidant vitamins and coronary artery disease. However, this is probably overly simplistic as the results from these studies may reflect the overall behavioral attitudes of the people regularly taking high doses of antioxidants over many years.[13] A number of large studies have investigated these proposed effects of vitamin E and have provided conflicting results.

The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) prevention trial examined the use of vitamin E (300 mg daily) in MI survivors. This multicenter open-label trial was performed over a period of 3.5 years and included 11,324 patients. Vitamin E did not affect long-term complications post-MI (eg, death, nonfatal MI, nonfatal stroke) to any clinically important extent. However, subsequent results of a secondary analysis suggested that there was a possible benefit of vitamin E with regard to cardiovascular deaths. A relative risk reduction of 23% (95% CI 3% to 39%) was demonstrated. [13]

The HOPE (Heart Outcomes Prevention Evaluation) study investigated vitamin E (400 mg daily) in patients with a high risk for cardiovascular events. This randomized, placebo-controlled, double-blind trial was performed over a period of 4.5 years and included 9541 patients. HOPE demonstrated that vitamin E has no effect on cardiovascular outcomes.[14] SECURE (Study to Evaluate Carotid Ultrasound Changes in patients treated with Ramipril and vitamin E), a substudy of the HOPE trial, showed that vitamin E had a neutral effect on atherosclerosis progression. [15] Another trial of 4495 patients also showed lack of effect. [16]

Another randomized, double-blind, placebo-controlled study illustrated that the frequency of coronary events in 1862 men who had a previous MI was not affected by 50 mg of vitamin E per day.[17] The same investigators also found no effect on the recurrence and progression of angina. [18] This is in contrast to a previous case-control study (much smaller number of patients enrolled) demonstrating that some populations with a high incidence of coronary artery disease may benefit. This case study also suggested that plasma concentrations of vitamins C and E and carotene were significantly inversely related to the risk of angina. [19]

The SPACE (Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease) study investigated cardiovascular mortality in hemodialysis patients with pre-existing cardiovascular disease. The trial was randomized, double-blind, and placebo-controlled (n = 196). Patients receiving 800 mg of vitamin E per day had a reduction in the incidence of total MI. It was proposed that antioxidant therapy would be expected to have greater effects in patients with the most oxidative stress, ie, high-risk populations such as hemodialysis patients. [20]

In CHAOS (Cambridge Heart Antioxidant Study), 2002 patients were randomized in a double-blind manner to receive vitamin E (800 mg daily) or placebo. A reduction in the risk of nonfatal MI was observed but there was no benefit in terms of cardiovascular death or total mortality. [21]

To summarize, these studies emphasize that, to date, neither the dose of vitamin E that is most effective and safe nor the minimum duration of treatment are known. In view of these findings, the American Heart Association considers the most prudent and scientifically supportable recommendation for the general population is to consume a balanced diet with emphasis on antioxidant-rich fruits and vegetables and whole grains. This advice considers the role of the total diet in influencing disease risk.[10]

Cancer: Vitamin E acts as an antioxidant, protecting polyunsaturated fats and other lipids and lipid-soluble substances from oxidation. Dietary intake of antioxidants, particularly vitamins C, E, and ß-carotene, has been associated with a diminished risk of various malignancies. It has been suggested that the primary mechanism of chemoprevention by antioxidants is through the reduction of DNA-damaging free radicals. [22]

Trials in colorectal cancer patients have provided disparate results. Two small studies showed no positive effect of vitamin E. The first enrolled 12 patients with incurable colorectal cancer. They were treated conventionally with 5-fluorouracil (5-FU) and leucovorin. Vitamin E 3200 IU daily for 14 days was added. The authors concluded that their study appeared to be too small to determine efficacy. [22] In the second study, 77 patients with resected colorectal cancer, Dukes stage B-C, were randomized to receive daily 30,000 IU of vitamin A, 1 g of vitamin C, 70 mg of vitamin E, and 2 g of calcium or placebo for 6 months. The trial did not show any effect on cell kinetics of colon epithelium. [23] The Alpha Tocopherol, Beta Carotene cancer prevention (ATBC) study investigators published their results of the effects of vitamin E and ß-carotene on colorectal cancer. This large study of 29,133 male smokers, randomly allocated to receive vitamin E, ß-carotene, both, or placebo suggests that vitamin E supplementation may have a modest preventative effect. However, the 22% reduction in incidence was not significant. Additionally, vitamin E did not affect colorectal cancer survival time. [24]

The ATBC study investigators also showed that supplementation with vitamin E and ß-carotene does not have a statistically significant effect on the rate of incidence of pancreatic carcinoma or the rate of mortality caused by this disease. [25] The SELECT (Selenium and vitamin E Cancer prevention Trial) study investigating this patient population is currently underway with results anticipated in 2013. [26]

Other cancers studied in the literature are those of the urinary tract and lung. [27,28] The incidence is not influenced by vitamin E supplementation.

Mucositis: Mucositis is a common complication of chemotherapy, usually presenting as erythematous areas that undergo desquamation, leaving ulcers behind that are covered by exudate. The pain of mucositis may be sufficient to interfere with normal dietary intake. Vitamin E prevents the peroxidation of membrane polyunsaturated fatty acids and has a stabilizing function on many membranes. The Cochrane Collaboration identified 15 trials involving 876 patients that investigated agents with the ability to improve or eradicate mucositis. They located 1 trial that demonstrated that vitamin E was an effective eradication agent. [29,30] However, they do emphasize that their conclusions are based on weak and unreliable evidence as the study only evaluated 24 patients.

Age-related macular degeneration and visual loss: Age-related macular degeneration is a disease affecting the central area of the retina. Lipid material accumulates in deposits underneath the retinal pigment epithelium. These deposits, known as drusen, can be seen as pale yellow spots on the retina. It is the most common cause of blindness and visual impairment in industrialized countries.

Photoreceptors in the retina are subject to oxidative stress caused by exposure to light and oxygen. It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption.

A systematic review reports the effects of vitamin E in the primary prevention and progression of age-related macular degeneration. To assess prevention, 3 large, high-quality trials that randomized a total of 4879 participants were identified. There was no evidence that people without age-related macular degeneration should take antioxidant vitamin and mineral supplements to prevent or delay the onset of the disease. [31] It should be noted that because there were only a very few cases of late-stage, age-related macular degeneration, these studies may have limited power to detect efficacy.

To assess progression of age-related macular degeneration, 7 trials were located. In total, these trials randomized 4119 people with signs of disease. Most of the patients were from trials conducted by the Age-Related Eye Disease Study Research Group. [32,33] Antioxidant vitamin (including vitamin E) and mineral supplementation was addressed. The authors concluded that people with moderate to severe age-related macular degeneration may experience a modest delay in progression of their disease with antioxidant supplementation. Given that there are few other interventions that offer much in the way of disease prevention or cure, this is an important consideration. There is no evidence that people with early signs of the disease would benefit. [34]

Diabetes mellitus: Elevated levels of urinary albumin predict high risk for progression to end-stage renal disease in type 2 diabetes mellitus. Several studies support the concept that reduction in albumin excretion rate is a valid renoprotective treatment goal. [35] Short-term treatment with vitamin C and E in pharmacological doses was shown to lower urinary albumin excretion rate in type 2 diabetic patients with micro/macroalbuminuria. The study was small (n = 29), but a statistically significant reduction of 19% was noted.[35] Additionally, chronic vitamin E administration has been proposed to improve the ratio of cardiac sympathetic-to-parasympathetic tone in patients with type 2 diabetes, possibly by a decline in oxidative stress. [36]

Rheumatoid arthritis: Studies suggest that vitamin E could have a positive effect on autoimmune disease by decreasing pro-inflammatory cytokines and lipid mediators. Additionally, it appears that vitamin E might have clinical benefits and has been shown to significantly reduce pain. A trend toward a reduction in the duration of morning stiffness also has been noted. However, this latter effect is controversial. [37]

Alzheimer's disease: Free radical damage may be one of the mechanisms causing neuronal degeneration in Alzheimer's disease. Many studies have found evidence of increased level of oxidative damage to neurons in Alzheimer's disease. There have been reports of an association between low blood levels of vitamin E and impaired cognitive function. Average levels of vitamin E in the blood and cerebrospinal fluid of patients with Alzheimer's disease have been found to be lower than normal in several reports, although not in all. For their systematic review, the Cochrane Collaboration searched for all double-blind, randomized trials that examined the effects of vitamin E treatment versus placebo in patients with Alzheimer's disease. The 1 study of acceptable methodology was restricted to patients with moderate disease and the results are difficult to interpret. There was an excess of falls in the vitamin E group compared with placebo, which required further evaluation. It was concluded that there was insufficient evidence of possible benefit to justify other studies. [38]

Neuroleptic-induced tardive dyskinesia: There are numerous reports on the positive effects of vitamin E on tardive dyskinesia. A review of 10 controlled trials assessed the clinical effects of vitamin E in people with schizophrenia or other mental illnesses who developed neuroleptic-induced tardive dyskinesia. The reviewers concluded that small trials with uncertain quality of randomization indicate that vitamin E protects against deterioration of tardive dyskinesia but there is no evidence that vitamin E improves symptoms.[39]

TOXICOLOGY: The toxicity of vitamin E in adults appears to be low. Clinical trials have shown that large doses (200 to 800 mg daily) do not result in serious side effects, with the possible exception of individuals taking oral anticoagulant therapy and those with vitamin K-related clotting disorders. High levels of vitamin E can adversely affect the absorption of vitamins A and K, and long-term use of high doses may cause nausea, diarrhea, and blurred vision. High-dose therapy in infants may be associated with more serious side effects.[2]

SUMMARY: There are copious studies in the literature on the proposed effects of vitamin E. The strongest evidence exists for use in neuroleptic-induced tardive dyskinesia, rheumatoid arthritis, type 2 diabetes mellitus, treatment of age-related macular degeneration, and mucositis. A number of large randomized studies have investigated the role of vitamin E in the treatment of coronary artery disease. The American Heart Association recommends a diet rich in antioxidants.

PATIENT INFORMATION — Vitamin E

Uses: Vitamin E is used as part of a diet rich in antioxidants to reduce the risk of coronary artery disease. Under medical supervision, it is used for the treatment of neuroleptic-induced tardive dyskinesia, rheumatoid arthritis, type 2 diabetes mellitus, treatment of age-related macular degeneration, and mucositis. The role of vitamin E in many other conditions also has been reported in the literature.

Side Effects: Vitamin E (200 to 800 mg daily) does not have any serious side effects in most adults with the possible exception of individuals taking oral anticoagulant therapy and those with vitamin K-related clotting disorders.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "V" MONOGRAPHS
    VITAMIN E

"W" MONOGRAPHS

WALNUT

DATE OF ISSUE: MAR 2001

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Juglans regia* L. Family: Juglandaceae

COMMON NAME(S): English walnut, Persian walnut, Caucasian walnut, Circassian walnut, European walnut

BOTANY: There are about 15 species of *Juglans*(walnut genus) commercially; *J. regia* is the most important. This deciduous tree can grow to 45 m in height. The trunk is straight and clear, with silvery-gray bark. The crown of the tree is open and round-topped. Walnut tree leaves are feather-like and are between 15. and 30 cm long. The male flowers are long, drooping catkins, while the female flowers are in short spikes. Walnut trees self-pollinate and cross-pollinate. *J. regia* is originally from the Near East but is cultivated in France and other parts of Europe, North Africa, North America, and East Asia. [1,2,3,4,5]

HISTORY: Walnuts have been found in prehistoric deposits dating from the Iron Age in Europe, and they are mentioned in the Bible. King Solomon's nut garden dates back to 940 BC. The genus name *Juglans*comes from the Latin *Jovis glans*, meaning "nut of Jupiter" or "nut of the Gods." Many legends have been associated with the walnut. Greeks and Romans regarded them as symbols of fertility. In the Middle Ages, walnuts were thought to ward off witchcraft, the evil eye, and epileptic fits because of the belief that evil spirits lurked in the walnut branches. Medicinal uses of walnut branches included treatments for swollen glands, shingles, and sores. The oil was used for intestinal discomfort. [4]

Walnuts are a common food source and are used in cooking and baking. [2,4] Walnut extract is an old-fashioned hair dye and also has been used to darken (stain) the skin.[3,4] Walnut shell flour has been used as a carrier for insecticides, filler for building materials, and stuffing in toys. [4]

CHEMISTRY: Walnuts contain 3% to 4% water and 60% oil. Two essential fatty acids present include alpha linoleic acid (3.2 g/100 g) and linoleic acid (32 g/100 g).[2,6] Fatty acid content in New Zealand walnuts has been reported. [7] In another report, 45 volatile compounds were isolated from whole green walnuts. [8] Walnuts contain close to 700 calories/100 g. [2]

The chief known constituent in walnut is juglone (5-hydroxy-1,4-naphthagulone). Also present are alphahydrojuglone (1,4,5-trihydroxynaphthalene) and its glycoside beta-hydrojuglone, along with caffeic acid, ellagic acid, hyperin, and kaempferol. [3] Gamma lactones in walnut oils also have been determined. [9] Walnuts contain 15 to 20 g protein/100 g, as well as tannins galloylglucose and ellagitannins. [2] Minerals in walnut include iron and zinc (˜ 3 mg/100 g each), sodium (2 mg/100 g), selenium (19 mcg/100 g), calcium, magnesium, potassium, copper, and phosphorus.[2,6,10] Vitamins E and C also are found in walnut. [5,7]

PHARMACOLOGY: Some folk uses of walnut, which still may be employed today, include treating rickets, frostbite, and glandular disturbances, and as an astringent, tonic restorative, and disinfectant. [3,12] Constituent juglone is known to have a broad spectrum of antimicrobial effects, including antifungal. Some cultures use the bark as a toothbrush, which may improve oral hygiene as it is known to increase the pH of saliva. [13] Walnut's anthelmintic effects include its use for ringworm and tapeworm.[12] It is also helpful in inflammatory conditions, including rheumatoid arthritis, and certain skin disorders. Blisters, ulcers, scalp itching and dandruff, sunburn, and perspiration are some of the related conditions treated with various walnut preparations. [3,5,6]

A study from China found borneol-walnut oil to be superior to neomycin in treating otitis media without any toxic effects. [13] Historically, walnut oil was prescribed for colic and to soothe intestines, [4] and has been employed to relieve diarrhea and hemorrhoids.[1,5]

Nutrition: The walnut is a good source of nutrition, as it contains concentrated amounts of certain nutrients (see Chemistry), calories, and fiber. [2,6] It also is high in 2 essential fatty acids, alpha linoleic and linoleic, that are known to decrease blood cholesterol levels, discourage blood clots, and be beneficial against heart disease. [6] A 12% reduction in blood cholesterol was shown when walnuts replaced certain foods in the diets of healthy male subjects. [14] Similarly, LDL cholesterol in hypercholesterolemic male and female subjects was reduced by substituting walnuts for monounsaturated fats in their diets. [15] A cross-sectional French survey of 793 patients 18 to 65 years of age found walnut consumption beneficial for blood HDL cholesterol. [16] In another report, 78 g/day of walnuts favorably influenced the fatty acid profile in 21 hyperlipidemic men. [17]

TOXICOLOGY: Juglone, the naphthaquinone present in all of the family Juglandaceae, is a known toxin in horses and is claimed to be an allergic threat in certain humans as well.[18,19] Walnut has provoked idiopathic anaphylaxis from skin testing. [20] Oral allergy syndrome has been caused by walnuts in sensitive individuals. [21]

Juglone toxicity in moth larvae has been studied. [22] Aflatoxin was detected in 75% of certain walnut seed samples. [23]

SUMMARY: Walnuts have a long history as a food source. Other uses include its oil for paint and its powdered shells as a carrier for insecticides and as a general filler. Walnut possesses antimicrobial effects, making it useful as an anthelmintic, for skin conditions, and for GI problems. Its high concentration of essential fatty acids make the walnut beneficial in preventing heart disease. Constituent juglone is toxic in animals. Individuals sensitive to walnut may experience certain allergies.

PATIENT INFORMATION— Walnut

Uses: Walnut is used as a food source and in dyes, as a carrier for insecticides, and as building material fillers. Walnut may be beneficial in preventing heart disease.

Side Effects: Juglone, a constituent of walnut, is toxic in animals. Contact sensitivity and dermatitis and oral allergy to walnut have been reported in humans.

Dosing: Walnut leaves have been approved by the *German Commission E* for external application for excessive perspiration and skin inflammation. Daily dosage is 2 to 6 g.[24]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WALNUT

WHITE COHOSH

DATE OF ISSUE: OCT 1997

REPLACES MONOGRAPH DATED: FEB 1986

SCIENTIFIC NAME(S): *Actaea alba* (L.) Mill. (also known as *A. pachypoda* Ell.) and *A. rubra* (Ait.) Willd. Family: Ranunculaceae

COMMON NAME(S): White Cohosh, baneberry, snakeberry, coralberry, doll's eye

BOTANY: White cohosh is a bushy, herbaceous perennial, that can grow to 3 feet tall. Its wide leaves have 6 or more sharp leaflets. The small flowers are white and grow in clusters. The berries of the plant can be red or white. [1] The plant is found from Alaska to California and east to the mid-United States. [1] Anatomical structure has been investigated.[2]

HISTORY: The plant has been used in a manner similar to that of black and blue cohosh to stimulate menstruation and to treat other "female disorders." Certain tribes, such as Cherokee and Cheyenne, used the root to cure itching, colds and cough, urogenital disorders, stomach disorders and to revive those near death. It has also been used as a purgative and in childbirth. [3]

CHEMISTRY: The chemistry of the plant is poorly defined. A compound called protoanemonin is believed to be responsible for the irritant effect. In addition, the plant contains an essential oil. Fruits and seeds contain trans-aconitic acid. [3]

PHARMACOLOGY: Little is known about its pharmacologic effects. There are no studies confirming its effects in the treatment of women's disorders. Homeopaths have used the roots for arthritis and rheumatism.[3]

TOXICOLOGY: All parts of the plant are toxic, especially the roots and berries, which contain the toxic glycosides and an essential oil. Ingestion of these parts results in acute stomach cramping, headache, increased pulse rate, vomiting, delirium, and circulatory failure. As few as 6 berries can cause severe symptoms, persisting for hours.[4] The protoanemonin-like compound can inflame and blister the skin. [3] Gastric lavage, emesis, and supportive treatment are recommended if ingested.[1,3]

SUMMARY: There is no evidence that white cohosh is of any therapeutic value. Its ingestion can lead to toxicity. Its use should be discouraged. Few reports are available on this topic.

PATIENT INFORMATION — White Cohosh

Uses: White cohosh has been used historically to treat women's disorders. Homeopaths have used white cohosh to treat arthritis and rheumatism.

Side Effects: Ingestion of white cohosh results in stomach cramping, headache, increased pulse rate, vomiting, delirium, and circulatory failure.

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Document Bibliographic Information:

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  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WHITE COHOSH

WILD YAM

DATE OF ISSUE: MAY 1999

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Dioscorea villosa* L. Dioscoreaceae (Yams)

COMMON NAME(S): Wild yam root, colic root, yuma, devil's bones, rheumatism root, China root

BOTANY: *Dioscorea villosa* is a twining vine native to the central southeastern US and found less frequently in the Appalachian region. It is a dioecious plant with inconspicuous white to greenish yellow female flowers and smooth heart-shaped leaves. A Chinese species, *Dioscorea opposita* Thunb., is also occasionally found in herbal commerce. There are more than 500 species of *Dioscorea* worldwide.

HISTORY: Wild yam was popularized by the Eclectic medical movement in the 19th century for its supposed antispasmodic properties and prescribed for biliary colic and spasm of the bowel. More recently, it has been promoted for the relief of nausea in pregnancy, and for amenorrhoea and dysmenorrhea. [1] Further indications have been reported for urinary tract infections, rheumatoid arthritis, cholera, nervous excitement, and gas expulsion.

CHEMISTRY: While substantial amounts of chemical investigation have been made on other species of *Dioscorea*, there is little current work on *D. villosa*. As with many species of *Dioscorea*, *D. villosa* is a source of diosgenin.[2,3,4] It is not as prolific a producer of diosgenin as *D. zingiberensis*, *D. floribunda*, or other species. Diosgenin is not typically found in the free state in plants but commonly occurs as the saponins dioscin and gracillin. The saponins of *D. villosa* have not been elucidated, nor have other constituents of the species been investigated. A high performance liquid chromatography (HPLC) method for separation of dioscin, gracillin, and other *Dioscorea* saponins has been reported.[5]

PHARMACOLOGY: The root of *D. villosa* is reported to be diaphoretic and expectorant in a dose of 4 g. [6] Much of the current herbal use of wild yam is predicated on the misconception that the diosgenin contained in the product can be converted by the human body into steroid hormones, particularly progesterone, through the intermediate dehydroepiandrosterone (DHEA). This notion appears to be based on diosgenin's use as a synthetic precursor of cortisone [7] and of the steroids found in birth control pills. There is no scientific evidence to support the notion that diosgenin or dioscin can be converted by the body into human hormones. In a pilot study of women using wild yam products (*D. villosa*), it was found that progesterone synthesis appeared to be suppressed compared with controls. [8] No direct effect of wild yam extract on the estrogen or progesterone receptors was found.

Work with ginseng saponins has shown that metabolism by specific microbes in the gut can substantially enhance uptake of the metabolites into the body. [9,10] Thus, one may postulate a similar mechanism of uptake with other, otherwise poorly absorbed plant saponins such as dioscin. Research needs to be done to understand the pharmacodynamics of saponin-containing plants in humans.

Topical formulations of *Dioscorea* are also poorly understood, though it is unlikely that they can serve as "progesterone replacement" vehicles. The sale of supplemental DHEA as an "anti-aging" product has carried over to *Dioscorea* by analogy. In fact, several products containing *Dioscorea* and DHEA are available.

TOXICOLOGY: In large doses, *D. villosa* root may cause nausea, vomiting, and diarrhea.

SUMMARY: Wild yam root is currently recommended for the treatment of menstrual dysfunction; however, little scientific evidence supports its use in medicine. The potential for toxicity is modest; however, in the absence of evidence of benefit, it cannot be recommended. A monograph of wild yam can be found in the *British Herbal Pharmacopoeia*, vol. 2.[11]

PATIENT INFORMATION — Wild Yam

Uses: *Dioscorea* has been promoted for the treatment of menstrual dysfunction, nausea in pregnancy, urinary tract infections, rheumatoid arthritis, cholera, nervous excitement, and gas expulsion.

Side Effects: In large doses, *D. villosa* root may cause nausea, vomiting, and diarrhea.

Dosing: Wild yam root was used traditionally as a diaphoretic and expectorant at doses of 0.4 to 4 g/day, although there are no recent clinical studies to substantiate this dosage.[1]

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WILD YAM

WILLARD WATER

DATE OF ISSUE: OCT 2003

REPLACES MONOGRAPH DATED: JUN 1990

SCIENTIFIC NAME(S): None

COMMON NAME(S): Willard's water, catalyst altered water, CAW, carbonaceous activated water, Biowater

HISTORY: *Willard Water* is a product with a history that dates to the early 20th century. John Wesley Willard, PhD, a professor of chemistry at the South Dakota School of Mines and Technology developed this product. During the 1930s, Willard patented an industrial cleanser used to degrease and clean train parts. The liquid was named "carbonaceous activated water" or "catalyst activated water."[1]

However, over the years, the product became legendary among townsfolk who used *Willard Water* to treat practically every recognized animal and human disease. In the early 1970s, Willard distributed a product called *Dr. Willard's Water XXX* with lignite, which was advertised as a plant growth stimulator. In 1980, the CBS network program *60 Minutes* featured Dr. Willard and the water, showing fruits and plants that had grown to many times their normal size, allegedly because of treatment with *Willard Water*. Thereafter, a national sales system developed, with some distributors suggesting exaggerated indications for the product, including the treatment of arthritis, acne, anxiety, nervous stomach, hypertension, ulcers, and baldness, and for food preservation, in addition to serving as a laundry aid and a treatment for bovine and feline leukemia.[1]

The Willard family has acknowledged that the product does not have the capability to cure disease.

CHEMISTRY: The formula of *Willard Water* appears to have changed over the decades. The FDA has found that various products contain combinations of rock salt, lignite, sodium metasilicate, sulfated castor oil, calcium chloride, and magnesium sulfate.

The original manufacturers of *Dr. Willard's Water*, CAW Industries, Inc., document the following recipe on their Web site: water, sodium metasilicate, sulfated castor oil, CAW micelle, refined lignite, calcium chloride, and magnesium sulfate. During *Willard Water* preparation, the molecular structure of water is altered by a catalyst and a "CAW micelle" is created, "making it behave in a manner that heretofore has not been reported in the literature," as stated by Dr. Willard himself. [1]

PHARMACOLOGY: Recent literature searches find no peer-reviewed scientific studies on *Willard Water*. There is, however, continued interest in "genuine" *Willard Water*, even the incorporation of it into herbal products (ie, supplements, herbs, foods, vitamins, soaps), which claim to use the "real" or original recipe.

The reported uses of *Willard Water* are printed in the US Government Printing Office Committee Publication #96-240: *A Briefing on Catalyst Altered Water* by the Subcommittee on Health and Long Term Care of the Select Committee on Aging, U.S. House of Representatives, 96th Congress Second Session, July 7, 1980, Rapid City, South Dakota. Applications of *Willard Water* include the following: animal shampoo and itch reliever, fish tank purifier, injury (wound/cut/burn) healer, seed starter, prolongation of life of cut flowers, and houseplant fertilizer. Many human testimonials are also available, including the following: wound healing, alleviation of pain, dermatology application (ie, clear complexion), mild tranquilizer, hair care (ie, control frizz and dandruff), relief of sore throat, and potential antibacterial properties. *Willard Water* also may increase enzyme activity (eg, assimilate nutrients more efficiently) and immune system functioning.[1]

TOXICOLOGY: No toxicity had been reported to the FDA as of 1982, and the product has not been generally associated with significant toxicity problems. CAW Industries, Inc., the original manufacturers of *Dr. Willard's Water*, claim that *Willard Water* has been analyzed by many reputable laboratories and always has been found to be nontoxic, nonmutagenic, and noncarcinogenic.[1]

SUMMARY: *Willard Water* is a solution of electrolytes and other compounds, and was originally developed as an industrial cleanser. Over the past 70 years, exaggerated claims have been made for the product, including its use for the treatment of various diseases. There are no data to suggest the product is of any therapeutic value, but it seems to be nontoxic.[1]

PATIENT INFORMATION— Willard Water

Uses: Historically used as a cure-all or panacea, however there are no proven pharmacological effects of *Willard Water*. In the past it has been used as an industrial cleanser. The FDA does not recognize *Willard Water* as safe or effective.

Side Effects: The original manufacturers of *Dr. Willard's Water*, CAW Industries, Inc., claim that *Willard Water* has been analyzed by many reputable laboratories and always has found the product to be nontoxic, nonmutagenic, and noncarcinogenic.

Disease-State Concerns: None. Avoid use in patients with known hypersensitivity reactions to any of the *Willard Water* ingredients.

Dosage Concerns: Dosages vary according to application (eg, whether product is used in humans, pets or livestock, or plants). Review manufacturer's directions before using. When using *Willard Water* products manufactured by CAW Industries, Inc., any diluted solutions should be refrigerated for maximum benefits; boiling or freezing does not alter the efficacy of the products.[1]

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
      WILLARD WATER

WILLOW BARK

DATE OF ISSUE: MAR 2000

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Salix alba* L., *Salix purpurea* L., *Salix fragilis* L., and other species. Family: Salicaceae (willow family)

COMMON NAME(S): Willow, weidenrinde, white willow (*S. alba*), purple osier willow/basket willow (*S. purpurea*), crack willow (*S. fragilis*)

BOTANY: Willows are small trees or shrubs, many of which grow in moist places or along riverbanks in temperate and cold climates. Most of the several hundred species are dioecious, with male and female catkins (flowers) on separate plants. Largely insect pollinated, different species of willow hybridize freely. Medicinal willow bark is collected in the early spring from young branches (2 to 3 years of age) of the species listed above. Other species of *Salix* have similar chemistry and pharmacology.

HISTORY: For centuries, the bark of European willows has been used to treat fevers, headache and other pain, and arthritis. North American willows have also been used in folk medicine. Most of the European medicinal willows have been introduced to the Americas and have escaped cultivation. In the late 19th century, salicylic acid was widely used in place of willow bark, and its derivative aspirin was discovered to be less irritating to the mouth and stomach. [1,2]

CHEMISTRY: Salicylate derivatives are the primary medicinal constituents of willow bark. While small amounts of salicylic acid can be detected in most species, the principle salicylates of *S. alba* are the phenolic ester glycoside salicortin [3,4] and glycoside salicin, its acid hydrolysis product. Salicin is hydrolyzed in the intestine to saligenin (o-hydroxybenzyl alcohol), which is absorbed and then oxidized to salicylic acid. [5] Salicortin and other related salicylates are chemically unstable (for example, to the boiling water in teas) [6] and avoidance of loss of these compounds requires careful drying of the bark. [6,7,8] Extraction protocols that avoid decomposition of the native glycosides have been developed. Most standards for medicinal willow bark require salicylates to be greater than 1% of dry weight; however, this standard is difficult to achieve with many source species. This has stimulated surveys of the salicylate content of many other species of *Salix* [9,10] as well as aspen (*Populus*), which also contains salicylates. [11] While the leaves generally contain lower concentrations of salicylates than the bark, several species contain medicinally useful quantities of salicylates in their leaves. [12] Salicylates have been quantified in willows by spectrophotometry, [13] by thin-layer chromatography (TLC), [14] by high-performance liquid chromatography (HPLC) after enzymatic deglycosylation, [15] and by capillary electrophoresis. [16] A method using gas chromatography of silyl derivatives of salicylates gave comparable results to HPLC. [17] An HPLC method was used to compare the salicylate content of different cultivated clones of *Salix myrsinifolia* grown in a single location. [18] NMR spectra of the principle salicylates of willows have been reported and assigned. [19] The ecological role of salicylates has also been investigated. [20] Naringenin glycosides, [21] oligomeric procyanidins, [22] and condensed tannins presumably derived from the simpler flavonols have been obtained from commercial willow barks.

PHARMACOLOGY: The ester glycosides salicortin, tremulacin, and fragilin can be considered to be pro-drugs of salicylic acid, that deliver this compound into the systemic circulation without irritating the GI tract. [23] The pharmacokinetics of salicylic acid delivered from willow bark have been studied, and the plasma half-life is determined as approximately 2.5 hours. [24] The mechanism of action of salicylic acid is inhibition of cyclooxygenase enzymes, which are involved in prostaglandin synthesis. The anti-inflammatory efficacy of tremulacin (a derivative of salicin) has recently been studied. [25] A clinical trial of a willow bark preparation found mild efficacy in arthritis. [26]

TOXICOLOGY: There are no reports of adverse effects due to the use of willow bark; although, additive effects with synthetic salicylates must be considered. Use with caution in patients with peptic ulcers and other medical conditions in which aspirin is contraindicated.

SUMMARY: Willow bark was approved by the German Commission E for diseases accompanied by fever, rheumatic ailments, and headaches. It is monographed by ESCOP, the British Herbal Pharmacopeia, and is official in the German Pharmacopeia. An American Herbal Pharmacopeia monograph is due to be published shortly.

Willow bark can be an effective analgesic if the content of salicylates is adequate. Adverse effects are those of salicylates in general. Use with caution in patients with peptic ulcers and other medical conditions in which aspirin is contraindicated.

PATIENT INFORMATION — Willow Bark

Uses: Willow bark can be an effective analgesic if the content of salicylates is adequate.

Side Effects: Adverse effects are those of salicylates in general. Use with caution in patients with peptic ulcers and other medical conditions in which aspirin is contraindicated.

Dosing: Willow bark has been used for analgesia at daily doses of 1 to 3 g of bark, corresponding to 60 to 120 mg of salicin. A clinical study of low back pain used willow bark at a daily dose of 120 to 240 mg salicin. [27]

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Document Bibliographic Information:

- **Location In Book:**

- THE REVIEW OF NATURAL PRODUCTS (2004)
  "W" MONOGRAPHS
  WILLOW BARK

WINE

DATE OF ISSUE: DEC 1999

REPLACES MONOGRAPH DATED: JUL 1993

SOURCE: Wine is an agricultural product created by the natural fermentation of sun-ripened grape juice. Yeast-induced fermentation converts endogenous sugars to alcohol, and the flavors associated with each wine depend on the grape variety, harvest, and fermentation conditions. While most wines are derived from grapes, fermentation of other fruits and vegetables has yielded alcoholic wine-like beverages. Wine production includes a series of steps including extraction of juice, fermentation, clarification, and aging. [1,2]

HISTORY: Wine has played an important role in societal development for thousands of years. The first cultivated grapes were grown in Asia Minor around 6000 BC. Archaeologists have uncovered the remains of a 2600-year-old winery in Israel. [1] Egyptian accounts of wine-making date back to 2500 BC. The Bible mentions raising grapes to make wine.[2] Hippocrates (450 to 370 BC) was said to be the first physician to realize the healing value of wine. [3] The Romans disseminated the science and art of wine-making throughout much of the world, and Europe subsequently became the center of wine-growing expertise. Wine-making techniques were kept alive during the Dark Ages by the clergy. Early fermentation procedures produced heavy wines that often were exceedingly sweet. Refinement of the fermentation process resulted in the development of numerous varieties of wines, each with unique flavors and typical alcohol contents. Wine has had a role in societal interactions and many religious ceremonies. The growth of the American wine industry during the 20th century was halted by prohibition (1919 to 1933) but has risen steadily since. Today, almost every state in the US produces wines, with boutique wineries accounting for a growing proportion of the production. [1,2] Several historical articles discussing the history of wine and wine in the practice of medicine are available. [4,5,6,7,8,9,10,11,12,13]

CHEMISTRY: The chemical composition of wine is varied and complex. A typical wine contains more than 300 components other than alcohol, often containing minerals and vitamins not found in other fermented beverages.[1] Alcohol concentrations may vary from 10% to 14% for table wines and up to 20% for certain aperitifs. While the prevalent alcohol is ethanol, glycerol plus more than a dozen alcohols have been isolated from wines. [14] The polyphenols in wine have desirable biological properties, including phenolic acids (p-coumaric, cinnamic, caffeic, gentisic, ferulic, and vanillic) and trihydroxy stilbenes (polydatin, resveratrol). [12,15] One Japanese report analyzes resveratrol and piceid (and their isomers) content in 42 different wines. The average stilbene content was 4.37 mg/L in red wines and 0.68 mg/L in white.[16] Wine flavonoids are also present (1 to 3 g/L in red wines, 0.2 g/L in white) and include flavonols, anthocyanins, flavanols (catechins, quercetin), oligomers (procyanidins), and polymers (tannins) of the catechins. [12,17] Champagnes and sparkling wines contain ˜ 1.5% carbon dioxide. Other wine components include carbonyl compounds, organic acids, tannins, carbohydrates, and esters. [1,14]

PHARMACOLOGY: The correlation between wine consumption and reduced heart disease and mortality has been widely reported. World Health Organization data show that fat consumption is associated with coronary heart disease (CHD) mortality. However, certain populations where daily consumption of wine is highest (eg, Italy, Switzerland, France) had high-fat intake but low CHD mortality rates. This was termed the "French paradox." [18] Researchers previously had seen that there was a population-based association between CHD mortality and increased wine consumption. [19] Subsequent reports confirm that moderate intake of wine lowers CHD mortality.[20,21,22] In one study, the rate of CHD mortality per 1000 men decreased from ˜ 22 among those who did not drink alcohol to ˜ 8 for those who had 2 drinks per day.[23] The Copenhagen City Heart Study (CCHS) (Copenhagen, Denmark), initiated in 1976, analyzed 13,329 patients 45 to 84 years of age for 16 years to determine risk of first stroke. Although this report did not address factors such as genetic diversity, existing risk factors, or type (red or white) or amount of wine consumed, it confirmed that wine has beneficial effects. It was concluded that compounds other than ethanol in wine are responsible for the protective effect on risk of stroke.[24] The National Stroke Association (NSA) states that heavy drinking increases stroke risk. They agree that modest consumption, such as a 4 oz glass of wine per day, may lower stroke risk, provided that there is no other medical reason to avoid alcohol. [25]

Recent reports confirm the relationship between alcohol consumption and decrease in cardiovascular (CV) risk. A review of 30 population studies suggests this correlation but also emphasizes that the effect of alcohol and CV risk is highly dependent on other risk factors. Alcohol as a "heart medicine" was deemed insufficient in this report.[26] A later study agrees that alcoholic intake is associated with lower CHD risks but also comments that mortality can be influenced by lifestyle characteristics (eg, smoking, obesity).[27]

Red wine phenolic compound has positive effects on plasma antioxidant capacity. [28] Antioxidants prevent the oxidation of LDL cholesterol into plaque, which is known to clog arteries, leading to cardiovascular disease (CVD). [29] The most potent antioxidants for LDL (in descending order) are the phenolics (epicatechin, catechin, and resveratrol).[30] BR>
Several mechanisms have been suggested as to the beneficial CV effects of wine polyphenols. Nitric oxide production by vascular endothelium, modulation of lipoproteins by decreasing total cholesterol and increasing HDL levels, and carcinogenesis inhibition have all been reported. [12,31] Red wine polyphenols are thought to inhibit several pathways leading to CHD. A range of 300 to 500 mg of extract appears to protect against CVD. Its vasorelaxing activity and inhibition of platelet aggregation can be beneficial for disease prevention. [15]

Wine flavonoids and phenolics inhibit clotting by platelet aggregation inhibition. [17] This is apparently done by inhibition of either oxygenase enzymes [32] or thromboxane synthesis.[12]

Purple grape juice may have the same effects as red wine in reducing heart disease risk. [33] Fruit consumption has also correlated highly with reduced CHD mortality.[22]

Aside from cardiovascular disease, a large body of evidence has accumulated regarding the benefits of moderate wine intake in the management of other afflictions. These include emotional tension, anxiety, and inability to relax. The pharmacology of ethanol has been well characterized (including its effects on the CNS and smooth and skeletal muscles).[2,14] Also included are achlorhydria and related gastric disorders and malabsorption syndromes. [14,19] Certain substances in wine promote better absorption of minerals such as calcium, magnesium, phosphorus, and zinc. The aroma and taste of wine stimulate the appetite, especially in elderly and debilitated patients.[2,14] White wine also significantly shortens gastric emptying time. [34] Wine also may be of benefit topically to stimulate wound healing and to improve rheumatoid skin ulcerations. [35]

TOXICOLOGY: Alcohol consumption has detrimental physical, medical, social, and economic ramifications. This monograph will not address these well-known facets of alcohol (and wine) consumption. The danger of drinking too much wine is available in a concise summary. [2] In addition, a recent report on the management of heavy drinkers is referenced as well. [36]

Typically, adverse reactions to pure wine are rare. The vast majority of commercially prepared wines now contain sulfites as preservatives, and those sensitive to these chemicals may develop severe allergic reactions, including wheezing and tachycardia. Those sensitive to yeasts may experience allergies to some wines. While a glass of wine before bedtime has long been an accepted treatment for temporary insomnia, a larger amount may be counterproductive because it depresses respiration resulting in sleep apnea. [37]

Headaches following the ingestion of some wines (particularly chianti) have been associated with histamine or tyramine content although the relationship has not been firmly established. Tyramine may result in a severe drug interaction (eg, hypertensive crisis) in patients taking MAO inhibitors. [38]

Patients with gastroesophageal reflux should ingest wine cautiously because wine worsens reflux. [39,40]

A direct association has been made between increasing wine consumption and the rate of ovarian cancer in women in Italy. [41] Excessive wine consumption has been associated with a reversible rise in systolic blood pressure levels. [42]

Women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. Alcohol consumption is contraindicated in people with viral hepatitis such as hepatitis B and C.

SUMMARY: Wine has been a part of civilization for thousands of years. Wines are complex mixtures of flavors and fragrances. They have been used as beverages and as the basis for traditional medicines. The correlation between wine consumption and reduced heart disease has been shown in many reports. Other factors do play a role, including amount consumed, smoking, and certain lifestyle habits. Wine has antioxidant activity and inhibits clotting by altering platelet aggregation. Other benefits include reduction in anxiety and better absorption of certain nutrients. Adverse reactions to pure wine are rare. Some people may be sensitive to other ingredients in wine.

PATIENT INFORMATION— Wine

Uses: Studies suggest that wine may lower the incidence of cardiovascular disease.

Interactions: Tyramine in certain wines (particularly chianti) may cause life-threatening hypertensive crisis in patients receiving MAO inhibitors concurrently or for at least 4 weeks after MAO inhibitor therapy is discontinued. [43]

Side Effects: Adverse reactions to pure wine are rare. Headaches following the ingestion of some wines have been associated with histamine or tyramine content. Patients with gastroesophageal reflux should ingest wine cautiously because it may worsen reflux. Alcohol consumption is contraindicated in people with viral hepatitis such as hepatitis B and C.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
      WINE

WINTERGREEN

DATE OF ISSUE: NOV 2003

REPLACES MONOGRAPH DATED: AUG 1992

SCIENTIFIC NAME(S): *Gaultheria procumbens* L. and other related species. Family: Ericaceae

COMMON NAME(S): Wintergreen, teaberry, checkerberry, gaultheria oil, boxberry, deerberry, mountain tea, Canada tea, partridgeberry

BOTANY: The wintergreen is a perennial evergreen shrub with thin, creeping stems from which leathery leaves with toothed, bristly margins arise. It is a low-growing plant native to eastern North America and usually is found in woodland and exposed mountainous areas. Its small, waxy, white or pale pink flowers bloom in late summer, developing a scarlet fruit. The aromatic leaves and fruits are edible. [1,2,3]

HISTORY: American Indians reportedly used wintergreen for treating back pain, rheumatism, fever, headaches, and sore throats. [3] The plant and its oil have been used in traditional medicine as an anodyne, analgesic, carminative, astringent, and topical rubefacient.

Wintergreen oil is obtained by steam distillation of the warmed, water-macerated leaves. It is used interchangeably with sweet birch oil or methyl salicylate for flavoring foods and candies. The highest amount of methyl salicylate typically used in candy flavoring is 0.04%.

Wintergreen berries have been used to make pies. [4] A tea made from the leaves was used as a substitute for tea (*Camellia sinensis*) during the Revolutionary War. [3] The tea has been used to relieve cold symptoms and muscle aches. [5]

CHEMISTRY: Wintergreen oil contains approximately 98% to 100.5% of the methyl ester, methyl salicylate. [6] The plant has little odor or flavor until the methyl salicylate is freed. During steam distillation, the gaultherin (also described as primeveroside or monotropitoside) present in the leaves is enzymatically hydrolyzed to methyl salicylate. [1,7] The purified methyl salicylate is subsequently obtained through distillation. In addition to the sugars, D-glucose and D-xylose are obtained. The yield of oil from the leaves is in the range of 0.5% to 0.8%. [8]

PHARMACOLOGY: Small oral doses of wintergreen oil stimulate digestion and gastric secretion. [4] Topically, the oil is a counterirritant and may offer some analgesic effect because of the structural similarity of methyl salicylate to aspirin.

TOXICOLOGY: When ingested, the highly concentrated liquid methyl salicylate in the form of wintergreen oil, as with other volatile oils, can induce vomiting and is a notorious source for severe, often fatal, poisonings. [4,6]

Children often may associate the pleasant odor of wintergreen oil with "candy". However, the oil may be particularly toxic to children. One teaspoon (5 mL) of wintergreen oil is equivalent to approximately 7000 mg of salicylate or 21.5 adult aspirin tablets. [9] Ingestion of as little as 4 mL in a child and 6 mL in an adult has been fatal. [6,10,11] Because of this toxicity, official labeling requirements have been changed so that no drug product may contain more than 5% methyl salicylate. [12] No deaths have been reported from ingestion of the plant itself. [1]

The compound lectin has been shown to have mutagenic properties; [4] the extract is used in some insecticides. [1]

The essential oil and its component can be absorbed through the skin; thus, salicylate intoxications occur following topical application of methyl salicylate or wintergreen oil. Because of the structural similarity between methyl salicylate (a methyl ester of aspirin) and acetylsalicylic acid (aspirin), a toxic syndrome similar to that seen in salicylism has been observed in persons who have ingested wintergreen for prolonged periods of time. This syndrome has been characterized by tinnitus, nausea, and vomiting. [4]

A man 40 years of age became suddenly and acutely ill within 1 hour after an herbalist topically applied an herbal skin cream containing an unknown amount of wintergreen oil for the treatment of psoriasis. The patient developed tinnitus followed by hyperpnea, vomiting, diaphoresis, fever, and CNS disturbance (wintergreen oil in liquid form is a highly lipid soluble). [13]

An Asian woman 70 years of age, seeking relief for her chronic knee pain, developed similar clinical manifestations of methyl salicylate poisoning (eg, acid-base disturbance, endocrine abnormalities, fluid and electrolyte imbalances, CNS toxicity) after ingesting 60 mL of topical Koong Yick Hung Fa Oil (KYHFUO: contains 56.2 g of salicylic acid, the equivalent of 173 regular-strength, adult aspirin tablets) purchased at an Asian grocery store in Singapore. [14]

One case report documents a potential hypersensitivity reaction in a nonsmoking woman 21 years of age with a history of asthma; who complained of wheezing, dry cough, and bronchial pains after using a tartar-control toothpaste flavored with wintergreen. [15,16] Another case report documents a patient developing laryngeal edema after accidental ingestion of wintergreen oil. [9]

SUMMARY: Wintergreen and its oil are commonly used in topical analgesic and rubefacient preparations for the treatment of muscular and rheumatic pain. The oil is widely used as a flavoring agent. As with other volatile oils, ingestion of large amounts may be toxic, particularly to children.

PATIENT INFORMATION — Wintergreen

Uses: In addition to being used as a flavoring, wintergreen and its oil have been used in topical analgesic and rubefacient preparations for the treatment of muscular and rheumatic pain.

Side Effects: Wintergreen oil can induce vomiting, and in some cases, death. Oral or topical application is best avoided in children. Avoid use in patients with known hypersensitivity to any of the components in wintergreen oil. Counsel patients about the clinical manifestations of methyl salicylate poisoning (eg, tinnitus, acid-base disturbance, endocrine abnormalities, fluid and electrolyte imbalances, CNS toxicity).

Disease-State Concerns: Avoid use in patients with asthma, known salicylate allergy, or GI irritation or inflammation. Monitor for potentiation of warfarin anticoagulation in patients using methyl salicylate or wintergreen oil. [17]

Dosage Concerns: Because of toxicity concerns, follow the suggested manufacturer's oral or topical dosage form regimen: 1 teaspoon (5 mL) of wintergreen oil is equivalent to approximately 7000 mg of salicylate or 21.5 adult aspirin tablets.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WINTERGREEN

WITCH HAZEL

DATE OF ISSUE: JUL 1997

REPLACES MONOGRAPH DATED: SEP 1990

SCIENTIFIC NAME(S): *Hamamelis viginiana*L. Family: Hamamelidaceae

COMMON NAME(S): Witch hazel, hamamelis, snapping hazel, winter bloom, spotted alder, tobacco wood, hamamelis water.

BOTANY: Witch hazel grows as a deciduous bush or small tree, often reaching about 20 feet in height. The plant is found throughout most of North America. Its broad, toothed leaves are ovate, and the golden yellow flowers bloom in the fall. Brown fruit capsules appear after the flowers, then when ripe, eject its two seeds away from the tree. The dried leaves, bark and twigs are used medicinally. [1,2]

HISTORY: Witch hazel is a widely known plant with a long history of use in the Americas. One source lists more than 30 traditional uses for witch hazel including the treatment of hemorrhoids, burns, cancers, tuberculosis, colds, and fever. Preparations have been used topically for symptomatic treatment of itching and other skin inflammations and in ophthalmic preparations for ocular irritations. [3]

The plant is used in a variety of forms including the crude leaf and bark, fluid extracts, a poultice, and commonly as witch hazel water. The latter, also known as hamamelis water or distilled witch hazel extract, is obtained from the recently cut and partially dormant twigs of the plant. This plant material is soaked in warm water followed by distillation and the addition of alcohol to the distillate. Witch hazel water is the most commonly found commercial preparation, usually kept in most homes as a topical cooling agent or astringent. [2,3]

Traditionally, witch hazel was known to native North American people as a treatment for tumors and eye inflammations. Its internal use was for hemorrhaging. Eighteenth century European settlers came to value the plant for its astringency, and it is still used today for this and other purposes. [2]

CHEMISTRY: Witch hazel leaves contain about 7% to 10% of tannins. There is some dispute as to the actual composition of the tannin with hamamelitannin, digallyhamamelose and various gallotannins having been identified. [4] It is not clear whether hamamelitannin is found in the leaves. [5] Recent sources list from 8%[3,6] to no hamamelitanin in leaves. [1] The bark contains from 1% to 7% hamamelitannin and smaller amounts of condensed tannins. [7,8] Other components include flavonoids (eg, kaempferol, quercetin), gallic acid, saponins, a fixed oil, and a volatile oil. The volatile oil contains small amounts of safrole and eugenol and numerous other minor components, such as resin, wax, and choline. Because witch hazel water is a steam distillate of the extract, it does not contain any tannins. [2,6]

PHARMACOLOGY: Witch hazel leaves, bark, and its extracts have been reported to have astringent and hemostatic properties. These effects have been ascribed to the presence of a relatively high concentration of tannins in the leaf, bark, and extract. Tannins are protein precipitants in appropriate concentrations. [9]

Witch hazel water is absent of tannins but still retains its astringency. This suggests other constituents may possess astringent-like qualities. [2]

The mechanism of witch hazel astringency involves the tightening of skin proteins, which come together to form a protective covering that promotes skin healing. [2] This quality is desirable in treatment of hemorrhoids (including preventive measures for recurring hemorroids). [10] A preparation of tea has been used in cases of diarrhea, dysentery, and colitis. [1,2,3,6]

Skin problems are also treated with witch hazel. Its drying and astringent effects help treat skin inflammations such as eczema. Witch hazel's action on skin lesions also protects against infection. [2] Skin lotions may also contain witch hazel for these purposes. [1] Inflammation of mucous membranes including mouth, throat and gums may also be treated with witch hazel in the form of a gargle. [1]

Witch hazel is also used to treat damaged veins. Its ability to tighten distended veins and restore vessel tone is employed in varicose vein treatment and is also valuable for bruises and sprains. [1,2] This hemostatic property of witch hazel is said to stop bleeding instantly, and if used as an enema, offers a rapid cure for "inwardly bleeding piles." [3] In Europe, an alcoholic fluid extract is taken internally to treat varicose veins and fluid extracts administered parenterally to rabbits have been found to be vasoconstrictive. [11]

TOXICOLOGY: Although the volatile oil contains the carcinogen safrole, this is found in much smaller quantities than in plants such as sassafras. [3] Although extracts of witch hazel are available commercially, it is not recommended that these extracts be taken internally because the toxicity of the tannins has not been well defined. [6] Although tannins are not usually absorbed following oral administration, doses of 1 g of witch hazel will cause nausea, vomiting, or constipation, possibly leading to impactions; hepatic damage may occur if the tannins are absorbed to an appreciable extent. [1,12] Witch hazel water is not intended for internal use. Teas can be brewed from leaves and twigs available commercially in some health-food stores, but their safety is undefined.

At least one report is available discussing contact allergy to witch hazel. [13]

SUMMARY: Witch hazel leaves, bark, and extracts are high in tannins and have been used as topical astringents. Witch hazel water, most commonly found in the home, is a product of the steam distillation of the leaves and twigs; it contains no tannins, but is still used for its astringency. This "skin-tightening" effect of witch hazel is of value in treating hemorrhoids, other GI problems, skin afflictions and vein damage. It has anti-inflammatory and hemostatic properties as well. Witch hazel has a low toxicity profile, but internal use is not recommended.

PATIENT INFORMATION — Witch Hazel

Uses: Witch hazel has astringent and hemostatic properties, making it useful as a skin astringent to promote healing in hemorrhoid treatment, diarrhea, dysentery, and colitis, as well as other skin inflammations such as eczema. It can also be gargled to treat mucous membrane inflammations of the mouth, throat, and gums. Witch hazel has been used to treat damaged veins, bruises, and sprains; it rapidly stops bleeding making it useful as an enema.

Side Effects: Internal use is not recommended. Doses of 1 g of witch hazel will cause nausea, vomiting, or constipation, possibly leading to impactions. Hepatic damage may occur if the tannins are absorbed to an appreciable extent.

Dosing: Witch hazel leaves or bark have been used traditionally at daily oral doses of 2 to 3 g. Suppositories containing witch hazel contain from 0.1 to 1 g/dose. [14,15]

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "W" MONOGRAPHS
  WITCH HAZEL

WITHANIA

DATE OF ISSUE: OCT 2000

REPLACES MONOGRAPH DATED: JUL 1988

SCIENTIFIC NAME(S): *Withania somnifera* (L.) Dunal, also *W. coagulans* Dunal Family: Solanaceae (nightshade family)

COMMON NAME(S): Withania, Ashwagandha, Aswaganda, Winter Cherry, Indian ginseng, Ajagandha, Kanaje Hindi, Samm Al Ferakh, Asgand (Hindi), Amukkirag (Tamil), Amangura (Kannada), Asvagandha (Bengali), Ashvagandha (Sanskrit), Asundha (Gujarati), Kuthmithi, Clustered Wintercherry

BOTANY: *W. somnifera* is an erect, greyish, slightly hairy evergreen shrub with fairly long tuberous roots. It is widely cultivated in India and throughout the Middle East, and is found in eastern Africa. The flowers are small and greenish, single or in small clusters in the leaf axils. The fruit is smooth, round, fleshy, and has many seeds, orange-red when ripe, enclosed in a membranous covering.

HISTORY: The root of *W. somnifera* is used to make the Ayurvedic sedative and diuretic "Ashwagandha," which is also considered an adaptogen. Other parts of the plant (eg, seeds, leaves) are used as a pain reliever, to kill lice, and to make soap. The fresh berries have been used as an emetic.

CHEMISTRY: The principal bioactive compounds of *W. somnifera* are withanolides, highly oxygenated C-28 steroid derivatives. Over 40 withanolides have been isolated and identified from *W. somnifera*. Three chemotypes of the plant have been defined[1]: Indian (?), which contains withanone[2] and withaferin A[3,4] as major constituents; Israeli (??), whose major withanolides are withanolide D[5] and 27-hydroxywithanolide D;[1] and Israeli (???), containing principally withanolide E.[6] The biosynthesis of withanolides from the cholesterol pathway has been studied,[7] and the C-13 NMR spectra of withanolides have been assigned.[8] An HPLC separation of withanolides has been reported.[9]

W. somnifera roots also contain nicotine and assorted piperidine and pyrrolidine alkaloids.[10] The leaves have been found to contain flavonol glycosides and phenolic acids.[11]

PHARMACOLOGY: The majority of studies of *W. somnifera* pharmacology have not related bioactivity to specific chemical constitutents present. Given the noted variation in withanolides, it is obvious that this has limited reproducibility of results.

Adaptogenic effects: Pretreatment with the alcoholic extract of defatted seeds increased swimming endurance in mice, and significantly reduced cold-, stress-, restraint-, and aspirin-induced ulcers in rats.[12] A combination of withaferin A and two sterol glucosides from roots of *W. somnifera* showed antistress activity in a panel of tests.[13] Aqueous suspensions from the roots of Ashwagandha and ginseng were compared in a mouse swimming model and for anabolic activity (weight gain) in rats and both were found to possess oral activity when animals were treated for 7 days.[14] Ashwagandha extract given orally to rabbits and mice prevented stress-induced increases in lipid peroxidation.[15] Stress-induced increases in plasma corticosterone, phagocytic index, and avidity index were blocked by administration of *W. somnifera* to rats, while swimming time was increased.[16] Another study in rats and frogs found the extract to be adaptogenic when given as a pretreatment for up to 3 months, as measured by swimming tests, glycogen content of various tissues, coagulation time, and catecholamine content, among others.[17] The effect of *W. somnifera* extract on thyroid hormone levels[18] and corticosterone levels[19] in animals has been studied. A review of adaptogenic effects of *W. somnifera* and other Ayurvedic adaptogens has been published.[20]

Immunomodulatory and anti-inflammatory effects: *W. somnifera* extracts given IP suppressed rat paw edema induced by carrageenan,[21] as well as in a granuloma pouch assay.[22] Orally administered proprietary extracts of *W. somnifera* were found to have modest activity in an active paw anaphylaxis model and to suppress cyclophosphamide-induced delayed-type hypersensitivity.[23] Withanolides inhibit murine spleen cell proliferation,[24] and an extract of *W. somnifera* reversed ochratoxin's suppressive effect on murine macrophage chemotaxis.[25] Withanolide glycosides activated murine macrophages, phagocytosis, and increased lysosomal enzymatic activity secreted by the macrophages, while also displaying anti-stress activity and positive effects on learning and memory in rats.[26] Alpha-2 macroglobulin synthesis stimulated by inflammation was reduced by *W. somnifera* extract.[27] Similarly, the extract prevented myelosuppression caused by cyclophosphamide, azathioprine, or prednisolone in mice.[28]

The stimulation of macrophages was invoked to explain activity versus experimental aspergillosis in mice.[29] Similar activity in other experimental infections was observed in rats.[30]

Cancer: Withaferin A was first isolated as a cytotoxic agent,[3] and a considerable amount of investigation followed. The compound produced mitotic arrest in Ehrlich ascites carcinoma cells in vitro[31] while in vivo effects were mediated by macrophage activation.[26,32] Further investigations on peripheral blood lymphocytes determined that withaferin A destroyed spindle microtubules of cells in metaphase.[33] Mouse sarcoma cells showed similar effects, with additional effects on nuclear membranes of cells.[34] A structure-activity comparison of withaferin A analogues in P388 cells attributed reaction of its lactone and epoxide moieties with cysteine as important to its cytotoxicity.[35] Withaferin was synergistic with radiation treatment in a mouse Ehrlich ascites carcinoma model.[36] Recently, several withanolides were identified as inducers of differentiation of myeloid leukemia cells.[37]

CNS: Withania extract protected against pentylenetetrazol-induced seizures in a mouse anticonvulsant model when administered over a 9-week period.[38] The same research group found the extract active in a rat status epilepticus model.[39] A further study of the extract found that it inhibited the development of tolerance to morphine in mice, while suppressing withdrawal symptoms precipitated by naloxone.[40] A withanolide-containing fraction reversed morphine-induced reduction in intestinal motility and confirmed the previous finding of inhibition of development of tolerance to morphine.[41] A depressant effect on the CNS was indicated by potentiation of pentobarbital effects on the righting reflex in mice.[42] Effects on learning and memory attributed to the plant in Ayurvedic medicine were supported by an experiment in which ibotenic acid-induced lesions in intact rat brain which led to cognitive deficit, as measured by performance in a learning task, were found to be reversed by treatment with a withanolide mixture.[43]

Miscellaneous: *W. somnifera* seed extract was found to protect against carbon tetrachloride-induced liver damage in rats.[44] The leaf extract also showed a modest protective effect in a subacute model of liver damage, as well as an anti-inflammatory effect.[45] Damage to the bladder by cyclophosphamide was ameliorated by *W. somnifera* extract given IP,[46] as was leukopenia induced by cyclophosphamide.[47] The extract decreased arterial and diastolic blood pressure in normotensive dogs, while preventing the hypotensive effect of acetylcholine and increasing the hypertensive effects of adrenaline.[48]

TOXICOLOGY: Acute toxicity of *W. somnifera* is modest. In mice an LD-50 was determined to be 1750 mg/kg PO[12] in one study and 1260 mg/kg by the intraperitoneal route.[49] Subacute IP toxicity studies at 100 mg/kg/day for 30 days led to decreased spleen, thymus, and adrenal weights, but no mortality or hematological changes.[49] A longer-term study (180 days) in rats at a dose of 100 mg/kg PO found no lethality but unfavorable increases in catecholamine content of the heart and decreases in the adrenal glands.[17]

SUMMARY: Withania appears in the *WHO Monographs on Selected Medicinal Plants* (vol. 2). An American Herbal Pharmacopoeia monograph is forthcoming. A book-length review was published.[50] Ashwagandha is a well-known Ayurvedic drug with a multitude of observed pharmacologic effects. It is generally thought to be non-toxic. The withanolides are considered to be the principal bioactive compounds in the root; however, their complexity and variation have made correlation of the complex pharmacology with chemistry difficult.

PATIENT INFORMATION— Withania

Uses: Withania has adaptogenic, immunomodulatory, and anti-inflammatory effects in animals; it also has been studied in animals as a cytotoxic agent and has different CNS applications.

Side Effects: Acute toxicity of *W. somnifera* is modest. A 180-day study involving rats found unfavorable increases in catecholamine content of the heart and decreases in the adrenal glands.

Dosing: Despite a large volume of basic scientific studies on the plant, there is minimal evidence for a proper dose of this herb. A single study in which *W. somnifera* was the principal component of a polyherbal mixture administered 450 mg of root powder 4 times/day for arthritis. [51]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WITHANIA

WOODRUFF, SWEET

DATE OF ISSUE: NOV 2003

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Galium odoratum* (L.) Scop. Also known as *Asperula odorata* L. Family: Rubiaceae (Madder family)

COMMON NAME(S): Woodruff, sweet woodruff, master of the wood, woodward, waldmeister.[1]

BOTANY: Sweet woodruff is a small perennial that grows up to 30 cm in height. It has creeping rhizomes and lance-shaped, glossy leaves that form whorls around the stems. It is native to Eurasia and North Africa and grows throughout North America. The small, star-shaped, white flowers appear from April to June. The dried whole plant is used in traditional medicine. When cut, the plant develops a characteristic smell of fresh-cut hay. [1,2,3]

HISTORY: Sweet woodruff has been used as a sedative, antispasmodic, diuretic, and sweat inducer.[1,2,3] It is a flavoring component in May wines (woodruff soaked in sweet white wine), vermouth, and some bitters, and is used in food, candy flavorings, gelatins, and puddings. Sweet woodruff has been used to cure boils and heal inflammations.[1,3] In homeopathy, the plant is used as an antispasmodic and to treat liver impairment. The bruised leaves have been applied topically to reduce swelling and improve wound healing.[2] Extracts and teas have been administered as expectorants. Woodruff is usually administered as a tea. The dried herb is used in sachets, and the extract is used in perfumes and other fragrances.[2]

In traditional medicine it has been used to cure restlessness, insomnia, stomachache, migraine, neuralgia, and bladder stones. In European cultures, sweet woodruff is used for prophylaxis and therapy of respiratory conditions, and for gallbladder, kidney, and circulatory disorders. It also has been applied topically for venous conditions such as varicose veins and hemorrhoids.[1,2]

Modern herbalists have used the herb as a laxative and an antiarthritic.[4]

CHEMISTRY: Sweet woodruff contains coumarin (0.6%)[3] in a glycosidic form that is freed by enzymatic action during the drying process. However, at least one study did not detect any coumarins in sweet woodruff.

Medium pressure liquid chromatography revealed 225 substances within the plant. One of these substances, previously not found in nature, may be used as an indicator of illegal use of sweet woodruff in food aromas: 7,11,15-trimethyl-2-hexadecanone.[5]

The plant contains a number of minor components including asperuloside (0.05%), monotropein, tannins, iridoids, anthraquinones, flavonoids, traces of nicotinic acid, a fixed oil, and a bitter principle. The root contains a red dye of the alizarine type.[1,2,3,6]

PHARMACOLOGY: Asperuloside and components in the leaves of the plant are reported to have antiphlogistic or anti-inflammatory activity.[2] When evaluated in vivo in rats, an extract of *G. odoratum* administered orally inhibited carrageenan-induced, rat-paw edema by 25%; this compared favorably with the 45% inhibition observed following indomethacin administration.[7]

The coumarin and flavonoid components are responsible for its use in treating varicose veins and phlebitis.[3] The plant is also purported to have antibacterial activity.[2]

TOXICOLOGY: The plant is generally recognized as safe for use in foods as a flavoring. Some concern has been raised over the toxic potential of the coumarin content of the plant.[2] Average coumarin content found in dry weight of the plant is 1.06%.[8]

Dietary feeding of coumarin to animals has been associated with liver damage, growth retardation, testicular atrophy, and impaired blood clotting.[1,2] However, it is highly unlikely that these events would occur with normal dietary intake of the plant or its extracts. Excessive doses may lead to internal bleeding.

SUMMARY: Sweet woodruff is a common herb that is used as a fragrance and flavoring in foods. Although the plant has been used medicinally for a variety of purposes, there is little evidence supporting these claims.

PATIENT INFORMATION — Woodruff, Sweet

Uses: Sweet woodruff is reported to have anti-inflammatory and antibacterial activities but is commonly used as a fragrance and flavoring in foods.

Side Effects: The plant is generally recognized as safe for use in foods. There is some concern over the toxic potential of the plant's coumarin content; therefore, avoid use during pregnancy and lactation.

Drug Interactions: Although coumarin content is low, monitor for any potentially clinical significant interactions in patients being treated for cardiovascular conditions with conventional medications.

Dosing: Studies suggest the safety limit for preparation of spiced wine is less than 5 ppm of coumarin, which is approximately 3 to 3.5 g of fresh woodruff per liter of beverage.[8]

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
      WOODRUFF, SWEET

WORMWOOD

DATE OF ISSUE: APR 1991

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Artemisia absinthium* L. Family: Compositae

COMMON NAME(S): Wormwood, absinthium, armoise, wermut, absinthe, absinthites, ajenjo.

BOTANY: The wormwood is an odorous perennial shrub native to Europe. Today the plant is naturalized in the United States where it grows widely throughout the Northeast and North Central regions. The leaves and stems are covered with fine silky hairs and the plant grows to a height of about 3 feet. [1] The small flowers are green-yellow and the indented leaves have a silver-gray color.

HISTORY: The name wormwood is derived from the ancient use of the plant and its extracts as an intestinal anthelmintic. The leaves and flowering tops were used as a bitter aromatic tonic, sedative,[2] and flavoring. A tea of the plant was used traditionally as a diaphoretic. Wormwood extract was the main ingredient in absinthe, a toxic liqueur that induces absinthism, characterized by intellectual enfeeblement, hallucinations, [3] psychosis, and possible brain damage. The drink is now outlawed but had been popular until the early part of the 20th century. The emerald green color of absinthe liqueur came from chlorophyll; however, there had been reports of copper and antimony salts being added as colorants to inferior batches, with toxic consequences. Thujone-free wormwood extract is currently used as a flavoring, primarily in alcoholic beverages such as vermouth.

CHEMISTRY: The bitter taste of wormwood is due to the glucosides absinthin and anabsinthin and several related compounds. [4] The plant contains a pleasant-smelling volatile oil (about 1% to 2% by weight); up to 12% of the oil is a mixture of alpha- and beta-thujone with smaller amounts of phellandrene, pinene, azulene and more than a half-dozen other minor components.[5] Flowers may contain oil composed of up to 35% thujones. Cis- and trans-epoxyocimenes account for up to 57% of the volatile oil derived from Italian absinthium. [1]

PHARMACOLOGY: The anthelmintic activity of the plant is probably due to lactones related to santonin, found in wormseed and other species of Artemisia. [1] In addition, thujone can stun roundworms, which can then be expelled by normal intestinal peristalsis. [3]

TOXICOLOGY: In rats, injection of thujone in concentrations as low as 40 mg/kg induces convulsions, with a dose of 120 mg/kg being fatal. [4] The subcutaneous LD_{50} of thujone in mice is 134 mg/kg.[6]

Ingestion of absinthe may lead to a constellation of neurologic symptoms described as "absinthism." The syndrome is characterized by digestive disorders, thirst, restlessness, vertigo, trembling of the limbs, numbness of the extremities, loss of intellect, delirium, paralysis and death. [5] One commonly cited report indicates that 15 g of the volatile oil can cause convulsions and unconsciousness in humans. [5]

Thujone bears a superficial structural resemblance to camphor, pinene, anethole, and citral, and it has been postulated that Vincent van Gogh's demented craving for not only absinthe but also other terpenes, including turpentine, certain paints, and camphor, may have represented a type of pica. [7]

Although some of the nervous system effects of thujone are similar to those observed with camphor, comprehensive structural dimensional analyses suggest that thujone more likely conforms to the same receptor as tetrahydrocannabinol (THC). [8] Both compounds appear to have an affinity for a common receptor binding site and for similar oxidative metabolic pathways.

The FDA has classified wormwood as an unsafe herb, although thujone-free derivatives have been approved for use in foods.

The oil is used as an ingredient in rubifacient preparations; flowers may induce topical eruptions in sensitized persons. [5]

SUMMARY: Wormwood and its extracts have been used traditionally in the treatment of worm infections and as flavoring agents. Wormwood extract was the most important component of the liqueur absinthe, a toxic drink that was banned early in the 20th century. Wormwood toxicity is caused by thujone, which may exert its central effect by interacting with receptors for tetrahydrocannabinol.

PATIENT INFORMATION — Wormwood

Uses: Wormwood was traditionally used in the treatment of worm infections and as flavoring agents.

Side Effects: The FDA classified wormwood as an unsafe herb. Ingestion of wormwood may result in neurologic symptoms described as "absinthism." The syndrome is characterized by digestive disorders, thirst, restlessness, vertigo, trembling of the limbs, delirium, paralysis, and death.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "W" MONOGRAPHS
    WORMWOOD

"Y" MONOGRAPHS

YARROW

DATE OF ISSUE: APR 1998

REPLACES MONOGRAPH DATED: DEC 1987

SCIENTIFIC NAME(S): *Achillea millefolium* L.; Family: Compositae

COMMON NAME(S): Yarrow, thousand-leaf, mil foil, green arrow, wound wort, nosebleed plant

BOTANY: The name yarrow applies to any of roughly 80 species of daisy plants native to the north temperate zone. *A. millefolium* L. has finely divided leaves and whitish, pink, or reddish flowers. It can grow up to 3 feet in height. This hardy perennial weed blooms from June to November. Golden yarrow is *Eriophyllum confertiflorum*.[1,2]

HISTORY: Yarrow is native to Europe and Asia and has been naturalized in North America. Its use in food and medicine is ancient, dating back to the Trojan War, around 1200 BC.[3] In legend, Achilles used it on the Centaur's advice, hence the name. In classical times, yarrow was referred to as "herba militaris" because it stopped wound bleeding caused by war.[2] Yarrow leaves have been used for tea, and young leaves and flowers have been used in salads. Infusions of yarrow have served as cosmetic cleansers and medicines. Sneezewort leaves (*A. ptarmica*) have been used in sneezing powder, while those of *A. millefolium* have been used for snuff.[1] Yarrow has been used therapeutically as a "strengthening bitter tonic" and astringent. Chewing fresh leaves has been suggested to relieve toothaches. [3,4] Yarrow oil has been used in shampoos for a topical "healing" effect.

CHEMISTRY: As many as 82 constituents have been identified in the essential oil (of which yarrow yields 1%). [5] Some of these components include linalool, sabinene, allo-ocimene, azulene, eugenol, menthol, alpha-pinene, borneol, cineole (less than 10%), limonene (less than 11%), camphor (18% to 21%) and chamazulene (up to 50%).[2,3,5,6,7,8] Quantitative determination of chamazulene and prochamazulene has been performed.[9,10] Tetraploid species contain azulene, while hexaploid and octaploid species do not.[5,11] The precursors of azulene in the tetraploid species *A. millefolium* sp collina Becker are prochamazulenes that confirm the genera *Matricaria*, *Artemisia* and *Achillea* are closely related.[12]

Sesquiterpene lactones, including alpha-peroxyachifolid and others, have been determined. [13,14] Sesquiterpenoids, achimillic acids A, B, and C, and alpha-methylene sesquiterpene lactones have also been isolated from yarrow.[15] Two guaianolide-peroxides from the plant's blossoms have been found.[16] Other triterpenes and sterols identified in yarrow include beta-sitosterol, alpha-amyrin, stigmasterol, campesterol, cholesterol, beta-amyrin, taraxasterol, and pseudotaraxasterol. [17]

Flavonoids present in yarrow include apigenin, artemetin, casticin, luteolin, and rutin. [5,8] The alkaloids achiceine, achilletin, betaine, betonicine, choline, moschatine, stachydrine, and trigonelline have been found in yarrow. [3,8] Among the amino acids are alanine, histodine, aspartic acid, glutamic acid, and lysine. [3,8] Fatty acid constituents include linoleic, myristic, oleic, and palmitic. Other acids found are salicylic, ascorbic, caffeic, folic, and succinic. [8]

Other components found in yarrow include polyacetylenes, coumarins (± 0.35%), tannins (3% to 4%), and sugars (dextrose, glucose, mannitol, sucrose). [5,8] The constituents of yarrow have been reviewed in detail.[18]

PHARMACOLOGY: Yarrow is used as a sudorific (to induce sweating). It is also classified as a wound-healing herb because it stops wound bleeding. [4] It has been used for this purpose for centuries and is a component in some healing ointments, lotions, and percolates or extracts. [2,5] Its healing and regenerating effects have been reported when used as a constituent in medicated baths to remove perspiration and remedy inflammation of skin and mucous membranes.[5,19,20] One study reports wound-healing properties of yarrow oil in napalm burns. [21]

Chamazulene, a constituent in yarrow essential oil, has anti-inflammatory and anti-allergenic properties. In animal studies, this anti-inflammatory activity has been demonstrated using mouse and rat paw edema models.[8]

The yarrow component achilleine arrests internal and external bleeding. [2] IV injection (0.5 g/kg) in rabbits has decreased blood clotting time by 32%. Hemostasis persisted for 45 minutes with no toxic effect.[2] Achilletin has also reduced coagulation time in canines. [3]

Yarrow helps regulate the menstrual cycle and reduces heavy bleeding and pain. [2,8] It has been used as an herbal remedy for cerebral and coronary thromboses.[8] Yarrow has also been used to lower high blood pressure, improve circulation, and tone varicose veins. [2,3]

Antispasmodic activity of yarrow has also been documented, probably caused by the plant's flavonoid fractions [2,8] or azulene.[8] Yarrow has relieved GI ailments such as diarrhea, flatulence, and cramping.[5] Yarrow's antimicrobial actions have also been documented. In vitro fungistatic effect from the oil has been proven. [22] The oil has also exhibited marked activity against *S. aureus* and *C. albicans*.[23] Another report discusses antistaphylococcal activity from yarrow grass extract. [24] Antibacterial actions have also been demonstrated against *B. subtillus*,*E. coli*, *Shigella sonnei*, and *flexneri*.[8] One report found yarrow's sesquiterpenoids, achimillic acids, to be active against mouse leukemia cells in vivo.[15] Other actions of yarrow include: Growth inhibiting effects on seed germination caused by constituents phenylcarbonic acids, coumarins, herniarin, and umbelliferone, [25] marked hypoglycemic and glycogen-sparing properties [26] and CNS-depressant activity and sedative actions in mice.[8] Yarrow is a natural source for food flavoring and is used in alcoholic beverages and bitters. [8] Thujone-free yarrow extract is generally recognized as safe (GRAS) for use in beverages.

TOXICOLOGY: Contact dermatitis is the most commonly reported adverse reaction from yarrow. Guaianolide peroxides from yarrow have caused this reaction, [16] as have alpha-peroxyachifolid,[14] 10 sesquiterpene lactones, and 3 polyines.[13] A Danish report evaluates routine patch testing in 686 patients to determine sensitivity to compositae plants and their sesquiterpene lactones. Terpinen-4-ol, a yarrow oil component, has irritant properties and may contribute to its diuretic actions. [8] Thujone, a known toxin and minor component in the oil, is in too low a concentration to cause any health risk. [8] Yarrow is not generally considered toxic.[3,8]

SUMMARY: Yarrow is the name for many plant species used for teas, herbal infusions, and other remedies. Yarrow contains many diverse compounds (acids, alkaloids, flavonoids, and volatile oils), several of which have pharmacologic activity. It is used as a healing agent and for its anti-inflammatory properties. It has also been used for circulatory disorders and thromboses. The plant has choleretic, antispasmodic, antimicrobial, and other actions. Yarrow is contraindicated in individuals with an existing hypersensitivity to any member of the composite (asteraceae) family. The yarrow's volatile oil is not recommended during pregnancy or in epileptic patients.

PATIENT INFORMATION— Yarrow

Uses: Yarrow has been used to induce sweating and to stop wound bleeding. It can also reduce heavy menstrual bleeding and pain. It has been used to relieve GI ailments, for cerebral and coronary thromboses, to lower high blood pressure, to improve circulation, and to tone varicose veins. It has antimicrobial actions, is a natural source for food flavoring, and is used in alcoholic beverages and bitters.

Side Effects: Contact dermatitis is the most commonly reported side effect. It is generally not considered toxic.

Dosing: A typical dose of yarrow herb is 4.5 g/day for inflammatory conditions. However, there are no modern clinical studies to validate this dose.

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Document Bibliographic Information:

- **Location In Book:**
  THE REVIEW OF NATURAL PRODUCTS (2004)
  "Y" MONOGRAPHS
  YARROW

YELLOW DOCK

DATE OF ISSUE: SEP 1992

REPLACES MONOGRAPH DATED: MAY 1986

SCIENTIFIC NAME(S): *Rumex crispus* L. Family: Polygonaceae

COMMON NAME(S): Yellow dock, curly dock, curled dock, narrow dock, sour dock, rumex

BOTANY: A perennial herb that grows to 3 to 4 feet, yellow dock has narrow, slender light green leaves with undulated margins. It flowers in June and July. [1] Although native to Europe, it grows throughout the United States. The yellow roots (deep, spindle-shaped) and rhizomes are used medicinally.

HISTORY: The spring leaf stalks of this plant have been used as a potherb in salads but is disagreeable to some because of its tart sour-sweet taste. The plant must be boiled and rinsed thoroughly before being eaten. Due to its astringent properties, the plant has been used (generally unsuccessfully) in the treatment of venereal diseases and skin conditions. The powdered root has been used as a natural dentifrice. Larger amounts have been given as a laxative and tonic.

CHEMISTRY: The plant contains oxalate, most probably in the form of potassium oxalate crystals.[2] Anthroquinones (emodin, chrysophanic acid, physcion) have been identified, and the total anthroquinone content of the root (approximately 2%) exceeds that of medicinal rhubarb (Rheum rhaponticum, 1.4%), also a member of the family Polygonaceae.[3]

PHARMACOLOGY: Little is known about the pharmacology of yellow dock. The anthroquinone content most likely contributes to the laxative effect of the plant. The tannin component, however, may cause constipation. The related plant R. hymenosepalus (dock) contains a tannin that, upon hydrolysis, yields leucodelphinidin and leucopelargonidin, 2 compounds with potential antineoplastic activity. [4]

TOXICOLOGY: The oxalate crystals damage mucosal tissue resulting in severe irritation and possible tissue damage. The ingestion of large amounts of oxalates may result in gastrointestinal symptoms; systemic absorption of oxalates may result in kidney damage. Ingestion of the plant by livestock has resulted in death. The stewed leaf stalks can be eaten as a potherb, but mature and uncooked leaves should be avoided. Overdoses of the root extract may cause diarrhea, nausea, and polyuria in humans.

One traditional remedy for dermatitis and rashes suggest applying the juice of Rumex spp. However, sensitive people may develop dermatitis after contact with yellow dock.

SUMMARY: The roots of yellow dock and related Rumex species exert a laxative effect. The oxalate content of the leaf is significant enough to warrant boiling young leaves eaten as salads; older and uncooked leaves should not be eaten.

PATIENT INFORMATION— Yellow Dock

Uses: The roots of yellow dock exert a laxative effect.

Side Effects: The oxalate content of the leaves may result in GI symptoms or kidney damage. The stewed leaf stalks can be eaten as a potherb, but mature and uncooked leaves should be avoided. Overdose of the root may cause diarrhea, nausea, and polyuria.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
    YELLOW DOCK

YELLOW ROOT

DATE OF ISSUE: OCT 1998

REPLACES MONOGRAPH DATED: JUN 1987

SCIENTIFIC NAME(S): *Xanthorhiza simplicissima* Marsh. synon. with *Zanthorhiza apiifolia*. Family: Ranunculaceae.

COMMON NAME(S): Yellow root, parsley-leaved yellow root, yellow wart, shrub yellow root. Not to be confused with "yellow root," also referring to goldenseal (*Hydrastis canadensis L.*).

BOTANY: A shrub-like plant indigenous to the east coast of North America that grows from New York to Florida, yellow root is commonly found growing near stream banks and shady areas. It flowers in April and derives its names from the bright yellow color of the rhizome. [1]

HISTORY: Yellow root had been used by people living in the southern United States for the treatment of hypertension and diabetes. [1] It was popular in folk medicine and has been used for mouth infections and sore throat, diabetes, and childbirth. [2]

CHEMISTRY: Berberine is the major alkaloid in yellow root with the minor alkaloids jatrorhizine and mognoflorine also having been identified. [3] In addition, 2 cytotoxic isoquinoline alkaloids, liriodenine and palmatine have been isolated in a later report. [4] The major alkaloid berberine is present in 23 genera, spanning 7 plant families.[5] Berberine content in yellow root ranges between 1.2% to 1.3% [2] puntarenine, an isohomoprotoberberine alkaloid has recently been isolated as well. [6]

PHARMACOLOGY: Yellow root has been used as a source for yellow dye.[2] Various pharmacokinetic information of yellow root constituent berberine in animals is available.[5]

Berberine-containing plants have been used for thousands of years in China and India, mostly for treatment of diarrhea. Berberine is reportedly effective against diarrhea caused by such enterotoxins as *Vibrio cholerae* and *E. coli*. In several clinical trials, diarrhea treatment from berberine has proven successful. [7] However, some contraversy exists on the validity of this type of treatment in children, not only caused by underlying pathophysiological processes, but to the fact that berberine salts were often given as part of a mixture of agents (ie, with anticholinergic compounds). [5]

Yellow root constituent berberine has been used not only in folk medicine, but as an antibiotic, immunostimulant, anticonvulsant, sedative, hypotensive, uterotonic, and choleretic .[7]

Berberine produces a transient drop in blood pressure and appears to antagonize the pharmacologic effects of acetylcholine and histamine. [8] Its hypotensive effects have been studied in animals.[7]

Berberine decreases anticoagulant actions of heparin in dog and human blood. It exhibits antipyretic activity in rats. [7]

Yellow root has been used as a bitter tonic for mouth and gum sores, especially in denture care. [2]

A broad spectrum of antimicrobial action has been found for berberine, including activity against bacteria, fungi, and protozoa. [7] Yellow root extracts were found to exhibit antimicrobial activity against *Candida albicans*, *Cryptococcus neoformans*, and *Mycobacterium intracellularae*.[6] Extract of yellow root has also been shown to inhibit RNA and DNA synthesis in leukemia cells.[9]

Yellow root has also been reported to be used as an adulterant for the more expensive goldenseal. [10]

TOXICOLOGY: A case of a man who developed chronic arsenic poisoning after drinking yellow root tea for 2 years has been reported. Yellow root is not a natural concentrator of arsenic and the contamination was thought to be secondary to pollution in the plant's habitat. [11]

Yellow root constituent berberine is generally considered non-toxic (as other berberine plants). Coagulant activity opposing heparin's actions and cardiac stimulation have been reported from the plant, which may be of concern. In addition, berberine has been known to stimulate uterine activity; its use during pregnancy should be avoided.[7]

The oral LD-50 of berberine in mice is 3.29 mg/10 g. Experimentation with other laboratory animals being administered berberine in various amounts has produced GI irritation, tremors, emesis, and sedation.[5]

SUMMARY: Yellow root derives its name from the yellow color of the rhizome. It was a popular plant in folk medicine, with its major alkaloid being berberine. Berberine's activities include antibiotic, immunostimulant, anticonvulsant, sedative, hypotensive, utertonic, choleretic, and carminative. It is generally considered non-toxic, with exceptions being anticoagulation interactions, cardiostimulation, and uterine stimulatory.

PATIENT INFORMATION— Yellow Root

Uses: Yellow root has been used in folk medicine for mouth infections and sore throat, diabetes, and childbirth, and as an antibiotic, immunostimulant, anticonvulsant, sedative, hypotensive, utertonic, and choleretic.

Side Effects: It is generally considered non-toxic, exceptions being anticoagulation interactions, cardiostimulation, and uterine stimulatory. Berberine can stimulate uterine activity; use during pregnancy should be avoided.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
    YELLOW ROOT

YERBA SANTA

DATE OF ISSUE: MAR 1991

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): *Eriodictyon californicum* (Hook. & Arn.) Torrey. Also known as *E. glutinosum* Benth. and *Wigandia californicum*Hook. & Arn. Family: Hydrophyllaceae

COMMON NAME(S): Yerba santa, eriodictyon, tarweed, consumptive's weed, bear's weed, mountain balm, gum plant[1]

BOTANY: The plant is an evergreen aromatic shrub with woody rhizomes. The hairy, lance-shaped leaves are glutinous. [2] Native to the southwestern regions of North America, yerba santa is often cultivated as an ornamental shrub. The plant grows to more than 2 meters in height at elevations exceeding 3500 feet and has white to lavender flowers.

HISTORY: The name yerba santa ("holy weed") was given by the Spanish priests who learned early from the native American Indians of the medicinal value of the shrub. The plant has a long tradition of use in the United States. The thick sticky leaves, used either fresh or dried, were boiled to make a tea or taken as treatment for coughs, colds, asthma, and tuberculosis. The leaves have been powdered and used as a stimulating expectorant. [3] A liniment was applied topically to reduce fever. A poultice of fresh leaves was used to treat bruises and young leaves were applied to relieve rheumatisms. [4,5] The plant is contained in a number of over-the-counter herbal preparations. Yerba santa has been used as a pharmaceutical flavoring, particularly to mask the flavor of bitter drugs. [6] The fluid extract is used in foods and beverages.

CHEMISTRY: Yerba santa contains a volatile oil, up to 6% eriodictyonine, about 0.5% eriodictyol (the aglycone of eriodictin) and several related alcoholic compounds, ericolin and a resin.[2]

PHARMACOLOGY: Eriodictyol is reported to exert an expectorant action.[1] Little other animal or human experience with the plant has been published.

TOXICOLOGY: There are no reports of significant toxicity associated with the topical or systemic use of yerba santa.

SUMMARY: Yerba santa is a traditional American plant used widely by Native Americans for the preparation of a tea and medicinally for the management of bruises, inflammations and rheumatic pain. The plant is also used as an expectorant and in the treatment of respiratory diseases. There are no good studies to evaluate these effects.

PATIENT INFORMATION— Yerba Santa

Uses: Yerba santa has been used in tea, and medicinally for the management of bruises and rheumatic pain. The plant is also used as an expectorant and in the treatment of respiratory diseases.

Side Effects: There are no reports of significant toxicity associated with the topical or systemic use of yerba santa.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
    YERBA SANTA

YEW

DATE OF ISSUE: MAY 1993

REPLACES MONOGRAPH DATED: AUG 1991

SCIENTIFIC NAME(S): Taxus bacatta L. and *T. cuspidata* Sieb. and Zucc. The native species of the US, *T. canadensis* Marsh. is found throughout the eastern United States; other species found in North America include *T. floridana* Nutt. and the western or California yew, *T. brevifolia* Nutt. Family: Taxaceae

COMMON NAME(S): Yew, ground hemlock

BOTANY: This common evergreen is found throughout woods and forests and is often used as an ornamental hedge bush. The trunk supports a crown of spreading branches with long, narrow, dark green shiny leaves. It is dioecious, with male and female flowers being produced on different trees. The ovoid seed is black and is surrounded by a red, fleshy covering called the aril. Yews flower in March and April.

HISTORY: The Celts coated their arrows with yew sap as a nerve toxicant. The alkaloid taxine has been used as an antispasmodic. A tincture of the leaves had been used to treat rheumatisms and liver and urinary tract conditions. [1]

CHEMISTRY: The entire plant, with the exception of the red, fleshy aril, contains approximately 19 taxane alkaloids, of which the best known is taxine. [2] Other alkaloids (milossine, ephedrine), the glycoside taxicatin, paclitaxel and its derivatives, [3] and pigments are found throughout the plant. Bristol-Myers Squibb recently received FDA approval to market paclitaxel (*Taxol*)[4] as an antineoplastic agent for ovarian cancer, and concern has been raised regarding the environmental impact of debarking Pacific yew trees to harvest the drug. Consequently, methods have been developed to produce paclitaxel from precursors found in the leaves, twigs and needles of yews common in Europe and Asia, and others are attempting to synthesize paclitaxel from pinene, a common compound found in pine trees. Paclitaxel content varies from 0.00003% to 0.069% of the plant.[5] The approved generic name, paclitaxel, was previously referred to as "taxol." *Taxol* is now the trademarked brand name for paclitaxel.

PHARMACOLOGY: The compound paclitaxel is an anti-cancer agent that is available commercially in the United States and a number of countries. It is derived from several species of yew but primarily from the western yew, *T. brevifolia.* It has a novel mechanism of action causing mitotic abnormalities and arrest, and promoting microtubule polymerization into aggregated structures resulting in the inhibition of cell replication. [6]

Paclitaxel has been widely tested in the United States and approval has been swift. Clinical response has ranged up to approximately 40% with response periods lasting up to two years. Myelosuppression has been the most common adverse event.[7] In other clinical trials, intravenous paclitaxel has resulted in a 12% response rate among patients with metastatic melanoma, with durable response lasting 6 to 17 months.[6] Dose-limiting myelosuppression was observed in early trials that used single or divided intravenous doses. The drug was generally well tolerated except for significant hypersensitivity reactions occurring as skin rashes, bronchospasms, and anaphylaxis. These reactions have been limited by administering the drug as a slow infusion over 6 to 24 hours.

Taxotere, a derivative of paclitaxel derived from the more common English yew, is being investigated for treatment of ovarian, breast, and lung cancer.

TOXICOLOGY: Excluding the red aril, most of the plant is poisonous. Following ingestion, symptoms of dizziness, dry mouth, mydriasis and abdominal cramping develop rapidly. A rash may appear, and the skin can become pale and cyanotic. Bradycardia, hypotension, and dyspnea may be accompanied by coma, leading to death caused by respiratory or cardiac failure. A number of deaths in humans have been reported following the ingestion of yew leaves or teas brewed from yew. The administration of digoxin-specific FAB antibody fragments has been associated with the improvement of cardiac conduction abnormalities following ingestion of yew leaves and berries.[2]

General supportive measures have also been suggested for the management of yew intoxication. The stomach should be emptied and a charcoal slurry administered. The patient should be treated symptomatically. [8]

SUMMARY: The yew has been used in herbal medicine for centuries. The plant is now considered to be of major medical importance, with one extract approved for its antineoplastic activity. Because it is one of the most common foundation plantings in North America, it is often associated with childhood and animal poisonings. All parts of the plant are toxic with the exception of the red fruit.

PATIENT INFORMATION — Yew

Uses: The yew plant has been used to treat rheumatisms, liver and urinary tract conditions, and most recently to treat cancer cells.

Side Effects: The ingestion of the plant results in dizziness, dry mouth, mydriasis, and abdominal cramping. Rash and pale cyanotic skin may develop. It may eventually result in death.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
    YEW

YOGURT

DATE OF ISSUE: NOV 1998

REPLACES MONOGRAPH DATED: MAY 1995

SOURCE: Yogurt is the general term for a fermented, slightly acidic milk product that contains essentially no alcohol. Most commonly it is prepared by the addition of live cultures of *Streptococcus thermophilus*and *Lactobacillus bulgaricus* to heated whole or skimmed cow's milk. The mixture is incubated and homogenized to a semisolid. Condensed skimmed milk or dry milk solids are sometimes added to produce a custard-like texture. If cultures of *Lactobacillus acidophilus* are added, the product is called acidophilus milk. Bulgarian yogurt is yogurt that has been concentrated by a factor of about 1.5 and contains the highest amount of lactose.

PHARMACOLOGY

Lactose Intolerance: Yogurt has been at the center of a controversy regarding milk products that can be tolerated by people with lactose-deficiency syndromes. Although a *Lancet* editorialist concluded that "yogurt, cheese, and double creams contain little lactose and can be freely used by most patients," [1] numerous respondents suggested that the use of yogurt might be inadvisable.

Milk contains 4.6% lactose and yogurt about 3% (after fermentation). Bulgarian yogurt contains about 4.5% lactose, an amount almost equal to that in milk. High lactose levels in yogurt, however, seem to be better tolerated than similar levels in milk. This may be because of the microbial beta-galactosidase in yogurt, because pasteurized yogurt containing little of the enzyme produces more malabsorption of lactose than does active-culture yogurt. Nevertheless, yogurt tolerance by lactase-deficient individuals may be independent of malabsorption, because these individuals tolerate pasteurized yogurt well. [2]

Hydrogen breath tests of lactase-deficient persons have shown that hydrogen production is lower after ingestion of unflavored yogurt than after milk ingestion, with flavored yogurt producing intermediate levels. Neither yogurt type, however, produced symptoms of lactose intolerance. Subjects tolerated frozen yogurt to about the same extent as ice cream or ice milk.[3]

Patients with short-bowel syndrome have been found to better absorb lactose from yogurt than from milk; because a lactose dose of up to 20 g from yogurt was well-tolerated in this study, the investigators suggested that lactose in this form may not need to be excluded from the diets of these patients. [4]

Antimicrobial activity: Yogurt has been promoted to restore the GI flora after systemic antibiotic therapy and to alleviate anal pruritus, aphthous ulcers, and canker sores. Ingestion of yogurt may also be effective in the prevention of recurrent vaginal yeast infections. The large number of bacteria in active yogurt (each ml of commercial brands contains about 125 million *L. bulgaricus*and 125 million *S. thermophilus*) may hasten the colonization of the colon, thereby removing the reservoir of yeast infection. More than a decade ago, bacterial replacement therapy with live cultures was found to have "no established value in the prevention or treatment of such disorders."[5]

There has been some interest in the direct vaginal instillation of yogurt for the treatment of candida infections. While some lay texts suggest using dilutions of yogurt in water as a douche, its use in full-strength also has been reported. [6] Whatever effect is obtained might be because of the lactic acid content (about 1%) or low pH (about 4) of the product. One study assessed the effects of the intravaginal application of commercial yogurt in 32 pregnant women with bacterial vaginosis. A continuous improvement in vaginal pH and *Lactobacillus* flora was noted; the therapy was well-tolerated.[7] However, the clinical effects of this therapy have not been defined in well-controlled studies and this practice cannot be widely recommended, particularly in pregnant women.

Yogurt possesses intrinsic antibacterial activity against *Salmonella typhimurium*, probably because of its lactic acid content; the low oxidation-reduction potential of the product may also contribute. The small amount of acetic acid present (about 0.2%) is not sufficient for antibacterial activity. [8] The compound bulgaricum is elaborated by some strains of *L. bulgaricus* and has inhibitory activity against gram-negative and gram-positive bacteria. [9] This bacterium also produces amounts of hydrogen peroxide that are inhibitory to *Staphylococcus aureus*.[10] In vitro tests have shown yogurt to kill all 11 tested strains of *Campylobacter jejuni* within 25 minutes. Lactic acid is quite bactericidal against these organisms, but it is probably not the only factor in eliminating the bacteria. [11]

In spite of yogurt's antibacterial properties, it has been speculated that the product offers a suitable medium for the proliferation of toxic fungi. Conditions during the production of yogurt or during cooling (from 45°C to 4°C) meet the requirements for fungal growth; this has been associated with the production of small amounts of aflatoxin. It is unclear, however, whether lactic acid levels affect fungal growth and aflatoxin production. [12]

Two studies have shown that yogurt consumption increases the ability of weanling Sprague-Dawly rats to withstand gastrointestinal challenge by *Salmonella enteritidis* in comparison with milk. Although yogurt did not prevent disease, it reduced mortality and the decelaration of weight gain. The differences between yogurt and milk did not appear to be related to differences in vitamin and mineral content. [13,14] The clinical importance of these findings is poorly understood.

It should be noted, however, that particularly in the elderly, the live bacteria found in yogurt do not necessarily pass through the gut. In one study, only a mucosal-adhering strain of *Lactobacillus gasseri*passed through the intestinal tract after ingestion of yogurt, suggesting that some bacterial starins may have a greater ability to remain within the gut than others. [15] In another study, women given yogurt containing live *Lactobacillus* demonstrated significant changes in fecal enzymatic activity and also had significant increases in fecal bacterial counts, indicating that yogurt supplementation could modify the colonic bacterial environment. [16] However, recent evidence indicates that ingestion of yogurt supplemented with *Bifidobacterium longum* does not alter the normal fecal aerobic or anaerobic counts, suggesting that the bacterial composition of human fecal flora may not be readily influenced by dietary supplementation with active culture yogurt. [17]

Antineoplastic activity: Experiments with cells from murine Peyer's patches suggest that yogurt may boost host immunocompetence by potentiating cell-mediated immune responses. This involves increases in the percentage of B lymphocytes and PHA- and LPS-induced proliferation responses as shown in suspensions of Peyer's patch cells.[18]

Several Russian investigators have reported the isolation of compounds from the cell wall of *L. bulgaricus* capable of inhibiting the proliferation of tumors in laboratory animals, and others have isolated an antitumor compound produced by *L. bulgaricus* var. tumornecroticans. Yogurt has an inhibitory effect on Ehrlich ascites tumor cell proliferation.[19] In vivo antitumor activity was demonstrated in mice with similar tumors; the activity resides in the water-soluble fraction of yogurt and may be a component(s) with molecular weight of less than 14,000. This compound is active orally and parenterally. [20] A case-control study of nearly 3,000 subjects that analyzed consumption of alcohol and dairy products found that yogurt consumption was associated with a drop in the incidence of breast cancer. [21]

The results of a more recent study that followed 120,852 Dutch men for approximately 3 years found that the risk of colorectal cancer decreased slightly as the consumption of fermented dairy (ie, yogurt) increased; however, unlike the findings from some other studies, increases in the total dietary intake of calcium were not associated with decreases in the risk for colorectal cancer. [22]

Lipid-lowering effects: A study of the dietary habits of the Masai, a nomadic tribe inhabiting southern Kenya, found that the Masai had low serum cholesterol levels and a low incidence of ischemic heart disease. Their diet consisted mostly of fermented milk product similar to yogurt, and they rarely ate meat. When challenged with a "western" diet, their cholesterol levels increased, ruling out a protective genetic factor. [23]

The data suggest that Masai yogurt contained a component that influenced cholesterol levels in man. These findings have been disputed; on autopsy, many Masai were found to have significant atherosclerotic deposits in their aortas. However, because they are a robust nomadic people, their cardiac vessels were found to be significantly larger than in sedate persons, thereby providing relatively unobstructed blood flow even in the presence of atherosclerosis.

When western subjects had their normal diets supplemented with a daily intake of the yogurt from 2 or 4 L of whole milk, from 2 L of skimmed milk or simply 2 L of fresh milk, both the whole and skimmed milk yogurt produced significant reductions in cholesterol levels of up to 29% within 20 days. The ingestion of fresh milk

generally did not affect serum cholesterol levels.[24]

Results of other metabolic studies suggest that yogurt contains a factor that inhibits the synthesis of cholesterol from acetate, resulting in lower levels even when dietary cholesterol intake is large; the compound is thought to be hydroxymethyl glutaryl G coenzyme-A cholesterol biosynthesis. This finding has been disputed because the levels of HMG in yogurt are variable, indicating that HMG may not be solely responsible for the cholesterol-lowering effect. Other data suggest that the levels of calcium present in yogurt (equivalent to an intake of about 850 mg/day) may contribute to serum cholesterol reduction. [25]

In one test, rabbits were fed either yogurt, milk, or calcium, along with a high-cholesterol diet. When the study groups were compared after 16 weeks, the yogurt group showed significantly lower cholesterol levels than the milk group, but these decreases were similar to those observed in the calcium group. Because milk can also reduce cholesterol levels (to a lesser extent, however, than yogurt) calcium alone or with other factors such as HMG is responsible for yogurt's hypocholesterolemic effects.[26] Research continues into the identification of a hypocholesterolemic factor in milk and other dietary products. [27]

TOXICOLOGY: Yogurt is not associated with any significant adverse events. As described above, people intolerant to lactose may not be able to digest yogurt. One report of 11 children who developed hemolytic uremic syndrome from a toxic strain of *Escherichia coli* that contaminated a batch of yogurt in North West England suggests that stringent bacterial control must be applied to the production of this food product.

SUMMARY: Yogurt is a widely enjoyed milk product. It is a good source of calcium and may be more readily digested than milk by some lactose-deficient people. It has some antibacterial and antitumor activity, although the clinical implications are unknown. Reports of its use in treatment of enteric and vaginal infections are preliminary. The daily ingestion of yogurt may confer some protection against hypercholesterolemia, although the minimum amount of dietary yogurt required for this effect has not been established.

PATIENT INFORMATION— Yogurt

Uses: Yogurt has been used as a substitute for those who are lactose-intolerant and to prevent recurring vaginal yeast infections. Yogurt also inhibits other antimicrobial activity, antineoplastic activity, and lipid-lowering effects.

Side Effects: Yogurt is not associated with any significant adverse events.

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Document Bibliographic Information:
- **Location In Book:**
- THE REVIEW OF NATURAL PRODUCTS (2004)
  "Y" MONOGRAPHS
  YOGURT

YOHIMBE

DATE OF ISSUE: MAY 1993

REPLACES MONOGRAPH DATED: MAR 1990

SCIENTIFIC NAME(S): *Pausinystalia yohimbe* (K Schumann) Pierre. Synonymous with *Corynanthe johimbe*. Family: Rubiaceae. The alkaloid yohimbine also is obtained from *Aspidosperma quebracho blanco* and *Rauwolfia serpentina*.

COMMON NAME(S): Yohimbe, yohimbehe, yohimbine

BOTANY: This tree grows throughout the African nations of Cameroon, Gabon, and Zaire.

HISTORY: The bark of the West African yohimbe tree is rich in the alkaloid yohimbine, and both the crude bark and purified compound have long been hailed as aphrodisiacs. The bark has been smoked as a hallucinogen and has been used in traditional medicine to treat angina and hypertension. Today the drug is being investigated for the treatment of organic impotence.

CHEMISTRY: The bark contains approximately 6% yohimbine (also known as aphrodine, quebrachine or corynine). Yohimbine is an indole analog. Other minor alkaloids include corynantheidine and allo-yohimbine.

PHARMACOLOGY: Yohimbine is generally classified as an alpha-2-adrenergic blocking agent. Small doses have a stimulant action in humans resulting in autonomic and psychic changes commonly associated with the subjective experience of anxiety.[1] Yohimbine has been reported to be an inhibitor of monoamine oxidase[2] but more likely has a weak calcium channel blocking effect.[3]

Yohimbine dilates blood vessels, thereby lowering blood pressure; however, its use as an antihypertensive agent has long been abandoned. The drug causes a significant increase in blood pressure after an oral dose of 5 mg in patients with orthostatic hypotension secondary to pure autonomic failure or multisystem atrophy. This response is associated with an increased heart rate and increased plasma noradrenaline levels.

Because yohimbine can cause both the dilation of peripheral and mucous membrane blood vessels along with central nervous system stimulation, the drug has been investigated for the treatment of organic impotence. It should be noted that both the crude drug and yohimbine have a long history of use as aphrodisiacs.

Sexual-stimulant products available over-the-counter often contain yohimbine, sometimes combined with hormones such as methyltestosterone.

One older prescription product (*Afrodex*, Bentex Pharmaceuticals) combined 5 mg each of yohimbine HCl, methyltestosterone, and nux vomica in a capsule for the treatment of male climacteric and impotence. Although a number of clinical trials were conducted with this product,[4] the results were generally unimpressive leading the *Medical Letter* to conclude that "there is still no good evidence that *Afrodex* and similar drugs have more than placebo effects."[5]

More recent investigations now strongly suggest that higher doses of the drug (6 mg three times a day) may be effective in the treatment of organically impotent men.[6] One study found that 10 of 23 men treated with the drug derived a benefit from treatment. Eleven of the 23 men were diabetics.[7] One prescription product containing 5.4 mg yohimbine HCl (*Yocon*, Palisades Pharmaceuticals) is indicated as a sympathicolytic and mydriatic that also may have activity as an aphrodisiac. Yohimbine appears to be effective and may exert its activity by increasing the norepinephrine content of the corpus cavernosum.[8]

INTERACTIONS: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

TOXICOLOGY: Yohimbine may be toxic if ingested in high doses. The drug causes severe hypotension, abdominal distress, and weakness. Larger doses may cause central nervous system stimulation and paralysis. This drug should not be used in the presence of renal or hepatic disease. It has been suggested that because of its monoamine oxidase inhibiting activity the usual precautions for concomitant drug use with this class of agents be followed.[2] Yohimbine may precipitate psychoses in predisposed individuals. The drug or crude product should never be self administered, but should only be taken under supervision of a physician.

SUMMARY: Yohimbine is an alkaloid derived from the African yohimbe tree. Both the crude drug and purified alkaloid have been used as an aphrodisiac and hallucinogen. Recent studies suggest that the drug may be effective in the treatment of male organic impotence, in particular that associated with diabetes.

PATIENT INFORMATION— Yohimbe

Uses: Yohimbe has been investigated for the treatment of organic impotence, in particular those with diabetes, and for the use as aphrodisiacs.

Interactions: For potential interactions, refer to the "Potential Herb-Drug Interactions" appendix.

Side Effects: Yohimbe may be toxic if ingested in high amounts. It causes severe hypotension, abdominal distress, and weakness and may cause CNS stimulation and paralysis.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
      YOHIMBE

YUCCA

DATE OF ISSUE: MAR 1994

REPLACES MONOGRAPH DATED: JAN 1988

SCIENTIFIC NAME(S): *Yucca* spp. Family: Agavaceae

COMMON NAME(S): Yucca, Spanish bayonet, Our Lord's candle, Joshua tree, Adam's needle

BOTANY: The name yucca applies to as many as 40 species of trees and shrubs found mostly in arid portions of North America. The common names noted above can apply to different species. The Spanish bayonet is *Y. aloifolia* and Our Lord's candle is *Y. whipplei*.[1] Other common yuccas include *Y. schidigera* (Mohave yucca) and *Y. brevifolia* (Joshua tree), which grows to 60 feet in height and is commonly found at the bases of desert mountains. [2] Yucca plants are characterized by stiff, evergreen, sword-shaped leaves crowded on a stout trunk. There is a dense terminal flowerhead (panicle) faintly resembling a candle. The flowers are white or greenish. All yucca plants depend for pollination on nocturnal yucca moths (*Tegeticula*).[3] Each variety of moth is adapted to a single species of yucca.

HISTORY: Yucca plants have served American Indians for centuries for a variety of uses including fiber for rope, sandals and cloth; the roots have been used in soap. The Indians and early Californian settlers used the green pods for food. Indian uses included boiling and baking the fruits, eating the blossoms, chewing the raw leaves and fermenting the fruits to produce a beverage for high rituals. In modern times yucca has been used in soaps, shampoos and food supplements. Yuccas contain saponins that have a long-lasting soaping action. The plant has been purported to be beneficial for treating hypertension, arthritis, migraine headaches, colitis, and a variety of other disorders. A solid extract is derived from the leaves; [2] the Mohave yucca is the most common commercially used plant. Current commercial uses of yucca extracts include foaming agents in carbonated beverages, flavorings, and for use in drug synthesis research.

CHEMISTRY: The roots of the yucca contain saponin glycosides consisting of a sapogenin and a sugar. [4] Saponins are characterized by their bitter taste and their ability to foam when shaken with water.[1] Most species of Yucca contain sarsasapogenin and tigogenin.[2,5] Cortical cells in the roots of *Y. torreyi* have been found to contain microbodies containing crystalline nucleoid inclusions that have been identified as unspecialized peroxisomes. [6] *Y. aloifolia* leaves contain up to 1.4% tigogenin and this compound can be used as a starting point in the commercial synthesis of steroidal hormones.

PHARMACOLOGY: Aqueous alcoholic extracts of the flowers of *Y. glauca* have been shown to have antitumor activity against B16 melanoma in mice. Analysis of these extracts has identified two galactose-containing polysaccharides effective against B16 melanoma but ineffective against L1210 and P388 leukemias in mice. [7] Yucca leaf protein has been found to inhibit herpes simplex virus types 1 and 2 and human cytomegalovirus. [8] Some saponins have been shown to allow bacterial, plant and animal cells to thrive under harsh environmental conditions. However, yucca saponins do not enhance weight gain, food conversion, or digestive coefficients when fed to young turkeys.[9]

One report found that the oral administration of daily doses of a yucca saponin extract for up to 15 months was effective and well-tolerated for the treatment of various arthritic conditions.[1] However, the Arthritis Foundation found the study to be poorly controlled and designed, and the conclusions to have been based on inconsistent results.[1,10] Interestingly, the patients who received the extract for 6 months had significant reductions in blood pressure and serum cholesterol levels, and a reduction in the incidence of migraine headaches from baseline.

TOXICOLOGY: It is generally recognized that saponins are poisonous to lower forms of life, but are however, nearly nontoxic to humans when taken orally. However, their injection into the bloodstream causes hemolysis, dissolving red blood cells even if the saponins are present at extreme dilutions. This effect, however, is more pronounced in vitro than in vivo.[2] Little is known about the toxicity of yucca saponins. The effects of long-term ingestion of these saponins is not well defined. A 12-week feeding study in rats found Mohave yucca extract to be essentially nontoxic. [11]

SUMMARY: Yucca is a hardy plant native to arid areas of North America. It has long been used for a variety of purposes, including as a fiber, soap, and for consumable products. When taken orally, it appears to be relatively nontoxic. While some evidence suggests the extract may be effective in the management of arthritis, hypertension, and hypercholesterolemia, there is no published corroborative evidence. Extracts may have potential as antiviral agents.

PATIENT INFORMATION— Yucca

Uses: Yucca has been historically used as a fiber, soap, and for consumable products. Some evidence suggests the extract may be effective in the management of arthritis, hypertension, and hypercholesterolemia.

Side Effects: Little is known about the toxicity of yucca plants.

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Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Y" MONOGRAPHS
    YUCCA

"Z" MONOGRAPHS

ZINC

DATE OF ISSUE: JUL 2002

REPLACES MONOGRAPH DATED: N/A

SCIENTIFIC NAME(S): Zinc, Zn

COMMON NAME(S): Zinc

HISTORY: Zinc is an essential trace element necessary for normal human functioning. It serves as an enzyme cofactor and protects cell membranes from lysis caused by complement activation and toxin release.[1] The role of zinc in human health and functioning has primarily focused on dietary supplementation for the promotion of health and disease prevention. Aside from dietary zinc supplementation, zinc has been studied widely in a variety of disorders including atopic eczema, psoriasis, acne vulgaris, degenerative retinal lesions, age-related macular degeneration, inflammatory bowel disease, and various other disorders.[2,3,4,5,6,7] Zinc formulated as lozenges and in spray form has been used widely to treat symptoms associated with the common cold.

CHEMISTRY: Zinc is available in various salt forms, including zinc gluconate, zinc gluconate-glycine, zinc acetate, zinc ascorbate, zinc oroate, zinc citrate, zinc chloride, and zinc sulfate. Zinc gluconate, zinc gluconate-glycine, and zinc acetate have been studied most often in the lozenge form for the treatment of the common cold.

PHARMACOLOGY: Zinc lozenges and zinc spray are designed to release Zn ions in the oropharyngeal cavity. The exact mechanism of action of Zn ions is still controversial but may involve a combination of actions. According to in vitro studies, Zn ions (0.1mM) interfere with the formation of immature virus, specifically interfering with rhinoviral capsid proteins, thereby altering protease activity.[8,9,10] However, Zn ions have not been shown to affect mature rhinoviruses. The intracellular adhesion molecule-1 (ICAM-1), found on the surface of endothelial and epithelial cells, serves as a receptor for the human rhinovirus. Zn ions block human rhinovirus from binding to ICAM-1 and subsequently interferes with viral docking and the resulting inflammatory process.[11] Another mechanism for Zn may involve the inhibition of histamine release from mast cells and basophils.[12] This inhibition has led to astringent or drying effects that may be helpful in treating the rhinorrhea and lacrimation that occur during the common cold. In vitro studies suggest that zinc may also induce production of interferon. Other actions for zinc may involve nerve impulse inhibition, although more research is necessary.[13]

The efficacy for treating the common cold is based on Zn ion release characteristics. The zinc ions are activated by mouth saliva, allowing the Zn ions to be released in the respiratory passages at supra-physiologic concentrations, causing an osmotic gradient.[11] This gradient transfers Zn ions from the mouth to the nasal and mucosal passages, often referred to as a biologically closed electric circuit (BCEC), ultimately preventing rhinoviral binding and activation.[11,14] The Zn cation appears to be the most effective form of zinc necessary to interact with the electronegative cell surfaces in the oropharyngeal cavity.

Many studies have been conducted on the effects of zinc and the common cold (see Table). These studies have undergone a great deal of scrutiny from scientists and clinical researchers alike because of the variability in clinical outcomes. Many study flaws and other limitations exist, some of which are inherent to the nature of the common cold, while others involve poor study methodology. Some of the study design flaws include the following: Poor placebo matching (masking), lack of randomization information, lack of power analyses, small sample size, variations in dose, frequency of administration, time of first dose, varying patient populations, lack of patient follow-up, disparity in excipients or flavoring agents used. Other drawbacks that limit the applicability of the results involve a lack in documentation of rhinovirus infection, variations in the time of year studied and in location of study, differences in inoculum, and additional medications permitted.

Two meta-analyses have attempted to quantify the results from the various zinc lozenge trials.[25,26] One reviewed 8 randomized, double-blind, placebo-controlled clinical trials that had been published up to that time. Six of the 8 clinical trials, with a total of 540 patients, were analyzed. The 2 clinical trials that were excluded involved patients who were inoculated with the rhinovirus rather than acquiring the common cold naturally. Five of the trials used a form of zinc gluconate, while only 1 study used zinc acetate. A wide range of doses were administered, from 45 to 230 mg of elemental zinc per day (given in divided doses) every 1.5 or 2 hours while awake. In the original trials, 3 demonstrated a positive effect for zinc, and 3 showed that zinc was no better than placebo. Of the 2 trials that were excluded, 1 showed a positive benefit and the other was negative. The results of the meta-analysis showed that zinc was no more effective than placebo in reducing the signs and symptoms of the common cold.

The formulations of zinc used may have contributed to the study findings. It has been suggested that the zinc ion availability affects the ability of zinc to shorten the duration of colds because only positively charged zinc ions shorten the duration of common cold symptoms. The products used in many of the studies were analyzed and results showed that the 4 clinical trials demonstrating positive benefits had higher zinc ion availability than the 4 that did not show any benefit. In addition, some of the studies may have used inadequate doses of zinc. The excipients or inert ingredients used to formulate the zinc lozenges also may play a role. Ingredients such as sorbitol, mannitol, and citric acid might inactivate the zinc ion release characteristics. The most difficult issue with zinc lozenges involves blinding (masking). Many of the zinc formulations had a unique and often astringent-like taste, affecting blinding. The doses used in the clinical trials also varied greatly, and study lengths ranged from 6 days to an arbitrary time when the patient's cold symptoms resolved. In some cases, the duration of therapy lasted up to 14 days. The presence of allergies, which often can cause similar symptoms as the common cold, were not addressed.

Another double-blind, placebo-controlled study examined the effects of zinc acetate 9 mg taken for 14 days in 101 allergy-tested patients with symptoms of the common cold.[27] Subjects were instructed to use 1 lozenge every 1.5 hours while awake during the first day, then one lozenge every 2 hours while awake on the following days while symptoms were present. Lozenge use was to stop 6 hours after symptoms resolved. All patients were allergy tested because the common cold and nasal allergies cause many of the same symptoms. The authors found that the mean duration of symptoms was shorter in the zinc group with an average of 3.8 days compared with the placebo group, which had a mean of 5.1 days. For individual symptoms, only nasal drainage and nasal congestion were less in the zinc compared with the placebo group. The results also showed significant differences in symptom reduction between allergy and nonallergy suffers. Patients with allergies who received zinc had the shortest duration of nasal drainage (mean, 3.5 days) than those without allergies receiving zinc (mean, 4.7 days). The authors concluded that zinc acetate lozenges may shorten the duration of common cold symptoms and may relieve the symptoms associated with allergies.[27]

The original meta-analysis of clinical trials involving zinc was updated by the same researchers to include the 2 new clinical trials discussed above. Despite the new clinical trials, the authors came to a similar conclusion on the lack of evidence to support the use of zinc for the treatment of the common cold. However, these authors did not assess or comment on the differences in outcomes related to the formulation used.[26]

Zinc also has been formulated as a nasal gel administered via a nasal spray (the manufacturer describes the product as a nasal pump).[28] One clinical trial has been published. The study was a randomized, double-blind, placebo-controlled trial that examined the effects of zinc gluconate nasal gel on the duration and severity of common cold symptoms. One hundred eight patients were assigned to the zinc group and 105 to the placebo. The patients were instructed to begin using the spray within 24 hours of the onset of cold symptoms. They were further instructed to spray 1 dose into each nostril every 4 hours for as long as they experienced cold symptoms. The zinc nasal gel reduced the duration of cold symptoms, with the average symptom duration of 2.3 days in the zinc group vs 9.8 days in the placebo. The only side effect reported equally between the zinc and placebo group was a slight tingling or burning sensation.

One randomized, double-blind, placebo-controlled trial evaluated the effectiveness of zinc nasal spray for the treatment of the common cold in 160 patients.[29] Patients presenting with the symptoms of the common cold were included in the study. The zinc nasal spray used in this study contained 0.12% zinc (as zinc sulfate heptahydrate). Patients were instructed to administer 2 inhalations into each nostril 4 times daily until the symptoms resolved, up to a maximum of 14 days. Acetaminophen and multivitamins were allowed during the study. After the treatment period, there were no differences in the time to symptom resolution or cold duration; however, the zinc group had a lower symptom score compared with placebo.

The efficacy of zinc nasal spray appears similar to that of oral zinc lozenges, although zinc lozenges have been studied to a greater extent than zinc nasal spray. More research is needed to determine the best zinc formulation and method of administration in the common cold. Currently both oral lozenges and nasal spray appear equally effective.

Zinc lozenges have not been studied for other viral infections such as respiratory syncytial virus or influenza A or B. Oral dietary supplements and multivitamins that contain zinc are not able to release zinc in the oropharyngeal passages in a similar way as lozenges and therefore should not be used to treat the common cold in the same manner. Conversely, zinc lozenges should not be used to replace or fortify elemental zinc in the diet.

Wound healing: Wound healing involves many repair processes including adequate amounts of certain micronutrients. Vitamins A and C as well as metals such as copper, manganese, and zinc also are important. These micronutrients are often given to patients following surgery to help speed the wound healing process. Specifically, nutritional zinc deficiency has been associated with decreased wound healing by damaging epidermal cells and altering polymorphonuclear cell function, natural killer cell function, and complement activity. [30,31,32] Topical application of zinc oxide has been shown to stimulate the healing of wounds by reducing the inflammatory reaction that occurs in granulation tissue. This process can speed up the healing by causing re-epithelialization of the wound by increasing insulin growth factor-1 mRNA in the granulation tissue.[33] Zinc also appears to block a family of enzymes called matrix metalloproteinases (MMPs). These enzymes are responsible for degrading extracellular proteins and are thought to destroy collagen, elastin, and other key components within the dermal layers that are essential to wound healing. Two metalloproteinases called MMP-2 and MMP-9 are present in the granulation tissue during wound healing. MMP-9 appears to have greatest activity in the wound up to 7 days following acute cutaneous injury. [34] By blocking these enzymes, the wound is able to undergo re-epithelialization sooner, allowing for a more rapid healing time. Much of the research for wound healing has involved topical zinc preparations, although oral zinc is used more often clinically. [35] Oral zinc is routinely given to patients pre- and postoperatively to aid in surgical wound healing time. Two authoritative reviews have recently found no evidence to support the role of oral zinc sulfate in healing chronic venous ulcers. [36,37] Despite the lack of support for zinc in chronic venous ulcers, it is reasonable to replace any micronutrient deficiencies in order to ensure adequate wound healing. This is especially important in patients with diabetes, organ transplants, or other conditions that suppress the immune system.

TOXICOLOGY: The most common side effects reported in clinical trials for zinc lozenges were nausea, bad taste, diarrhea, vomiting, mouth irritations, and mouth sores. For the zinc spray, nasal irritation and throat irritation were reported most often. Long-term safety and efficacy have not been established. While no serious acute or chronic toxicity has been observed with zinc lozenges, they should not be used for more than 14 days because zinc is a trace metal that acts as an effective copper chelator. With high dose, chronic use (6 to 8 weeks), oral zinc has led to severe copper deficiencies causing anemia, neutropenia, and other consequences. [38]

SUMMARY: Approximately 13 studies have examined the efficacy of zinc gluconate lozenges 45 to 207 mg/day, zinc acetate lozenges 80 to 100 mg/day, and zinc gluconate nasal gel. Six of the trials have shown negative results and 7 have shown positive results. Symptoms resolved within 1.5 to 4.5 days for the zinc products, compared with 5.1 to 9.8 days in the placebo group. Lozenges should be taken every 1 to 2 hours while awake, while the gel should be used 4 times daily. Zinc products should be used at the first sign of a cold or within approximately 24 to 48 hours. Zinc products should be taken for no longer than 7 to 10 days (maximum 14 days) or taken until 6 hours after cold symptoms resolve. Side effects are generally mild but can lead to intolerance and discontinuation. Some patients may develop a bad taste, nausea, vomiting, diarrhea, and mouth sores. There is also a formulation issue with zinc products, because studies have shown that zinc ion availability and inactive ingredients may be important determinants for zinc efficacy. Despite concern about the possibility of resistance occurring and the unknown effects of long-term use, the short-term use of zinc appears to be safe in otherwise healthy adults.

PATIENT INFORMATION— Zinc

Uses: Zinc has been used in the treatment of common cold symptoms and in wound healing.

Interactions: None reported to date. Absorption from the lozenges and spray are probably not sufficient to cause any clinically relevant drug interactions.

Side Effects: The most common side effects of zinc lozenges are nausea, bad taste, diarrhea, vomiting, mouth irritation, and, rarely, mouth sores. Nasal irritation and throat irritation may occur with the zinc spray.

Dosing: For the treatment of the common cold, zinc lozenges (between 10 to 24 mg elemental zinc) should be taken every 1 to 2 hours while awake until cold symptoms resolve. Zinc lozenges should not be used for more than 14 days. Zinc nasal spray is used 4 times daily until symptoms resolve.

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Z" MONOGRAPHS
    ZINC
    DATE OF ISSUE

Summary of Clinical Trials: Zinc Lozenges and the Common Cold

Author/Study design	Sample size	Patient population	Duration of symptoms	Dose/Excipient(s)	Initiation/Duration of treatment
Eby, et al[15] R*, DB, PC	N = 65 ZG = 37 P = 28	Community-acquired (autumn)	= 3 days	Adults: 46 mg initially, then 23 mg every 2 hours while awake Max: 12/day Children (< 27 kg): 11.5 mg every 2 hours while awake Max: 6/day	Within 3 days/until symptom free for 6 hours
Al-Nakib, et al[16] R*, DB, PC	PS N = 57 ZG = 29 P = 28 TS N = 12 ZG = 6 P = 6	HRV-2 10^2 $TCID_{50}$ inoculation	N/A	PS: Adults: 23 mg every 2 hours while awake Max: 12/day TS: Adults: 23 mg every 2 hours while awake Max: 12/day	PS: 24 hours prior to inoculation; continued for 3.5 days after inoculation TS: 6 days
Farr , et al[17] R*, DB, PC	T1: N = 32 ZG = 16 P = 16 T2: N = 41 ZG = 21 P = 20	T1: RV-39 inoculation T2: RV-13 inoculation	N/A	T1: Adults: 46 mg initially, then 23 mg every 2 hours while awake Max: 8/day (Citric acid) T2: Adults: 23 mg every 2 hours while awake Max: 8/day (Citric acid)	T1: 36 hours after inoculation; continued for 5 days T2: 2 hours after inoculation; continued for 7 days
Douglas, et al[18] R*, DB, PC	N = 55 ZA = 35 P = 35	Community- acquired	Two symptoms for 1 day or 1 symptom for 2 days	Adults: 10 mg every 2 hours while awake Max: 6 to 8/day (Tartaric acid)	Duration 3 to 6 days
Smith, et al[19] R*, DB, PC	N = 110 ZG = 57 P = 53	Community-acquired (spring)	Not stated	Adults: 4 lozenges (11.5 mg each) initially then 2 every 2 hours while awake (Mannitol/Sorbitol)	Duration 7 days or 24 hours after symptom disappearance
Weismann, et al[20] R, DB, PC	N = 130 ZG = 61 P = 69	Community-acquired (spring and winter)	At symptom onset	Adults: 1 lozenge (4.5 mg) every 1 to 1.5 hours while awake Max: 10/day	Duration of cold up to 10 days
Godfrey, et al[14] R*, DB, PC	N = 73 ZGG = 35 P = 38	Community-acquired	= 2 days	Adults: One 23.7 mg lozenge every 2 hours while awake Max: 8/day	Duration of cold/complete elimination of symptoms
Mossad, et al[21] R, DB, PC	N = 99 ZGG = 49 P = 50	Community- acquired (autumn)	= 24 hours	Adults: 13.3 mg every 2 hours while awake	Duration of cold symptoms
Macknin, et al[22] R, DB, PC	N = 249 ZGG = 117 P = 122	Community- acquired (winter)	= 24 hours	Children (grades 1 to 6): 10 mg 5 times/day Children (grades 7 to 12): 10 mg 6 times/day	Symptom resolution for 6 hours
Prasad, et al[23] R, DB, PC	N = 48 ZA = 25 P = 23	Community acquired (year-round)	= 24 hours	Adults: 12.8 mg every 2 to 3 hours while awake	Duration of cold symptoms

Turner, et al[24] R, DB, PC	Study 1: N = 281 ZG = 68 ZA = 72 ZA = 68 P = 71 Study 2: N = 273 ZG = 69 ZA = 66 ZA = 70 P = 67	Community- acquired (year-round) Inoculated with RV-39	= 36 hours 24 hours after challenge if symptoms present	Adults: ZG 13.3 mg ZA 5 mg ZA 11.5 mg Every 2 to 3 hours while awake Max 6/day Adults: ZG 13.3 mg ZA 5 mg ZA 11.5 mg Every 2 to 3 hours while awake Max: 6/day	Until symptoms resolved up to 14 days

R = Random allocation and selection
R* = Random allocation
DB = Double-blind
PC = Placebo-controlled
CO = Crossover

PS = Prophylactic study
TS = Therapeutic study
ZG = Zinc gluconate
ZGG = Zinc gluconate-glycine
ZA = Zinc acetate
HRV-2 = Human rhinovirus 2

$TCID_{50}$ = Tissue culture-infecting dose
P = Placebo
RV = Rhinovirus
T1 = Trial 1
T2 = Trial 2

Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    "Z" MONOGRAPHS
    ZINC
    TABLE 1: SUMMARY OF CLINICAL TRIALS: ZINC LOZENGES AND THE COMMON COLD

APPENDIX

POTENTIAL HERB-DRUG INTERACTIONS

DATE OF ISSUE: NOV 2002

REPLACES MONOGRAPH DATED: DEC 2000

INTRODUCTION

With the exception of a few herbal products (eg, grapefruit juice), most documentation regarding potential interactions between natural products and drugs in humans is based on case reports and often lacks relevant information. Evaluating these reports is difficult because of medications the patient may be receiving concurrently or because of the presence of comorbidity. In addition, the lack of herbal product standardization, purity, and potency, as well as multiple ingredients in products, product adulteration, misidentification, and batch-to-batch variations in crop conditions and yield complicate the assessment of drug interactions with herbs. The absorption, metabolism, distribution, and elimination characteristics and physiologic effects of most herbal products are poorly understood. Until this information is available, many herb-drug interactions remain speculative and one cannot predict the clinical outcome of potential interactions. Take special care when considering the use of natural products in patients taking drugs with a narrow therapeutic index. Ask patients experiencing adverse reactions if they are using herbal products, especially if the reaction cannot be attributed to another cause.

Because herb-drug interactions are sporatically reported and epidemiologically derived, practictioners should report any potential interactions to the Food and Drug Administration through its MedWatch program by phone at 1-800-FDA-1088 or via the Internet at http://www.accessdata.fda.gov/scripts/medwatch/.

Potential Herb-Drug Interactions

Herbal Product: Artemether
Drug or Drug Class: Grapefruit
Potential Interaction:
Documentation: Noncontrolled trial.[1]
Effect: Grapefruit juice may increase the bioavailability of artemether.
Management: No special precautions are necessary.

Herbal Product: Ascorbic Acid (Vitamin C)
Drug or Drug Class: Propranolol
Potential Interaction:
Documentation: Noncontrolled trial.[2]
Effect: The pharmacologic effects of propranolol may be decreased.
Management: No special precautions are necessary with usual doses of ascorbic acid. Advise patients taking propranolol to avoid excessive amounts of ascorbic acid (> 500 mg/day).

Herbal Product: Avocado
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports.[3]
Effect: Decreased anticoagulant effect of warfarin.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent ingestion of avocado.

Herbal Product: Betel Nut
Drug or Drug Class: Procyclidine
Potential Interaction:
Documentation: Case reports.[4]
Effects: The risk of occurrence of extrapyramidal symptoms may be increased.
Management: Avoid concurrent use.

Herbal Product: Bitter Melon
Drug or Drug Class:
Potential Interaction: See Karela.

Herbal Product: Boldo
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case report.[5]
Effect: Enhanced anticoagulant effect of warfarin, increasing the risk of bleeding.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Broccoli
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Controlled trial and case reports.[6,7]
Effect: The anticoagulant effect of warfarin may be antagonized.
Management: Because warfarin has a narrow therapeutic index, patients receiving warfarin should avoid ingestion of large daily amounts of broccoli.

Herbal Product: Caffeine
Drug or Drug Class: Clozapine
Potential Interaction:
Documentation: Controlled trial and case reports.[8,9,10,11]
Effect: Elevated clozapine plasma levels, which may increase the risk of side effects.
Management: Substantial fluctuations in caffeine intake may affect the response to clozapine. Adverse responses are most likely in patients drinking more than 4 cups of caffeinated coffee daily or who ingest large quantities of caffeine (ie, more than 400 mg/day) from other sources.
Drug or Drug Class: Lithium
Potential Interaction:
Documentation: Noncontrolled trial and case reports.[12,13]
Effect: Decreased lithium serum levels, which may decrease the therapeutic effect.
Management: Inform patients who ingest large amounts of caffeine (ie, at least 4 cups of coffee daily)to inform their physician or pharmacist before eliminating caffeine and to avoid large fluctuations in their caffeine intake.
Drug or Drug Class: Theophylline
Potential Interaction:
Documentation: Open-label study in healthy volunteers.[14]
Effect: Elevated plasma theophylline levels, increasing the risk of toxicity.
Management: Advise patients to avoid drastic fluctuations in their daily caffeine intake.

Herbal Product: Capsaicin
Drug or Drug Class: ACE Inhibitors (eg, captopril)
Potential Interaction:
Documentation: Controlled study (capsaicin inhalation) and case report (capsaicin topical). [15,16]
Effect: Increased risk of cough.
Management: Avoid concomitant use.

Herbal Product: Coenzyme Q10
Drug or Drug Class:
Potential Interaction: See Ubiquinone.

Herbal Product: Cucurbita
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports.[17]
Effect: Increased anticoagulant effect of warfarin.
Management: No special precautions are necessary.

Herbal Product: Danshen
Drug or Drug Class: Digoxin
Potential Interaction:
Documentation: Controlled trial.[18]
Effect: Digoxin plasma levels measured by the fluorescence polarization immunoassay may be falsely elevated and levels measured by the microparticle enzyme immunoassay may be falsely decreased.
Management: No special precautions are warranted. Use the ultrafiltration technique to measure digoxin plasma levels. Monitor free digoxin levels.
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports.[19,20,21]
Effect: Increased anticoagulant effect of warfarin.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Dong Quai
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case report.[22]
Effect: Increased anticoagulant effect of warfarin.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Eleutherococcus (Siberian Ginseng)
Drug or Drug Class: Digoxin
Potential Interaction:
Documentation: Case report.[23]
Effect: Falsely elevated digoxin serum assay or increased digoxin plasma levels.
Management: Because digoxin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Fenugreek
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case report.[5]
Effect: The anticoagulant effect of warfarin may be enhanced, increasing the risk of bleeding.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Fiddleheads
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case report.[24]
Effect: The anticoagulant effect of warfarin may be antagonized.
Management: Because warfarin has a narrow therapeutic index, question patients about their food and beverage consumption. Avoid ingestion of large daily amounts of fiddleheads.

Herbal Product: Garlic
Drug or Drug Class: Saquinavir
Potential Interaction:
Documentation: Controlled trial.[25]
Effect: Reduced saquinavir plasma levels, decreasing the pharmacologic effects.
Management: Avoid concurrent use.
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Based on inhibition of platelet aggregation in individuals ingesting garlic. [26,27,28,29,30,31,32]
Effect: The risk of bleeding may be increased.
Management: No special precautions are necessary.

Herbal Product: Ginger
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Based on inhibition of platelet aggregation in individuals ingesting ginger. [33,34,35,36]
Effect: The risk of bleeding may be increased.
Management: No special precautions are necessary.

Herbal Product: *Ginkgo biloba*
Drug or Drug Class: Aspirin
Potential Interaction:
Documentation: Case report.[37,38]
Effect: Increased risk of bleeding.
Management: Avoid concurrent use.
Drug or Drug Class: Nifedipine
Potential Interaction:
Documentation: Controlled trial.[39]
Effect: Elevated nifedipine plasma levels, which may increase the pharmacologic and adverse effects.
Management: Avoid concurrent use.

Drug or Drug Class: Trazodone
Potential Interaction:

Documentation: Case report.[40]
Effect: Increased risk of sedation.
Management: Avoid concurrent use.
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Case reports.[41],[42],[43]
Effect: Increased risk of bleeding.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Ginseng
Drug or Drug Class: Furosemide
Potential Interaction:

Documentation: Case report.[44]
Effect: Decrease in diuretic effect of furosemide.
Management: Avoid concurrent use.
Drug or Drug Class: Nifedipine
Potential Interaction:

Documentation: Controlled trial.[39]
Effect: Elevated nifedipine plasma levels, which may increase the pharmacologic and adverse effects.
Management: Avoid concurrent use.
Drug or Drug Class: Phenelzine
Potential Interaction:

Documentation: Case reports.[45],[46]
Effect: Manic-like symptoms, headache, and tremulousness have been reported.
Management: Avoid concurrent use.
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Case report.[47]
Effect: Anticoagulant effect of warfarin may be decreased.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Ginseng, Siberian
Drug or Drug Class:
Potential Interaction: See Eleutherococcus.

Herbal Product: Glycyrrhizin
Drug or Drug Class:
Potential Interaction: See Licorice.

Herbal Product: Grapefruit Juice
Drug or Drug Class: Amlodipine
Potential Interaction:

Documentation: Controlled trials.[48],[49]
Effect: Elevated amlodipine serum levels, increasing the pharmacologic and adverse effects.
Management: Avoid simultaneous administration. However, patients who routinely drink grapefruit juice may have been stabilized on a higher than usual dose and should not abruptly stop drinking grapefruit juice.
Drug or Drug Class: Amprenavir
Potential Interaction:

Documentation: Controlled trial.[50]
Effect: Amprenavir peak levels may be slightly decreased.
Management: No special precautions are necessary.
Drug or Drug Class: Benzodiazepines (ie, midazolam, triazolam)
Potential Interaction:

Documentation: Controlled trials and product information.[51],[52],[53],[54],[55],[56],[57]
Effect: Pharmacologic effects may be increased and onset delayed.
Management: Avoid coadministration. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Buspirone
Potential Interaction:

Documentation: Controlled trial.[58]
Effect: Elevated plasma levels of buspirone, increasing the pharmacologic and adverse effects.
Management: Avoid concomitant use. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Carbamazepine
Potential Interaction:

Documentation: Controlled trial.[59]
Effect: Carbamazepine plasma levels may be elevated, increasing the pharmacologic and adverse effects.
Management: Avoid concomitant ingestion. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Cisapride (available from the manufacturer on a limited-access protocol)
Potential Interaction:

Documentation: Controlled trials.[60],[61],[62]
Effect: Elevated cisapride plasma levels with increased risk of adverse effects, including life-threatening cardiac arrhythmias (eg, torsades de pointes).
Management: Cisapride is contraindicated in patients receiving grapefruit juice.
Drug or Drug Class: Clomipramine
Potential Interaction:

Documentation: Case reports.[63]
Effect: Elevated plasma levels of clomipramine and reduced levels of the desmethylclomipramine, which may improve outcome in treatment of obsessive-compulsive disorders.
Management: Avoid concurrent use unless coadministration of clomipramine and grapefruit juice is being used to improve symptom control of obsessive-compulsive disorder.
Drug or Drug Class: Cyclosporine
Potential Interaction:

Documentation: Controlled trials, noncontrolled trials, case reports, and product information.[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76]
Effect: Trough cyclosporine whole blood concentrations may be elevated, increasing the risk of toxicity.
Management: Because cyclosporine has a narrow therapeutic index, avoid concurrent use.
Drug or Drug Class: Digoxin
Potential Interaction:

Documentation: Controlled trial.[77]
Effect: Digoxin plasma levels may be slightly elevated.
Management: No special precautions are warranted.

Drug or Drug Class: Erythromycin
Potential Interaction:

Documentation: Controlled trial.[78]
Effect: Erythromycin plasma levels may be elevated, increasing the risk of side effects.
Management: Avoid taking erythromycin with grapefruit products. Take erythromycin with a liquid other than grapefruit juice.
Drug or Drug Class: Estrone
Potential Interaction:

Documentation: Controlled trial.[79]
Effect: Estrone serum levels may be increased.
Management: The effect of grapefruit or grapefruit juice ingestion on estrone is unlikely to result in a clinically important interaction.
Drug or Drug Class: Ethinyl Estradiol
Potential Interaction:

Documentation: Controlled trial.[80]
Effect: Ethinyl estradiol serum levels may be increased.
Management: Advise patients to avoid grapefruit and grapefruit juice while taking ethinyl estradiol.
Drug or Drug Class: HMG-CoA Reductase Inhibitors (ie, atorvastatin, lovastatin, simvastatin)
Potential Interaction:

Documentation: Controlled trials.[81,82,83,84,85]
Effect: The AUC and elimination half-life of atorvastatin may be increased. Lovastatin and simvastatin plasma levels may be elevated, increasing the risk of side effects (eg, rhabdomyolysis).
Management: Take with a liquid other than grapefruit juice.
Drug or Drug Class: Indinavir
Potential Interaction:

Documentation: Controlled trial and product information.[86,87]
Effect: Taking indinavir with grapefruit juice may delay the time to reach indinavir peak plasma concentrations.
Management: Because indinavir is a substrate for CYP3A4 and grapefruit inhibits CYP3A4, patients taking indinavir should avoid chronic ingestion of grapefruit products.
Drug or Drug Class: Itraconazole
Potential Interaction:

Documentation: Controlled trials.[88,89] Data are conflicting.
Effect: Plasma levels and therapeutic effects of itraconazole may be decreased.
Management: Avoid coadministration. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Losartan
Potential Interaction:

Documentation: Controlled trial.[90]
Effect: The rate and magnitude of losartan metabolism to its major active metabolite may be decreased.
Management: Advise patients to take losartan with a liquid other than grapefruit juice.
Drug or Drug Class: Nicardipine
Potential Interaction:

Documentation: Controlled trial.[91]
Effect: Nicardipine plasma levels may be elevated, increasing the pharmacologic and adverse effects.
Management: Avoid grapefruit products and take nicardipine with a liquid other than grapefruit juice.
Drug or Drug Class: Nisoldipine
Potential Interaction:

Documentation: Controlled trials.[92,93,94]
Effect: Elevated plasma levels of nisoldipine, increasing the pharmacologic and adverse effects.
Management: Avoid coadministration. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Praziquantel
Potential Interaction:

Documentation: Controlled trial.[95]
Effect: Elevated praziquantel plasma levels, increasing the pharmacologic and adverse effects.
Management: Avoid taking praziquantel with grapefruit products. Take praziquantel with a liquid other than grapefruit juice.
Drug or Drug Class: Quinidine
Potential Interaction:

Documentation: Controlled trials.[53,96,97]
Effect: The onset of action of quinidine may be delayed.
Management: Avoid coadministration. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Saquinavir
Potential Interaction:

Documentation: Controlled trials and product information.[98,99,100]
Effect: Elevated plasma levels of saquinavir, increasing the pharmacologic and adverse effects.
Management: Avoid coadministration. Take with a liquid other than grapefruit juice.
Drug or Drug Class: Scopolamine
Potential Interaction:

Documentation: Controlled trial.[101]
Effect: Scopolamine absorption may be delayed and bioavailability may be increased.
Management: No special precautions are needed.
Drug or Drug Class: Sildenafil
Potential Interaction:

Documentation: Controlled trial and case report.[102,103]
Effect: Sildenafil plasma levels may be increased and absorption delayed.
Management: A clinically important interaction is unlikely; however, it would be prudent to take sildenafil with a liquid other than grapefruit juice.
Drug or Drug Class: Verapamil
Potential Interaction:

Documentation: Controlled trial.[104]
Effect: Verapamil plasma concentrations may be elevated, increasing the pharmacologic and adverse effects.
Management: Avoid grapefruit products. Take with a liquid other than grapefruit juice.

Herbal Product: Green Tea
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Case report.[105]
Effect: The anticoagulant effect of warfarin may be antagonized.
Management: Because warfarin has a narrow therapeutic index, question patients about food and beverage consumption. Avoid ingestion of large amounts (more than 4 cups/day)of green tea.

Herbal Product: Guar Gum
Drug or Drug Class: Metformin
Potential Interaction:

Documentation: Controlled trials.[106,107]

Effect: Metformin serum levels may be reduced, decreasing the hypoglycemic effect.
Management: No special precautions are necessary.

Herbal Product: Ispaghula
Drug or Drug Class: Lithium
Potential Interaction:

Documentation: Case report.[108]
Effect: Possible decrease in lithium absorption, reducing the pharmacologic effect.
Management: Avoid concomitant use.

Herbal Product: Karela
Drug or Drug Class: Chlorpropamide
Potential Interaction:

Documentation: Case report.[109]
Effect: A greater than expected hypoglycemic response may occur.
Management: Avoid concurrent use of karela and chlorpropamide.

Herbal Product: Kava
Drug or Drug Class: Alprazolam
Potential Interaction:

Documentation: Case report.[110]
Effect: CNS side effects may be increased.
Management: It would be prudent to avoid concurrent use.

Herbal Product: Khat
Drug or Drug Class: Penicillins (ie, amoxicillin, ampicillin)
Potential Interaction:

Documentation: Noncontrolled trial.[111]
Effect: Antimicrobial effectiveness may be reduced.
Management: Avoid khat chewing or take the penicillin 2 hours after khat chewing.

Herbal Product: Licorice (Glycyrrhizin)
Drug or Drug Class: Prednisolone
Potential Interaction:

Documentation: Controlled trials.[117,118,119]
Effect: Prednisolone plasma levels may be elevated, increasing the pharmacologic and adverse effects.
Management: Avoid excessive ingestion of licorice-containing products while taking prednisolone.

Herbal Product: Lime Juice
Drug or Drug Class: Felodipine
Potential Interaction:

Documentation: Controlled trial.[120]
Effect: Elevated felodipine serum levels, increasing the pharmacologic and adverse efffects.
Management: Until more clinical data are available, it would be prudent to avoid lime juice while taking felodipine.

Herbal Product: *Lycium barbarum* L.
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Case report.[121]
Effect: The anticoagulant effect of warfarin may be increased.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Mango
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Noncontrolled trial.[122]
Effect: Increased anticoagulant effect of warfarin.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Melatonin
Drug or Drug Class: Fluvoxamine
Potential Interaction:

Documentation: Noncontrolled trials.[123,124,125]
Effect: Elevated plasma levels of melatonin, increasing the effects (eg, drowsiness).
Management: No special precautions are necessary.
Drug or Drug Class: Nifedipine
Potential Interaction:

Documentation: Controlled trial.[126]
Effect: Interference with antihypertensive effect, which may increase blood pressure.
Management: Avoid concurrent use. If melatonin use cannot be avoided, it may be necessary to adjust the nifedipine dose when starting or stopping melatonin.

Herbal Product: Milk Thistle
Drug or Drug Class: Indinavir
Potential Interaction:

Documentation: Controlled trial.[127]
Effect: Pharmacologic effects of indinavir may be decreased.
Management: A clinically important interaction is unlikely; however, be prepared to make appropriate changes in dosage if there is evidence of a decrease in virologic effect.

Herbal Product: Oat Bran
Drug or Drug Class: Lovastatin
Potential Interaction:

Documentation: Noncontrolled trial.[128]
Effect: The pharmacologic effect of lovastatin may be decreased.
Management: Do not take oat bran and lovastatin at the same time. If both must be taken, separate oat bran ingestion and lovastatin administration by as much time as possible.

Herbal Product: Orange Juice
Drug or Drug Class: Fexofenadine
Potential Interaction:

Documentation: Controlled trial.[129]

Effect: Fexofenadine plasma levels may be decreased, reducing the clinical effect.
Management: A higher dose of fexofenadine may be required when taken with orange juice. Take with a liquid other than orange juice.
Drug or Drug Class: Itraconazole
Potential Interaction:
Documentation: Controlled trial.[89]
Effect: Plasma levels and therapeutic effects of itraconazole may be reduced.
Management: Avoid coadminstration. Take with a liquid other than orange juice.

Herbal Product: Orange Juice (calcium fortified)
Drug or Drug Class: Ciprofloxacin
Potential Interaction:
Documentation: Controlled trial.[130]
Effects: Ciprofloxacin plasma levels may be reduced, decreasing the clinical effect.
Management: Avoid concurrent use.

Herbal Product: Pectin
Drug or Drug Class: Lovastatin
Potential Interaction:
Documentation: Noncontrolled trial.[128]
Effect: Decreased pharmacologic effect of lovastatin.
Management: Avoid concurrent use. If concomitant use cannot be avoided, separate pectin ingestion and lovastatin administration by as much time as possible.

Herbal Product: Peppermint Oil
Drug or Drug Class: Felodipine
Potential Interaction:
Documentation: Controlled trial.[131]
Effect: Elevated felodipine serum levels, increasing the pharmacologic and adverse effects.
Management: Avoid concurrent use.
Drug or Drug Class: Simvastatin
Potential Interaction:
Documentation: Controlled trial.[131]
Effect: Elevated simvastatin serum levels, increasing the pharmacologic and adverse effects.
Management: Avoid concurrent use.

Herbal Product: Plantain (Psyllium)
Drug or Drug Class: Lithium
Potential Interaction:
Documentation: Case report.[108]
Effect: Lithium plasma levels may be reduced, decreasing the pharmacologic efficacy.
Management: Avoid coadministration.

Herbal Product: Psyllium
Drug or Drug Class:
Potential Interaction: See Plantain.

Herbal Product: Quinine
Drug or Drug Class: Amantadine
Potential Interaction:
Documentation: Controlled trials.[132,133]
Effect: Elevated amantadine levels in men but not women, increasing the risk of toxicity in men.
Management: Although the effect of drinking quinine beverages on amantadine levels has not been assessed, it would be prudent to limit quinine ingestion during amantadine administration.
Drug or Drug Class: Carbamazepine
Potential Interaction:
Documentation: Controlled trials.[133,134]
Effect: Elevated carbamazepine plasma levels, increasing the pharmacologic and adverse effects.
Management: Although the effect of quinine in tonic beverages has not been assessed, it would be prudent to limit quinine ingestion during carbamazepine administration.
Drug or Drug Class: Digoxin
Potential Interaction:
Documentation: Controlled studies using prescription doses of quinine (ie, at least 200 mg). [133,134,135,136,137,138,139]
Effect: Elevated digoxin levels, increasing the risk of digoxin toxicity. However, studies have not reported digoxin toxicity.
Management: If used concurrently, it may be necessary to decrease the dose of digoxin. Closely monitor the patient and digoxin serum levels. However, the effect of quinine in tonic beverages has not been assessed. Until studied, it would be prudent to limit quinine ingestion during digoxin administration.
Drug or Drug Class: Phenobarbital
Potential Interaction:
Documentation: Controlled trials.[133,134]
Effect: Elevated phenobarbital plasma levels, increasing the pharmacologic and adverse effects.
Management: Although the effect of drinking quinine beverages has not been assessed, it would be prudent to limit quinine ingestion during phenobarbital administration.
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports of excessive hypoprothrombinemia and bleeding during concurrent use.[140,141]
Effect: Increased anticoagulant activity, increasing the risk of bleeding.
Management: Closely monitor anticoagulant parameters and adjust the warfarin dose as needed.

Herbal Product: Saw Palmetto
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports.[17]
Effect: The anticoagulant effect of warfarin may be increased.
Management: No special precautions are necessary.

Herbal Product: Seaweed
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case report.[142]
Effect: The anticoagulant effect of warfarin may be antagonized.
Management: Because warfarin has a narrow therapeutic index, advise patients receiving warfarin to avoid ingestion of large amounts of vitamin K-containing seaweed.

Herbal Product: Spinach
Drug or Drug Class: Warfarin
Potential Interaction:

Documentation: Controlled trials.[6,7]
Effect: The anticoagulant effect of warfarin may be antagonized.
Management: Because warfarin has a narrow therapeutic index, advise patients receiving warfarin to avoid ingestion of large daily amounts of spinach.

Herbal Product: St. John's Wort (See Appendix: "Potential Drug Interactions with St. John's Wort" for additional interactions.)
Drug or Drug Class: Amitriptyline
Potential Interaction:

Documentation: Noncontrolled trial.[143]
Effect: Amitriptyline plasma levels may be reduced, decreasing the pharmacologic effects.
Management: If use of St. John's wort cannot be avoided, assess the patient's clinical response to amitriptyline when St. John's wort is started or stopped. Adjust the amitriptyline dose as needed.
Drug or Drug Class: Contraceptives, Oral
Potential Interaction:

Documentation: Case report.[144]
Effect: The efficacy of oral contraceptives may be reduced.
Management: Inform women of increased risk of oral contraceptive failure with concomitant use of St. John's wort. If use of St. John's wort cannot be avoided, consider an alternative nonhormonal contraceptive or an additional method of contraception.
Drug or Drug Class: Cyclosporine
Potential Interaction:

Documentation: Case reports.[145,146,147,148,149,150]
Effect: Cyclosporine levels may be reduced, resulting in organ transplant rejection.
Management: Because cyclosporine has a narrow therapeutic index, avoid St. John's wort.
Drug or Drug Class: Digoxin
Potential Interaction:

Documentation: Controlled trial and noncontrolled trial.[151,152]
Effect: Decreased digoxin plasma levels and clinical efficacy.
Management: If use of St. John's wort cannot be avoided, the patient's response to digoxin should be assessed when St. John's wort is started or stopped. Monitoring digoxin plasma levels may be useful.
Drug or Drug Class: Fexofenadine
Potential Interaction:

Documentation: Noncontrolled trials.[153,154]
Effect: Fexofenadine plasma levels may be reduced, decreasing the pharmacologic effect. Increased fexofenadine concentrations have been reported after a single dose of St. John's wort.
Management: If use of St. John's wort cannot be avoided, assess the patient's clinical response to fexofenadine when St. John's wort is started or stopped. Adjust the fexofenadine dose as needed.
Drug or Drug Class: Indinavir
Potential Interaction:

Documentation: Noncontrolled trial and product information.[155,156]
Effect: Indinavir plasma levels may be reduced, decreasing the clinical efficacy.
Management: Avoid coadministration.
Drug or Drug Class: Midazolam
Potential Interaction:

Documentation: Controlled trial and noncontrolled trial.[153,157]
Effect: Midazolam plasma levels may be reduced, decreasing the pharmacologic effect.
Management: If use of St. John's wort cannot be avoided, assess the patient's clinical response to midazolam when St. John's wort is started or stopped. Adjust the midazolam dose as needed.
Drug or Drug Class: Nefazodone
Potential Interaction:

Documentation: Case report.[158]
Effect: A "serotonin syndrome"(eg, CNS irritability, shivering, myoclonus, altered consciousness) may occur.
Management: Avoid concurrent use. Patients taking nefazodone should inform their physician or pharmacist before taking St. John's wort.
Drug or Drug Class: Nevirapine
Potential Interaction:

Documentation: Case reports.[159]
Effect: Nevirapine plasma levels may be reduced, decreasing the clinical efficacy.
Management: Avoid coadministration of nevirapine and St. John's wort.
Drug or Drug Class: Nifedipine
Potential Interaction:

Documentation: Controlled trial.[39]
Effect: Nifedipine plasma levels may be reduced, decreasing the pharmacologic effects.
Management: If use of St. John's wort cannot be avoided, assess the patient's clinical response to nifedipine when St. John's wort is started or stopped. Adjust the nifedipine dose or discontinue St. John's wort if needed.
Drug or Drug Class: Nortriptyline
Potential Interaction:

Documentation: Noncontrolled trial.[143]
Effect: Nortriptyline plasma levels may be reduced, decreasing the pharmacologic effects.
Management: If use of St. John's wort cannot be avoided, assess the patient's clinical response to nortriptyline when St. John's wort is started or stopped. Adjust the nortriptyline dose as needed.
Drug or Drug Class: Paroxetine
Potential Interaction:

Documentation: Case report.[160]
Effect: Increased sedative-hypnotic effects.
Management: Avoid concurrent use. When starting paroxetine in patients receiving St. John's wort, discontinue St. John's wort = 2 weeks prior to starting paroxetine. Patients taking paroxetine should inform their physician or pharmacist before taking St. John's wort.
Drug or Drug Class: Propofol
Potential Interaction:

Documentation: Case report.[161]
Effect: Delayed emergence from general anesthesia.
Management: Discontinue St. John's wort at least 5 days prior to surgery.
Drug or Drug Class: Sertraline
Potential Interaction:

Documentation: Case reports.[158]
Effect: A "serotonin syndrome" (eg, CNS irritability, shivering, myoclonus, altered consciousness)may occur.
Management: Avoid concurrent use. Patients taking sertraline should inform their physician or pharmacist before taking St. John's wort.
Drug or Drug Class: Sevoflurane
Potential Interaction:

Documentation: Case report.[161]

Effect: Delayed emergence from general anesthesia.
Management: Discontinue St. John's wort at least 5 days prior to surgery.
Drug or Drug Class: Simvastatin
Potential Interaction:
Documentation: Controlled trial.[162]
Effect: Cholesterol-lowering effect of simvastatin may be reduced.
Management: Avoid concurrent use.
Drug or Drug Class: Theophylline
Potential Interaction:
Documentation: Case report.[163]
Effect: Decreased theophylline plasma levels.
Management: If use of St. John's wort cannot be avoided, assess the patient's response to theophylline when starting or stopping St. John's wort. Closely monitor theophylline plasma levels and adjust the dose as needed.
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Controlled trial and case reports.[144,164]
Effect: Anticoagulant effect of warfarin may be decreased.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use of St. John's wort. If concomitant use cannot be avoided, closely monitor coagulation parameters when starting or stopping St. John's wort and adjust the warfarin dose as needed.

Herbal Product: L-Tryptophan
Drug or Drug Class: Fluoxetine
Potential Interaction:
Documentation: Noncontrolled study.[112]
Effect: Symptoms related to central and peripheral toxicity may occur.
Management: Avoid concurrent use. The FDA requested a nationwide recall of all nonprescription supplements containing L-tryptophan as the major component because of a possible link with eosinophilia myalgia.
Drug or Drug Class: MAO Inhibitors (ie, isocarboxazid, phenelzine, tranylcypromine)
Potential Interaction:
Documentation: Case reports.[113,114,115,116]
Effect: Possible additive effect, leading to serotonin syndrome (eg, CNS irritability, motor weakness, shivering, altered consciousness).
Management: Concomitant use of MAO inhibitors and L-tryptophan is contraindicated. The FDA requested a nationwide recall of all nonprescription supplements containing L-tryptophan as the major component because of a possible link with eosinophilia myalgia.

Herbal Product: Tyramine-Containing Foods
Drug or Drug Class: MAO Inhibitors(ie, isocarboxazid, phenelzine, tranylcypromine)
Potential Interaction:
Documentation: Controlled trial, noncontrolled trial, case reports, and product information.[165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188]
Effect: Marked elevation in blood pressure, hypertensive crisis, hemorrhagic stroke, and death may occur.
Management: Advise patients taking isocarboxazid not to eat foods high in tyramine or other pressor amine content during and for at least 2 weeks after isocarboxazid therapy is discontinued.

Herbal Product: Ubiquinone(Coenzyme Q10)
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports.[189]
Effect: Anticoagulant effect of warfarin may be decreased.
Management: Because warfarin has a narrow therapeutic index, avoid concurrent use.

Herbal Product: Vitamin E-Containing Herbs(eg, sunflower seeds)
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Case reports and controlled study.[12,190,191,192]
Effect: Increased risk of bleeding caused by vitamin E interference with vitamin K-dependent clotting factors.
Management: Minimize variable consumption of foods or nutritional supplements containing vitamin E. Monitor coagulation parameters during coadministration of warfarin and vitamin E supplements.

Herbal Product: Vitamin K-Containing Herbs (eg, alfalfa)
Drug or Drug Class: Warfarin
Potential Interaction:
Documentation: Resistance to warfarin has been associated with vitamin K content of foods and nutritional supplements.[193,194,195,196]
Effect: Decreased anticoagulant activity.
Management: Minimize variable consumption of foods or nutritional supplements containing vitamin K.

Herbal Product: Watercress
Drug or Drug Class: Chlorzoxazone
Potential Interaction:
Documentation: Controlled trial.[197]
Effect: Elevated chlorzoxazone plasma levels, increasing the therapeutic and adverse effects.
Management: Advise patients taking chlorzoxazone to avoid watercress and that concurrent use could lead to increased chlorzoxazone side effects(eg, CNS depression).

Herbal Product: Yohimbe
Drug or Drug Class: Tricyclic Antidepressants(eg, clomipramine)
Potential Interaction:
Documentation: Controlled study in depressed patients.[198]
Effect: May cause hypertension in patients receiving tricyclic antidepressants.
Management: Avoid concomitant use.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    POTENTIAL HERB-DRUG INTERACTIONS

POTENTIAL DRUG INTERACTIONS WITH ST. JOHN'S WORT

DATE OF ISSUE: JAN 2001

REPLACES MONOGRAPH DATED: N/A

INTRODUCTION

For further information on St. John's wort interactions, refer to the preceding "Evidence-Based Herb-Drug Interaction" monograph.

St. John's wort (*Hypericum perforatum*) is a natural product that is used in various herbal preparations, primarily for the treatment of anxiety and depression. Among other components, St. John's wort consists of flavonoids, glycosides, phenols, and tannins; however, the anthraquinone derivative, hypericin, which is considered to have antidepressant activity, may be the best-known component. While St. John's wort has been considered to be safe, several potentially serious drug interactions have been identified (see Appendix: Potential Herb-Drug Interactions). Because of the increasing and widespread use of St. John's wort, health care providers should be aware of potential drug interactions with this product, patients should be encouraged to discuss their use of herbal products with their health care providers, and standardization of products is desirable. [1]

The precise mechanisms of many drug interactions with St. John's wort are not known. It has been suggested that St. John's wort induces CYP1A2, CYP2C9, and CYP3A4 hepatic metabolism. In addition, it is suspected that St. John's wort induces P-glycoprotein transporter, interfering with drug absorption. Although these mechanisms are not mutually exclusive, it is important to determine the mechanisms of reported interactions in order to anticipate other drugs that may interact with St. John's wort. Numerous drugs are potential substrates for enzymes, depending on the CYP isozymes that may be induced (see Table 1). Many drugs are potential substrates for the P-glycoprotein transporter (see Table 2). P-glycoprotein is found in high amounts in normal tissues, including the large and small intestines, kidneys (eg, proximal tubules), liver (eg, biliary hepatocytes), brain, testes, adrenal gland, and pregnant uterus. [2,3,4] Although the exact function of P-glycoprotein is not known, it does protect humans and other organisms against toxic compounds by acting as a transporter to excrete these substances into the intestinal lumen, bile, and urine.[2,3,4] Thus, if a drug is a substrate of P-glycoprotein in the renal tubules, active secretion into the urine could result, whereas, if a drug is a substrate of P-glycoprotein in the GI tract, uptake from the intestine will be incomplete (ie, decreasing drug levels). [2,3,4] Inhibition of P-glycoprotein in the proximal tubules by a substance (eg, drug, natural product) may reduce the elimination of another compound or drug, resulting in increased levels of that substance. Without standardization of natural products, it is difficult to determine the amount of the ingredient (eg, hypericin) an individual may be ingesting, which may confound the prediction of possible drug interactions. It is unlikely that clinically important interactions will occur with St. John's wort and many of the drugs listed in Tables 1 and 2. Naturopathic physicians, herbalists, and those taking St. John's wort are not seeing or reporting many difficulties. However, until more information is available, it would be prudent to use caution when patients taking these agents are starting or stopping St. John's wort. When possible, consider avoiding use of St. John's wort in patients taking drugs listed in Tables 1 and 2, especially when the drug has a narrow therapeutic index (eg, cyclosporine, digoxin, theophylline, tolbutamide, warfarin).

Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    POTENTIAL DRUG INTERACTIONS WITH ST. JOHN'S WORT
    DATE OF ISSUE

Table 1. Cytochrome P450[2-19]

Substrates of CYP1A2

Acetaminophen	Olanzapine	TCAs (demethylation)
Caffeine	Ondansetron	Amitriptyline
Clozapine (major)	Phenacetin	Clomipramine
Cyclobenzaprine	Propafenone	Desipramine
Diazepam	Propranolol	Imipramine
Fluvoxamine	Riluzole	Nortriptyline
Haloperidol	Ritonavir	Verapamil
Isotretinoin	Ropivacaine	R-warfarin
Methadone	Tacrine	Zileuton
Mexiletine (minor)	Tamoxifen	Zolpidem
Mirtazapine	Testosterone	
Naproxen	Theophylline (major)	

Substrates of CYP2C9

Barbiturates	Indomethacin	Torsemide
Hexobarbital	Losartan	TCAs
Mephobarbital	Mefenamic acid	Amitriptyline
Carvedilol	Mephenytoin	Imipramine
Celecoxib	Mirtazapine	S-warfarin
Cilostazol	Montelukast	Zafirlukast
Dapsone	Naproxen	Zileuton
Diclofenac	Phenytoin	
Dronabinol	Piroxicam	
Fluoxetine	Ritonavir	
Flurbiprofen	Suprofen	
Fluvastatin	Terbinafine	
Glimepiride	Tetrahydrocannabinol	
Ibuprofen	Tolbutamide	

Substrates of CYP3A4

Acetaminophen	Ethinyl estradiol	Paclitaxel (minor)
Alfentanil	Ethosuximide	Pimozide
Alprazolam	Etoposide	Progesterone
Amiodarone	Exemestane	Propafenone
Amlodipine	Felodipine	Quinidine
Astemizole	Fentanyl	Quinine
Atorvastatin	Finasteride	Ritonavir
Benzphetamine	Flutamide	Salmeterol
Bromocriptine	Granisetron	Saquinavir
Busulfan	Halofantrine	Sertraline
Carbamazepine	Hydrocortisone	Sildenafil
Cerivastatin	Ifosfamide	Simvastatin
Chlorpromazine	Indinavir	Sufentanil
Cisapride	Isradipine	Tacrolimus
Citalopram	Itraconazole	Tamoxifen
Clarithromycin	Ketoconazole	Teniposide
Clindamycin	Lansoprazole	Terfenadine
Clonazepam	Lidocaine	Testosterone
Clozapine	Loratadine	Theophylline (minor)
Cocaine	Losartan	Tiagabine
Codeine	Lovastatin	Tolterodine
Colchicine	Methadone	Tretinoin
Cyclobenzaprine	Mibefradil	Triazolam
Cyclophospha-mide	Miconazole	TCAs (demethylation)
Cyclosporine	Midazolam	Amitriptyline
Dapsone	Mifepristone	Clomipramine
Delavirdine	Mirtazapine	Imipramine
Dexamethasone	Montelukast	Troglitazone
Dextromethor-phan	Navelbine	Troleandomycin
Diazepam	Nefazodone	Venlafaxine
Digitoxin	Nelfinavir	Verapamil
Diltiazem	Neviramine	Vinblastine
Disopyramide	Nicardipine	Vincristine
Docetaxel	Nifedipine	R-warfarin
Dolasetron	Nimodipine	Yohimbine
Donepezil	Nisoldipine	Zileuton
Doxorubicin	Nitrendipine	Zolpidem (major)
Dronabinol	Omeprazole	
Erythromycin	Ondansetron	

Effect uncertain or minimal.

Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    POTENTIAL DRUG INTERACTIONS WITH ST. JOHN'S WORT
    TABLE 1: CYTOCHROME P450

Table 2. Substrates for P-Glycoprotein [2-20]

Amiodarone	Indinavir	Quinidine
Chlorpromazine	Itraconazole	Reserpine
Clarithromycin	Ivermectin	Saquinavir
Cyclosporine	Ketoconazole	Spironolactone
Dactinomycin	Levofloxacin	Tacrolimus
Daunorubicin	Loperamide	Tamoxifen
Dexamethasone	Mefloquine	Teniposide
Digoxin	Mithramycin	Terfenadine<
Diltiazem	Mitomycin-C	Topotecan
Dipyridamole	Mitoxantrone	Trifluoperazine
Doxorubicin	Nelfinavir	Triflupromazine
Epirubicin	Nicardipine	Trimetrexate
Erythromycin	Ondansetron	Verapamil
Etoposide	Paclitaxel	Vinblastine
Fluphenazine	Pimozide	Vincristine
Hydrocortisone	Promethazine	
Idarubicin	Propafenone	

Document Bibliographic Information:
- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      POTENTIAL DRUG INTERACTIONS WITH ST. JOHN'S WORT
        TABLE 2: SUBSTRATES FOR P-GLYCOPROTEIN

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Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    POTENTIAL DRUG INTERACTIONS WITH ST. JOHN'S WORT
    REFERENCES

HERBAL DIURETICS

DATE OF ISSUE: NOV 1998

REPLACES MONOGRAPH DATED: MAY 1989

PHARMACOLOGY

Diuretics remain among the most frequently prescribed drugs in the United States. In addition to the widespread use of prescription diuretics, over-the-counter (OTC) and natural diuretics continue to play an important role in the self-treatment of menstrual distress, edema, and hypertension.

Numerous OTC menstrual distress preparations contain xanthine alkaloids such as caffeine and theobromine, which are most often derived from inexpensive natural sources. Of these compounds, only caffeine has been found to be both safe and effective for use as an OTC diuretic. In its review of these products, the FDA Advisory Review Panel on Menstrual Drug Products concluded that the frequently used dandelion root (*Taraxacum officinale* Wiggers), a preparation once thought to have strong diuretic properties, is safe but ineffective in the treatment of dysmenorrhea. Nor is there evidence that dandelion is an effective diuretic.

Teas and extracts of buchu (*Barosma betulina*) and quack grass (*Agropyron* spp.) are popular, but their diuretic activity is probably no greater than that of the xanthine alkaloids in coffee or ordinary tea. Significant toxicity from buchu and quack grass have not been reported. [1]

Diuretic teas that should be avoided include juniper berries (*Juniperus communis*), which contain a locally irritating volatile oil capable of causing renal damage, and shave grass or horsetail (*Equisetum* spp.) a weakly diuretic plant that contains several toxic compounds including aconitic acid, equisitine (a neurotoxin), and nicotine. [2] In grazing animals, the ingestion of horsetail has caused excitement, convulsions, and death. Thiamine deficiency has been reported in sheep after the experimental administration of shave grass.

Other teas, such as ephedra (ma huang), contain the mildly diuretic stimulant ephedrine. These teas should be used with caution by hypertensive patients.

All plants and herbal extracts included in OTC products for use as diuretics are not toxic; however, the majority are either clinically ineffective or no more effective than caffeine. The following table lists plants that have been reported to possess diuretic activity. This list has been compiled from old materia medica, herbals, and when documentation is available, the scientific literature. There is generally little scientific evidence to justify the use of most of these plants as diuretics. Some are toxic even in very low doses. The fact that some have been used for centuries in herbal medicine does not necessarily attest to their effectiveness; rather it suggests that such plants have a relatively broad margin of safety and their use does not usually result in toxicity.

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Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      HERBAL DIURETICS
        DATE OF ISSUE

HERBAL DIURETICS

Scientific Name	*Common Name*	*Part Used*
Abutilon indicum	—	Bark
Acalypha evrardii	—	Flower, leaf
Acanthus spinosus	—	Entire plant
Acorus calamus*	**Calamus**	**Rhizome**
Adonis vernalis	Pheasant's eye herb	Above ground
Agave americana	Agave	Roots
Agrimonia eupatoria	**Agrimony**	**Entire plant**
Agropyron	**Couch grass**	**Rhizomes, roots, stems**
Alchemilla arvensis	**Lady's mantle**	**Entire plant**
Alisma plantago	—	Entire plant
Allium cepa	Onion	Bulb
Ammi visnaga	—	**Fruit**
Anemone spp.*	Windflower	Entire plant
Apium graveolens*	**Celery**	**Stalk, oil**
Apocynum cannabinum*	—	Entire plant
Arctostaphylos uva-ursi*	**Uva ursi**	**Leaves**
Arctium lappa	**Burdock**	**Root**
Asparagus officinale	**Asparagus**	**Roots**
Bacopa monnieri	—	Entire plant
Barosma spp.	**Buchu**	**Leaves**
Begonia cucullata	Begonia	Entire plant
Betula alba*	Betula	Leaves, twigs
Blumea lacera	—	Entire plant
Boerhaavia diffusa	—	Entire plant
Borago officinalis	**Borage**	**Leaves, tops**
Buddleja americana	—	Bark, leaf, root
Callistris arborea	—	Gum
Calystegia soldanella	—	Entire plant
Camellia sinensis	Common tea	Leaves
Capsella bursa-pastoris	Shepherd's purse	Above ground
Carex arenaria	—	Entire plant
Chamaelirium luteum	—	Root
Chelidomium majus	Celandine	Root, leaves, latex
Chicorium intybus	**Chicory**	**Root**
Chimaphilia umbellata	Pipsissewa	Above ground
Claytonia sibirica	—	Entire plant
Clematis spp*	—	**Entire plant**
Coffea arabica	Coffee	Fruit
Collinsonia canadensis	Stoneroot	Root
Convallaria majalis*	Lily of the valley	Flowering tops
Costus spicatus	—	Sap
Curanga fel-terrae	—	Leaf
Cynanchium vincetoxicum	—	Entire plant
Cytisus scoparius*	**Broom**	**Flowering tops**
Daucus carota	**Carrot**	**Root**
Digitalis purpurea*	**Foxglove**	**Leaves**
Drosera rotundifolia	Drosera	Entire plant
Ephedra spp.	**Ephedra**	**Stems**
Equisetum spp.	**Horsetail**	**Above ground**
Eryngium yuccifolium	—	Entire plant
Fumaria officinalis	**Fumitory**	**Flowering tops**
Gaillardia pinnatifida	—	Entire plant
Galega officinalis	Goat's rue	All but root
Galium aparine	Cleavers	Above ground
Glycyrrhiza glabra	**Licorice**	**Rhizome, root**
Helianthus annus	Sunflower	Seeds
Hemidesmus indicus	—	Entire plant
Herniaria glabra	Rupturewort	Above ground
Hibiscus spp.	**Hibiscus**	**Flowers**
Hydrangea arborescens*	Hydrangea	Roots
Hypericum perforatum	**St. John's Wort**	**Entire plant**
Hypochoeris scarzonerae	—	Entire plant
Ilex paraguayensis*	**Mate**	**Leaves**
Iris florentina	Orris	Peeled rhizome
Juniperus communis*	**Juniper**	**Berries**
Laportea meyeniana	—	Leaf, root
Levisticum officinale	**Lovage**	**Roots**
Paullinia cupana	**Guarana**	**Seeds**
Petroselinum crispum*	**Parsley**	**Leaves, seeds**
Peumus boldus	**Boldo**	**Leaves**
Pinus silvestris	Pine	Cones

Psoralae corylifolia	—	Seeds
Rafnia perfoliata	—	Leaf
Rehmannia lutea	—	Entire plant
Sambucus nigra	**Elderberry**	**Flowers**
Santalum album	**Sandalwood**	**Oil**
Sassafras albidum	**Sassafras**	**Root**
Senecionis herba	Senecio herb	Above ground
Serenoa repens	**Saw palmetto**	**Ripe fruits**
Smilax spp.	Sarsaparilla	Roots
Solanum dulcamara*	**Bittersweet**	**Twigs, branches**
Spiranthes diuretica	—	Entire plant
Tagetes multifida	—	Entire plant
Taraxacum officinale	**Dandelion**	**Leaves**
Theobroma cacao	**Cocoa**	**Seeds**
Trianthema portulacastrum	—	Leaves
Tribulus terrestris	—	Fruit
Urginea maritima*	**Squill**	**Bulb**
Urtica dioica*	**Nettle**	**Leaves**
Viola odorata	Violet	Leaves, flowers
Withania somnifera*	**Withania**	**Root**

* Noted as toxic in reference; all others should not be considered safe for general use in the absence of valid safety.
Plants in **bold** are described in their own monograph in this system.

Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      HERBAL DIURETICS
        TABLE: HERBAL DIURETICS

MUSHROOM POISONING DECISION CHART

DATE OF ISSUE: NOV 1998

REPLACES MONOGRAPH DATED: DEC 1987

INTRODUCTION

Mushroom poisoning represents an important aspect of plant toxicology. The toxic events caused by mushrooms are not limited to any group by age, race, or sex. Infants and children readily eat wild mushrooms because of their unique texture and often mild flavor. Adults experimenting with freshly collected, but misidentified, mushrooms often fall victim to intoxication.

Despite the many varieties of mushrooms that grow throughout North America, only a few types are responsible for the majority of mushroom intoxications. Therefore, determining the general type of mushroom intoxication is not always an impossible task.

While it is important to obtain a sample of the mushroom suspected in the poisoning, this is not always practical or possible. Consultation with a local mycologist and poison control center should always be considered when establishing the cause of a mushroom poisoning event (see monograph "Mushroom Societies"). If a mushroom intoxication is suspected, asking 6 simple questions will usually provide sufficient information to make a tentative determination of the causative agent. These are:

1.) When were the mushrooms eaten and how long after this did the symptoms first occur?

2.) What were the initial symptoms?

3.) Was more than 1 kind of mushroom eaten?

4.) Did anyone who did not eat mushrooms become sick?

5.) Did everyone who ate the mushrooms become sick?

6.) Was an alcoholic beverage consumed within 72 hours after the mushroom meal?

These questions, formulated by Lampe and McCann,[1] are useful in establishing a causative association between the mushroom and the intoxication.

The following flow chart is designed to aid in determining the possible causative genus in a suspected mushroom intoxication. This chart should be used as a guide in determining which mushroom was most likely involved in the intoxication. The clinician should recognize that factors such as the amount of mushroom ingested, the season, individual sensitivities, and the possibility that toxic materials other than the mushroom may have been ingested, can confuse the diagnostic picture.

[1] *AMA Handbook of Poisonous and Injurious Plants*, AMA, Chicago Review Press, 1985.

Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    MUSHROOM POISONING DECISION CHART
    DATE OF ISSUE

Document Bibliographic Information:

- **Location In Book:**

  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      MUSHROOM POISONING DECISION CHART
        DIFFERENTIAL EVALUATION OF MUSHROOM INTOXICATIONS BY SYMPTOMS

MUSHROOM SOCIETIES

DATE OF ISSUE: JUN 2001

REPLACES MONOGRAPH DATED: NOV 1998

Mushroom poisonings remain one of the most important causes of plant toxicities. The management of these poisonings varies depending on the type of mushroom ingested. Therefore, proper identification of the mushroom suspected to have caused the toxicity is of primary importance.

In order to facilitate the identification of a mushroom, it is important to obtain a fresh, undamaged specimen. It is not uncommon for several species of mushroom to grow close together. Therefore, the identification of a single mushroom from a collected batch may mislead the clinician in the treatment of the poisoning. Ideally, several mushrooms will be available for use in identification. The mushrooms should be placed in a paper bag (not plastic) and refrigerated.

Identification of cooked mushrooms is much more difficult. However, material from the meal should be obtained for physical and chemical analysis.

The Infectious Disease Section of the Centers for Disease Control and Prevention in Atlanta, GA (USA), offers assistance in cases of suspected mushroom poisoning. Information is also available from local mycological societies, botany departments of local universities, and poison control centers. The following list provides the contact information for organizations that may be helpful in offering assistance in the identification of edible and toxic mushrooms:

American Association of Poison Control Centers
3201 New Mexico Ave., Ste. 310
Washington, DC 20016
202/362-7217
http://www.aapcc.org

American Society for Microbiology Division F Medical Mycology
http://www.asmusa.org/division/f/divf_main.htm

Boston Mycological Club
6 Oak Ridge Dr. #4
Maynard, MA 01754-2470
781/259-3426
http://www.bostonmycologicalclub.org

Botanical Society of America
Business Office
1735 Neil Ave.
Columbus, OH 43210-1293
614/292-3519
http://www.botany.org

International Mycological Association
James B. Anderson, Secretary-General
Department of Botany
Louisiana State University
Baton Rouge, LA 70803
lsb380.plbio.lsu.edu/ima/index.html

International Society for Human and Animal Mycology (ISHAM)
http://www.leeds.ac.uk/isham

International Society for Mushroom Science
c/o Dr. K.S. Burton, Executive Secretary
196 Rugby Rd.
Leamington Spa, Warwickshire CV32 6DU England
http://www.hri.ac.uk/isms

Mycological Society of America
c/o Joan W. Bennett, *Mycologia* Editor-in-Chief

Department of Cell and Molecular Biology
Tulane University
New Orleans, LA 70118
http://MSAfungi.org

c/o Lorelei L. Norvell, Secretary
Pacific NW Mycology Service
6720 NW Skyline Blvd.
Portland, OR 97229
503/297-3296
http://MSAfungi.org

National Center for Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Rd.
Atlanta, GA 30333
404/639-3311
http://www.cdc.gov/ncidod

North American Mycological Association
http://www.namyco.org

Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      MUSHROOM SOCIETIES

POISON CENTER HOTLINE

DATE OF ISSUE: OCT 2000

REPLACES MONOGRAPH DATED: NOV 1998

The American Association of Poison Control Centers (AAPCC) has established a national toll-free poison center hotline. Now everyone in the United States can call 1-800-222-1222 to reach the local poison center. Poison Center services are available 24 hours a day, 7 days a week.

The phone number can be used for a poison emergency, or questions about poisons and poison prevention.

Regardless of where the call is placed, the hotline automatically connects callers to the closest poison control center. Existing local poison center numbers will still connect callers to their poison centers.

Callers who use a TTY/TDD and non-English speaking callers can also use this hotline.

Document Bibliographic Information:

- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
    POISON CENTER HOTLINE

SCIENTIFIC AND TRADE ORGANIZATIONS

DATE OF ISSUE: JUN 2001

REPLACES MONOGRAPH DATED: NOV 1998

The following list provides the contact information for organizations that may be helpful in providing information in specific areas of natural product research, evaluation, and education:

American Association of Oriental Medicine
433 Front St.
Catasauqua, PA 18032
610/266-1433
FAX: 610/264-2768
http://www.aaom.org

American Botanical Council
P.O. Box 144345
Austin, TX 78714-4345
512/926-4900
FAX: 512/926-2345
http://www.herbalgram.org

American Herbal Products Association
8484 Georgia Ave., Ste. 370
Silver Spring, MD 20910
301/588-1171
FAX: 301/588-1174
http://www.ahpa.org

American Herbalists Guild
1931 Gaddis Rd.
Canton, GA 30115
770/751-6021
FAX: 770/751-7472
http://www.americanherbalistsguild.com/top.htm

American Nutraceutical Association
5120 Selkirk Dr., Ste. 100
Birmingham, AL 35242
205/980-5710
FAX: 205/991-9302
http://www.americanutra.com

American Society of Pharmacognosy
http://www.phcog.org

Association of Natural Medicine Pharmacists
P.O. Box 150727
San Rafael, CA 94915-0727
415/453-3534
FAX: 415/453-4963
http://www.anmp.org

Association of Traditional Chinese Medical Doctors
2430 Wawona St.
San Francisco, CA 94116
415/753-2168

Botanical Society of America
1735 Neil Avenue
Columbus, OH 43210-1293
614/292-3519
FAX: 614/247-6444
http://www.botany.org

Centers for Disease Control and Prevention
Department of Health and Human Services
1600 Clifton Rd.
Atlanta, GA 30333
404/639-3311
http://www.cdc.gov

Council for Responsible Nutrition
1875 Eye St., NW, Ste. 400
Washington D.C. 20006-5194
202/872-1488
FAX: 202/872-9594
http://www.crnusa.org

Ginseng Research Institute of America
7 Menard Plaza
Wausau, WI 54401-4119
715/845-7300
FAX: 715/845-8006

HerbNet (Herb Association Listings)
http://www.herbnet.com/associations_p2.htm

Herb Research Foundation
1007 Pearl St., Ste. 200

Boulder, CO 80302
303/449-2265
800/748-2617
FAX: 303/449-7849
http://www.herbs.org

International Herb Association
4456 Corporation Lane, Ste. 120
Virginia Beach, VA 23462
757/497-4143
FAX: 757/497-0010
http://www.iherb.org/index.html

Mycological Society of America
P.O. Box 1897
Lawrence, KS 66044-8897
785/843-1221, ext. 210
800/627-0629
FAX: 785/843-1274
http://www.erin.utoronto.ca/w3msa

National Association for Alternative Medicine
4433 Eagle Rock Blvd. #435
Los Angeles, CA 90041
naam-legal.apk.org

National Center for Complementary and Alternative Medicine
The National Institutes of Health
P.O. Box 8218
Silver Spring, MD 20907-8218
888/644-6226
FAX: 301/495-4957
nccam.nih.gov

National Center for Natural Products Research
Thad Cochran Research Center
University of Mississippi - School of Pharmacy
P.O. Box 1848
University, MS 38677
662/915-1005
662/915-1006
http://www.olemiss.edu/depts.ncnpr

National Council Against Health Fraud
119 Foster Street
Peabody, MA 01960
978/532-9383
http://www.ncahf.org

National Nutritional Foods Association
3931 MacArthur Blvd., Ste. 101
Newport Beach, CA 92660
949/622-6272
FAX: 949/622-6266
http://www.nnfa.org

Rocky Mountain Herbal Institute
Chinese Herbal Sciences
http://www.rmhiherbal.org

The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine
cpmcnet.columbia.edu/dept/rosenthal/botanicals.html

Society for Economic Botany
P.O. Box 1897
Lawrence, KS 66044
800/627-0629
785/843-1235
http://www.econbot.org

Document Bibliographic Information:
- **Location In Book:**
  - THE REVIEW OF NATURAL PRODUCTS (2004)
    APPENDIX
      SCIENTIFIC AND TRADE ORGANIZATIONS

SOURCES OF NATURAL PRODUCT INFORMATION

DATE OF ISSUE: JAN 2004

REPLACES MONOGRAPH DATED: AUG 2001

NATURAL PRODUCT INFORMATION - WHERE ELSE TO LOOK

The burgeoning field of biomedical science has created an almost overwhelming amount of information that often makes finding useful facts difficult. Of the many biomedical journals and newsletters published in the US alone, only a few address the study of natural products.

A full appreciation of natural products requires an understanding of their origin, history, nomenclature, chemistry, pharmacology, toxicology, availability, and therapeutic uses. Little more than a dozen journals deal specifically with these topics. Many of the remaining scientific and medical journals represent excellent secondary sources of information about natural products.

Table 1 presents a selected list of American and foreign periodicals devoted to the study of natural products.

Books continue to be valuable sources of data about natural products. Many original works, no longer in publication, continue to set the standards in their fields (eg, Ernest Guenther's, *The Essential Oils*, Vols. 1-5 D, Van Nostrand Co, NY, 1948-1952). Table 2 is not an all-inclusive book list; rather, it offers suggestions for a well-rounded library on natural products.

With the increasing use of computer-accessible data bases, online indexing systems have become critical in the retrieval of references describing natural products. The biomedical field has at its disposal a variety of internet databases. Of these, few specialty databases are available for the field of natural products (Table 3). However, several excellent broad-based services do provide adequate access to information about natural products.

Many of the periodicals listed here are available at university or medical libraries. PubMed, the National Library of Medicine's online citation index also indexes some journals related to the use of natural products.

Hopefully, this review of information sources will make the task of data retrieval and evaluation easier.

TABLE 1: PERIODICALS

American Journal of Botany, Botanical Society of America, St. Louis, MO
http://www.amjbot.org

Australian Journal of Medical Herbalism, National Herbalists Association of Australia, Morisset, NSW, Australia
http://www.nhaa.org.au/journal.html

Botanical Review, the New York Botanical Garden, Bronx, NY
http://www.nybg.org/bsci/spub/botr/frntpg3b.html

Canadian Journal of Herbalism, Ontario Herbalists' Association, Ontario, Canada
http://www.herbalists.on.ca/journal/

Economic Botany, The Society for Economic Botany, The New York Botanical Garden, Bronx, NY
http://www.econbot.org/journal/back_issues.html

Fitoterpia, Elsevier Science, New York, NY
http://www.elsevier.com/locate/fitote

Herb Companion and *Herbs for Health*, Ogden Publications, Topeka, KS
http://www.discoverherbs.com

Herb Quarterly, San Anselmo, CA
http://www.herbquarterly.com

HerbalGram, the American Botanical Council and the Herb Research Foundation, Austin, TX
http://www.herbalgram.org/herbalgram

International Journal of Aromatherapy, Elsevier Science, New York, NY
http://www.harcourt-international.com/journals/ijar

Journal of Ethnopharmacology, the International Society of Ethnopharmacology, Elsevier Science, Philadelphia, PA
http://www.elsevier.com/locate/jethpharm

Journal of Natural Products, The American Chemical Society and the American Society of Pharmacognosy, Columbus, OH
http://pubs.acs.org/journals/jnprdf/index.html

Medical Herbalism: A Journal for the Clinical Practitioner, Bergner Communications, Boulder, CO
http://medherb.com/MHHOME.SHTML

Natural Health, Weider Publications
http://www.naturalhealth1.com

Natural Product Reports, The Royal Society of Chemistry, Cambridge, UK
http://www.rsc.org/is/journals/current/npr/nprpub.htm

Natural Products Research (formerly *Natural Product Letters*), Taylor & Francis Group, London, England
http://www.tandf.co.uk/journals/titles/14786419.html

NCAHF News, The National Council Against Health Fraud, Peabody, MA
http://www.ncahf.org/nl/nlindex.html

Pharmaceutical Biology, Swets & Zeitlinger, Royersford, PA
http://www.extenza-eps.com/extenza/contentviewing/viewJournal.do?journalID=46

Phytochemistry: The International Journal of Plant Biochemistry and Molecular Biology, the Phytochemical Society of Europe and the Phytochemical Society of North America, Elsevier Science, New York, NY
http://www.elsevier.nl/locate/inca/273

Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, Elsevier, Germany

http://www.elsevierdeutschland.de/artikel/647598

Phytotherapy Research, John Wiley & Sons, New York, NY
http://www3.interscience.wiley.com/cgi-bin/jhome/12567

Plant Foods for Human Nutrition, Kluwer Academic Publishers, Norwell, MA
http://www.kluweronline.com/issn/0921-9668/contents

Planta Medica: Natural Products and Medicinal Plant Research, Thieme, New York, NY
http://www.thieme.de/plantamedica/fr_inhalt.html

Toxicon, the International Society on Toxicology, Elsevier Science, New York, NY
http://www.elsevier.com/locate/toxicon

TABLE 2: BOOKS

Aikman L. *Nature's Healing Arts: From Folk Medicine to Modern Drugs*. Washington, DC: National Geographic Society; 1977.

Baslow MH. *Marine Pharmacology: A Study of Toxins and Other Biologically Active Substances of Marine Origin*. 2nd ed. Huntington, NY: RE Krieger Co; 1977.

Blackwell WH. *Poisonous and Medicinal Plants*. Englewood Cliffs, NJ: Prentice Hall; 1990.

Blumenthal M, ed. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; 1998.

Blumenthal M, ed. *Herbal Medicine: Expanded Commission E Monographs*. Austin, TX: American Botanical Council, 2000.

Bricklin M. *The Practical Encyclopedia of Natural Healing*. Rev ed. New York, NY: Penguin Books; 1990.

British Herbal Medicine Association. Scientific Committee. *British Herbal Pharmacopoeia*. London, England: British Herbal Medicine Association; 1971.

Bucherl W, Buckley EE, Deulofeu V, eds.
Venomous Animals and Their Venoms. 3 vols. New York, NY: Academic Press; 1968-1971.

Buckingham J, exec ed. *Dictionary of Natural Products*. London, England: Chapman & Hall; 1994.

Castleman M. *The Healing Herbs: The Ultimate Guide to the Curative Powers of Nature's Medicines*. Emmaus, PA: Rodale Press; 1991.

Densmore F. *How Indians Use Wild Plants for Food, Medicine, and Crafts* [reprint]. New York, NY: Dover; 1974.

Der Marderosian AH, Liberti LE. *Natural Product Medicine: A Scientific Guide to Foods, Drugs, Cosmetics*. Philadelphia, PA: G.F. Stickley; 1988.

Duke PA. *Handbook of Medicinal Herbs*. 2nd ed. Boca Raton, FL: CRC Press; 2002.

Evans WC. *Trease and Evans' Pharmacognosy*. 15th ed. Edinburgh, England: WB Saunders; 1996.

Eskinazi D, Blumenthal M, Farnsworth N, Riggins CW, eds. *Botanical Medicine: Efficacy, Quality Assurance, and Regulation* . Larchmont, NY: Mary Ann Liebert, Inc. Publishers; 1999.

Facciola S. *Cornucopia: A Source Book of Edible Plants*. Vista, CA: Kampong Publications; 1990.

Facciola S. *Cornucopia II: A Source Book of Edible Plants*. Vista, CA: Kampong Publications; 1998.

Foster S, Tyler VE. *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies*. 4th ed. New York: Haworth Herbal Press; 1998.

Henslow G. *The Plants of the Bible: Their Ancient and Mediaeval History Popularly Described*. London, England: Masters; 1906.

Hoffmann D. *Medical Herbalism: The Science and Practice of Herbal Medicine*. Rochester, VT: Healing Arts Press; 2003.

Hoffmann D, ed. *The Information Sourcebook of Herbal Medicine*. Freedom, CA: Crossing Press; 1994.

Kerr RW. *Herbalism through the Ages*. 7th ed. San Jose, CA: Supreme Grand Lodge of AMORC; 1980.

Kingsbury JM. *Deadly Harvest: A Guide to Common Poisonous Plants*. New York, NY: Holt, Rinehart, and Winston; 1965.

Lampe KF, McCann MA. *AMA Handbook of Poisonous and Injurious Plants*. Chicago, IL: American Medical Association; 1985.

Leung AY. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*. 2nd ed. New York, NY: Wiley; 1996.

Lewis WH, Elvin-Lewis MP. *Medical Botany: Plants Affecting Man's Health*. 2nd ed. New York, NY: Wiley;
2003.

Liener IE, ed. *Toxic Constituents of Plant Foodstuffs*. 2nd ed. New York, NY: Academic Press; 1980.

Meyer JE. *The Herbalist*. Rev ed. Glenwood, IL: Meyerbooks; 1986.

Micoozzi MS, ed. *Fundamentals of Complementary and Alternative Medicine*. 2nd ed. Philadelphia, PA: Saunders; 2001.

Morton JF. *Major Medicinal Plants of Middle America: Bahamas to Yucatan*. Springfield, IL: Thomas;
1981.

Ody P. *The Complete Medicinal Herbal*. New York, NY: Dorling Kindersley; 1993.

Osol A, Pratt R, eds. *The United States Dispensatory*. 27th ed. Philadelphia, PA: Lippincott; 1973.

Reader's Digest Editors. *Magic and Medicine of Plants*. Sydney, Australia: Reader's Digest Association Inc.; 1986.

Robinson T. *The Organic Constituents of Higher Plants: Their Chemistry and Interrelationships*. 6th ed. North Amherst, MA: Cordus Press; 1991.

Schauenberg P, Paris F. *Guide to Medicinal Plants* [reprint]. New Canaan, CT: Keats; 1990.

Simon JE, Chawick AF, Craker LE. *Herbs, An Indexed Bibliography, 1971-1980: The Scientific Literature on Selected Herbs, and Aromatic and Medicinal Plants of the Temperate Zone*. Hamden, CT: Archon Books; 1984.

Spoerke DG. *Herbal Medications*. Santa Barbara, CA: Woodbridge Press; 1990.

Steiner RP, ed. *Folk Medicine: The Art and the Science*. Washington, DC: American Chemical Society; 1986.

Swain T, ed. *Plants in the Development of Modern Medicine*. Cambridge, MA: Harvard University Press; 1972.

Sweet M. *Common Edible and Useful Plants of the East and Midwest*. Healdsburg, CA: Naturegraph Publishers; 1975.

Sweet M. *Common Edible and Useful Plants of the West*. Healdsburg, CA: Naturegraph Publishers; 1976.

World Health Organization. *WHO Monographs on Selected Medicinal Plants*. Geneva, Switzerland: World Health Organization; 1999.

Zohary M. *Plants of the Bible: A Complete Handbook to All the Plants with 200 Full-color Plates Taken in the Natural Habitat*. New York, NY: Cambridge University Press; 1982.

TABLE 3: DATABASES

AGRICOLA (AGRICultural OnLine Access), bibliographic database of citations created by the National Agricultural Library covers the international journal literature and monographs on agriculture and related subjects. Includes data on how to grow herbs and medicinal plants.
http://www.nal.usda.gov/ag98/

AMED (Allied and Complementary Medicine Database), is a unique bibliographic database produced by the Health Care Information Service of the British Library with information about published journal articles in fields allied to medicine and alternatives to conventional medicine. Contains bibliographic citations with abstracts covering subjects such a acupuncture, osteopathy, Chinese medicine, homeopathy, herbalism, holistic treatments, etc.
http://www.bl.uk/services/information/amed.html

BIOSIS (Biological Abstracts), the world's largest collection of abstracts and bibliographic references to worldwide biological and medical literature. Useful for researching the botanical aspects of medicinal plants.
http://www.biosis.org

CAS (American Chemical Society), world's largest and most comprehensive databases of chemical information. Products include: *SciFinder*, *STD* (includes *International Pharmaceutical Abstracts* and *NAPRALERT*), and *Chemical Abstracts*.
http://www.cas.org

Dr. Duke's Phytochemical and Ethnobotanical Databases (Agricultural Research Services, USDA).
http://www.ars-grin.gov/duke/

HerbMed (Alternative Medicine Foundation, Inc.), provides hyperlinked access to the scientific data underlying the use of herbs for health. It is an evidence-based information resource for professionals, researchers, and general public.
http://www.herbmed.org

MEDLINEPlus: Alternative Medicine (National Library of Medicine), provides bibliographic references to scientific-based studies in alternative and complementary medicine.
http://www.nlm.nih.gov/medlineplus/alternativemedicine.html

The National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH), supports research on complementary and alternative medicine. Databases located on the NCCAM Web site include: *CAM on PubMed*, a subset of the National Library of Medicine's PubMed, which provides access to complementary and alternative medicine journal citations; and *CHID* (the Combined Health Information Database), a reference tool for patient education materials.
http://nccam.nih.gov/

Poisonous Plant Database (FDA, Center for Food Safety & Applied Nutrition), is a set of working files of scientific information about the animal and human toxicology of vascular plants of the world. The initial files were created in 1994, and are updated periodically.
http://vm.cfsan.fda.gov/~djw/readme.html

PubMed (National Library of Medicine), includes over 14 million citations for biomedical articles back to the 1950s. These citations are from MEDLINE and additional life science journals. Includes links to many sites providing full-text articles and other related resources.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

For more information consult the following: The *Directory of Databases* of the Richard & Hinda Rosenthal Center for Complementary and Alternative Medicine, Columbia University, includes significant holdings of primarily bibliographic references to complementary and alternative medicine research resources compiled to facilitate access to the widely scattered data and literature. Updated regularly.
http://www.rosenthal.hs.columbia.edu/Databases.html

TABLE 4: WEB SITES

The Alternative Medicine HomePage (University of Pittsburgh)
http://www.pitt.edu~cbw/altm.html

American Botanical Council
http://www.herbalgram.org

American Herbal Pharmacopoeia
http://www.herbal-ahp.org

American Herbalists Guild
http://www.americanherbalistsguild.com

Council for Responsible Nutrition
http://www.crnusa.org

Herb Research Foundation
http://www.herbs.org

Herbal Education Services
http://www.botanicalmedicine.org

HerbNet
http://www.herbnet.com

International Herb Association
http://www.iherb.org

National Cancer Institute
(Complementary and Alternative Medicine)
http://www.concer.gov/cancerinfo/treatment/cam

National Center for Complementary and Alternative Medicine (National Institutes of Health)
http://nccam.nih.gov/

The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine (Columbia University)
http://www.rosenthal.hs.columbia.edu

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