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Coming Clean on Supplements Designated the 'Dirty Dozen'

PART 2 OF A SERIES ON POTENTIALLY HAZARDOUS SUPPLEMENTS

By Francis Brinker, ND

THE MAY 2004 ISSUE OF *CONSUMER REPORTS* (CR) DESIGNATED 12 dietary supplements as hazardous.[1] One (aristolochic acid) was categorized by *CR* as definitely hazardous, while five (germander, comfrey, chaparral, kava, and androstenedione) were described as very likely hazardous. The first part of this review *[see the August 2004 issue of* Alternative Medicine Alert*]* confirmed the *CR* assessment of botanical products containing aristolochic acid and included germander preparations as definitely hazardous. The other four were described as potentially hazardous with long-term internal use. This categorization was based, with respect to the botanicals, on there being isolated cases of liver toxicity associated with long-term use of certain preparations of comfrey, chaparral, and kava. (There were also appropriate uses and benefits without evidence of significant adverse effects noted with short-term use of certain preparations of these three.) Finally, as a steroid precursor, androstenedione is intended for long-term

Editor's Note—*From time to time,* Alternative Medicine Alert *breaks from its typical format to present unique information requiring significant space. Such is the case this month, as one of the world's foremost experts on herbal dietary supplements addresses issues of safety in the now infamous* Consumer Reports *"Dirty Dozen." While many, if not most,* Alternative Medicine Alert *readers do not routinely use the agents mentioned by* Consumer Reports*, it is nonetheless important to understand the distinctions between preparations and patterns of use. This is what most determines safe use vs. risk. In this regard, what is necessary in most cases is education and information involving appropriate label warning requirements (as opposed to universal bans). It is especially important to recognize the degree of scientific support, or lack thereof, behind such classifications of safe and unsafe.*

—Russell H. Greenfield, MD

VOLUME 7 • NUMBER 10 • OCTOBER 2004 • PAGES 109-120

consumption that influences circulating sex hormone levels. Substances like androstenedione are subject to abuse by athletes and may affect gender expression, especially in children and fetuses. For these reasons the federal government appears poised to ban such steroid precursors from the dietary supplement marketplace.

This second part reviews the six dietary supplements *CR* identified as likely hazardous. Based on the evidence and known pharmacology of these agents, four will be discussed as hazardous with acute excessive dosage. One of these contains an essential oil with known toxicity to the liver, while the other three contain alkaloids that affect both central and peripheral neural functions. Another two are deemed unlikely hazardous. As in Part 1, classifications compiled by competent herbalists and naturopathic doctors as published in the 1997 *Botanical Safety Handbook* (*BSH*) will be relied upon as a practical expert perspective on safety concerns for the five botanical products.[2] Judgments expressed here as to the relative danger imposed by these botanical substances are based on the author's 25 years of experience and study involving potentially toxic botanicals, including the publication in 1983 of the first edition of a clinical toxicology handbook on such preparations.[3]

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $48 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$339 per year (Student/Resident rate: $165).
Multiple Copies
Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

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Alternative Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for Elective credit hours. Term of approval covers issues published within one year from the beginning distribution date of July 1, 2003. This volume has been approved for up to 24 Elective credit hours. Credit may be claimed for one year from the date of this issue.
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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Education guidelines, physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Brinker, Dr. Gaudet, Dr. Heber, Dr. Jacobs, Dr. Kemper, Dr. Kreitzer, Dr. Liebowitz, and Dr. Schneider report no relationships with companies related to the field of study covered by this CME program. Dr. Greenfield is a consultant for Nature's Way, Inc., and serves on the scientific advisory board for Polaris, Inc. Dr. Vohra receives research funding from CIHR.
This publication does not receive commercial support.

Category 3: Hazardous with Acute Excessive Dosage
1. Pennyroyal oil (from *Hedeoma pulegioides* leaves and tops)

The *CR* article identifies pennyroyal oil as a product of the North American species *Hedeoma pulegioides*, but an equivalent oil with similar phytochemistry can be obtained from the European pennyroyal species, *Mentha pulegium*. Pennyroyal oil is a volatile distillate, often referred to as an aromatic or essential oil as distinct from vegetable oils used as food. Like other essential oils it is a potent concentrate, since it accounts for only 1-2% of the weight of the fresh plant.

In general, volatile components are mucosal irritants unless dispersed in a suitable vehicle like honey, vegetable oils, glycerine, or alcohol. These components are rapidly absorbed, metabolized, conjugated in the liver, and excreted by the kidneys. Some free volatiles are expelled in the lungs. The volume of a single drop of essential oil is about 0.05 mL, and the oral dosage range is usually 0.5-1.0 mL/d (10-20 drops daily) for adults and 0.15-0.3 mL/d (3-6 drops daily) for a 50 lb child. Essential oils should not be used systemically during pregnancy without professional supervision, but may be used as topical applications in concentrations of 2% or less. Essential oils should not be applied in or near the eyes, around the noses of children younger than 5 years of age, orally in those weighing less than 45 lbs, or topically in those younger than 2 years of age. Children are more prone to adverse effects from essential oils, and their skin tends to be more thin, sensitive, and permeable. Camphor, menthol, and eucalyptol (cineole), found in many plant essential oils and topical products, can produce serious mucosal irritation and central nervous system (CNS) dysfunction following inhalation by young children.[3,4]

The oil from American pennyroyal is 60-80% pulegone, compared to 55-95% pulegone in European pennyroyal. The acute oral lethal dose of pulegone in 50% of rats (LD_{50}) is 0.5 g/kg, and the LD_{50} for the essential oil is 0.4 g/kg. In Europe, the proportion of pulegone allowed in food as flavoring is 0.025 g/kg. The purified essential oils of both pennyroyal species are considered severely toxic and should not be used therapeutically, either internally or externally.[4] Pulegone is converted to toxic menthofuran by several cytochrome P450 isozymes in the liver.[5] Amounts of the essential oil considered toxic are 4-10 mL, while lethal doses lie in the range of 15-30 mL.[3]

In 1975, the Food and Drug Administration (FDA) designated both species of pennyroyal as "generally recognized as safe."[6] Adults may safely consume up to 10 g/d of the dried herb powder, but more commonly

Table 1

Dietary supplements designated likely hazardous by *Consumer Reports*

Agent	Mechanism (Toxin)	Potential Toxicity	Major Effects/Uses	Precautions
Pennyroyal oil (*Hedeoma pulegioides*; *Mentha pulegium*) from aerial plant	Hepatotoxic and nephrotoxic (pulegone)	Vomiting, weakness, dizziness; coma, cardiopulmonary arrest; death possible	Carminiative for dyspepsia; diaphoretic for colds; uterine stimulant as emmenogogue	Avoid all use of volatile oil. Only 1-2 cups of tea (1 tsp herb per cup) or up to 10 mL tincture daily; avoid in children and pregnancy.
Yohimbe (*Pausinystalia yohimbe; Corynanthe yohimbe*) bark	Alpha2-adrenergic antagonist (yohimbine)	Hypertension, tachycardia, anxiety, vomiting, weakness, incordination, dizziness; rarely, death possible	Erectile dysfunction	Avoid large doses (> 6 mg yohimbine) or long-term use. Avoid in children and pregnancy, in prostatitis, liver disease, cardiovascular disease, anxiety, and depression. Do not mix with psychotropics or antihypertensives.
Lobelia (*Lobelia inflata*) aerial parts	Binds nicotinic receptors (lobeline)	Nausea, vomiting, dizziness, stupor, tachypnea, arrhythmias; rarely, death possible	Bronchodilator for bronchitis or asthma; topically as antispasmodic for muscle spasms	Avoid large doses (> 5 mg lobeline) in heart disease, dyspnea, hypertension, pneumonia; avoid in pregnancy, young children, the elderly, chronic anxiety with fatigue.
Bitter orange (*Citrus aurantium*) peel	Adrenergic agonist (synephrine)	Hypertension, arrhythmias	Bitter tonic for indigestion, sedative insomnia; concentrated extract for obesity	Avoid concentrate with tachycardia, hypertension, glaucoma; with MAO inhibitors.
Skullcap (*Scutellaria lateriflora*) leaves	Unsubstantiated	Purported to be hepatotoxic	Sedative/anxiolytic for insomnia; antispasmodic for muscle spasms	Stop if jaundice, dark urine, or pale stools develop.
Organ and glandular extracts	Cows older than age 30 months can harbor prions.	Theoretical risk of mad cow disease (wasting of brain tissue)	Organ-specific hormone precursor and/or nutrient sources	Seek label content indicating FDA compliance.

consumption involves 1-2 cups/d of a tea (made from one teaspoon herb per cup) or up to 10 mL/d of the tincture. These can be used on occasion either warm as a carminative to relax circular smooth muscle spasms for dyspepsia, or hot as a diaphoretic to induce sweating with colds. All pennyroyal preparations should be avoided during pregnancy,[3,7] as well as in those with liver and kidney disease.[3] The *BSH* acknowledges pregnancy as a contraindication for both species.[2]

Two cases of pennyroyal and/or pulegone-associated toxicity occurred with Hispanic infants in California given home-grown pulegone-containing mint teas for respiratory symptoms or colic. One infant aged 8 weeks suffered multiple organ failure and died after consumption of 4 oz of the tea; menthofuran was found in two serum samples. A 6-month old infant who had received 3 oz of the tea threes time weekly for three months suffered from lethargy, seizures, and liver failure but survived after two months of hospitalization. Pulegone and menthofuran were detected in the serum. No pulegone-containing herb preparations should be used with infants.[8] Brook mint (*Mentha arvensis*), also known as field mint or poleo, grows along the Pacific coast and also contains pulegone, though in lesser amounts than the pennyroyal species.[9]

Around 1980, pennyroyal essential oils were taken in toxic doses in several unsuccessful attempts by women about 20 years old to induce abortions. Oral doses of 7.5 mL essential oil proved to be mildly toxic but an ineffective abortifacient in two women. They

experienced nausea, vomiting, dizziness, and/or digital paresthesia, but no liver damage or sequelae were detected.[10] Another woman ingested 10 mL pennyroyal oil as an abortifacient, having used pennyroyal leaves many times for inducing tardy menstruation with no ill effects. She became dizzy and was hospitalized for two days with normal physical and laboratory findings.[11] Another woman used a teaspoon of pennyroyal leaves per cup of tea three times daily off and on for two weeks, in addition to three pennyroyal leaf capsules. After failing to menstruate she consumed 15 mL of pennyroyal oil and began vomiting within two hours. Following hospitalization and treatment with gastric lavage, magnesium citrate, activated charcoal, acetylcysteine, and intravenous steroids, her condition stabilized after 12 hours. Released after four days, a two-week follow-up found no physical or laboratory abnormalities.[12] In a suspected abortion or suicide attempt, a single 1 oz (30 mL) dose proved fatal after seven days due to massive hepatic necrosis. This woman had frequently used pennyroyal tea in the past to induce menses.[10,11]

Another series of four cases in the mid-1990s included two cases of young women drinking 1 cup or 3 cups of pennyroyal tea (one teaspoon per cup) to induce menses that resulted in dizziness and weakness for one hour or abdominal cramps for four days, respectively, with no residual symptoms. Another young woman ingested repeated doses of a pennyroyal tincture and black cohosh root extract for two weeks in an attempt to induce abortion, followed by a final additional dosing of unknown quantity. She developed chills, vomiting, cramping, and syncope, then cardiopulmonary arrest and coma, and died 46 hours after the final ingestion. Lastly, a 22-month-old girl accidentally consumed an unknown quantity of pennyroyal oil. Examined 15 minutes later, she received gastric lavage and activated charcoal and sorbitol along with oral N-acetylcysteine. Serum samples obtained after 10 hours contained menthofuran. Her liver enzymes and clinical course were otherwise unremarkable. This case series included a review of the 22 published cases (four fatal, nine severe or moderate, and nine mild, not including the two fatal California infant cases) of pennyroyal poisoning over 127 years. It revealed that 18 were due to pennyroyal oil or essence (one part oil to seven parts alcohol). All cases followed a large acute dosing. Documented contemporary fatal cases had evidence of liver and kidney damage within 24 hours, whereas 15 survivors had no documented liver damage.[13]

While toxicity can be experienced with any form of pennyroyal product based on dosage, the preparations with the most concentrated pulegone content (especially essential oil, but also pennyroyal essence and even alcoholic extract) carry the highest risks. Use by infants and pregnant women should be avoided entirely.

2. Yohimbe (*Pausinystalia yohimbe*, syn. *Corynanthe yohimbe*) bark

Yohimbe has a traditional African and modern American use as an aphrodisiac. From five to 10 teaspoons of the shaved bark are used to make a decoction with one pint of water. Extracts are also sold. The potential benefits and risks of yohimbe have been tied to the effects of its major alkaloidal component, yohimbine. It is the most abundant of its many alkaloids whose content depends on the portion of the bark utilized. Total alkaloid content is 2.7-5.9% in stem bark. In samples with 5.3-5.7% total alkaloids, yohimbine yield accounted for about 1.1-2.2%.[14] Yohimbine has been marketed for more than 80 years to treat sexual difficulties. It has no apparent effect on sex drive in humans, but has demonstrated benefit for erectile disorder due to its antagonism of alpha2-adrenoceptors at therapeutic doses of 5-10 mg three times daily. Yohimbine is usually well tolerated, though it can increase systolic blood pressure, heart rate, and anxiety levels in certain individuals, especially at the higher dose of 30 mg per day but also in amounts as low as a single 5 mg dose.[14,15]

The *BSH* notes that yohimbe is contraindicated in liver and kidney disease and chronic inflammation of sexual organs or the prostate gland. It warns that yohimbe is not appropriate for excessive or long-term use and that it may potentiate monoamine oxidase (MAO) inhibitors.[2] Other noteworthy contraindications include pregnancy, children, coronary artery disease, hypertension, and depression. It should be avoided by those suffering from agoraphobia or panic attacks. Adverse effects include nausea, vomiting, abdominal distress, weakness, loss of coordination, dizziness, and excitation. Its toxicity can also be increased by other drugs including CNS stimulants, phenothiazines, and other adrenergic antagonists.[3] Most concerns about the possible risks of unmonitored use of yohimbe are based on yohimbine's potential for drug interactions and influence on specific medical conditions. While 15-20 mg of oral yohimbine can induce anxiety or increase blood pressure in otherwise healthy individuals, only 12 mg daily is needed to cause hypertension in patients using tricyclic antidepressants, and 10 mg can elicit mania in bipolar patients. Yohimbine also can antagonize therapeutic effects of antihypertensive drugs like clonidine.[16]

A case of lupus-like syndrome with generalized skin eruption and progressive renal failure occurred in a man following use of 16 mg of yohimbine for impotence.[17]

The risk of yohimbine abuse exists not only for those desperate to regain sexual function, but also among youth for whom the drug is inappropriately touted as an aphrodisiac, stimulant, and/or hallucinogen. In one case a 16-year-old girl ingested about 250 mg of a white powder purported to be yohimbine. A urine toxicological assay identified salicylates, caffeine, and two unidentified alkaloids that may (or may not) have been yohimbine metabolites. Though she experienced chest pain, anxiety, nausea, sweating, fine tremors, tachypnea, and tachycardia, by the next morning she was asymptomatic.[18]

Analytical evidence shows, however, that an American "yohimbe" product contained no yohimbine but may have been adulterated with caffeine instead.[16] One analysis compared authentic yohimbe bark with 7,089 parts per million (ppm) yohimbine to 18 commercial products in America supposedly containing yohimbe bark or its extract. Seven were combination products with < 0.1-12.3 ppm yohimbine. Of the yohimbe monopreparations, nine contained < 0.1-2.3 ppm yohimbine, while two others contained 296 and 489 ppm.[19] A recent European analysis of 20 commercial products found that, based on the maximal dose per day as indicated on the label, the amount of yohimbine delivered ranged from 1.32 mg to 23.16 mg.[20] One risk of yohimbe preparations with low or no alkaloid content lies in becoming accustomed to consuming what is marketed as a high dose and then switching to a more potent product.

The risks of using the isolated drug yohimbine are clear, but it has not been established that these effects are equivalent to those of the complex alkaloid combinations that exist in authentic yohimbe bark. For example, yohimbe bark is used in traditional medicine to treat angina and hypertension, conditions contraindicated for isolated yohimbine.[14] The other yohimbe alkaloids are less potent, but may compete with yohimbine, alter its pharmacokinetics, antagonize certain of its pharmacodynamic effects, act synergistically for other effects, or all of the above. Besides research on the bark and its extracts, what is needed at a minimum are requirements for good manufacturing practices that provide consistent levels of yohimbine in a given product. In addition, clear label instructions noting yohimbine content per dose should be accompanied by warnings for those with conditions or on medications that put them at higher risk.

3. Lobelia (*Lobelia inflata*) aerial plant

Also known as Indian tobacco and emetic weed, lobelia has long been a favorite in American herbalism for treating respiratory conditions as an expectorant. Due to its antispasmodic properties, it was an early standard for use in bronchial asthma and whooping cough. Yet, due to its effect on the nervous system and emetic effect in large doses, it has long been recognized as potentially toxic and best used as professionally manufactured preparations taken under medical supervision.[7] The dried herb powder has usually been taken in doses of 65-195 mg (average 100 mg) and the tincture in doses of 0.3-1.8 mL (5-30 drops), but some people are sensitive to even therapeutic doses. The toxic dose range is normally about 0.6-1.0 g of the dried leaf powder, while 4 g is considered potentially lethal. Tobacco smokers are typically less sensitive, since the effect of the alkaloid lobeline is similar to nicotine but about 1/10 as potent. Signs and symptoms of overdose include esophageal burning, nausea, vomiting, anxiety, dizziness, headache, weakness, stupor, rapid breathing, and cardiac arrhythmias.[3] The *BSH* warns that lobelia should not be used during pregnancy or taken in large doses, since dose-dependent cardioactivity has been noted. Due to the rapid induction of vomiting in large doses, the absorption of fatal amounts of lobeline is unlikely under normal circumstances. In cases of toxic exposure, activated charcoal is not advocated since this may block the emetic effect; gastric lavage is preferable.[2]

Dried mature lobelia contains a group of structurally related alkaloids,[21] and lobeline accounts for 20-40% of the total alkaloids.[22] Lobeline decreases with age from 1.95% in juvenile to 1.46% in adolescent to 0.76% in mature plants.[21,23] Its content varies from 0.38% in the leaves and 0.58% in the stems to 3.03% in the flowers.[23] In a comparative study, lobeline was found inferior to gastric lavage and syrup of ipecac for gastric evacuation of a barium sulfate test meal.[24] An aerosol with lobeline and a local anesthetic was patented 50 years ago as a quick, effective, long-lasting bronchodilating treatment for asthma and respiratory infections.[25] Lobeline acts as a primary stimulant and secondary depressant of parasympathetic and sympathetic ganglia, the adrenal medulla, carotid and aortic bodies, and neuromuscular junctions. Clinically, lobeline was used as a short-acting respiratory stimulant in cases of respiratory insufficiency due to poisoning by alcohol, soporifics, morphine, or spinal anesthesia and asphyxia in newborns. It has been replaced for these purposes by more effective agents. Yet, a recently discovered potential application is the use of lobeline as a treatment for amphetamine and methamphetamine abuse. Lacking its own addiction liability, it has been shown to inhibit amphetamine-induced hyperactivity and release of dopamine.[26]

Lobeline is potent in competing for the binding site that mediates the nicotine discriminative stimulus in the brains of rats[27] and is a strong nicotine antagonist,

blocking prostration, seizures, and the mortality caused by nicotine in rats.[28] A major clinical application of lobeline has been as a smoking deterrent. In an early 1960s placebo-controlled, double-blind study completed by 63 subjects, 0.5 mg of lobeline was taken about 10 times per day the first week, reduced to about five, then four, then three times per day over the following three weeks. By the fourth week, 66.6% of the lobeline group decreased their cigarette consumption 51-100%, with 13.8% stopping completely, compared to the 14.8% in the placebo group that had reduced their consumption with no one stopping entirely. The only side effects were mild nausea and a burning sensation in the throat or mouth during the first two weeks.[29] Another randomized, placebo-controlled, double-blind clinical trial of 313 subjects in eight clinics used 5 mg lobeline tablets morning and evening with 0.5 mg lobeline lozenges during the day (up to 10 lozenges/d) in the treated group. After seven days 66% of the treated subjects had stopped smoking, compared with 50% in the placebo group.[30] Lobeline was available until December 1993, when the FDA banned nonprescription aids for smoking cessation. Still, of about 30 published reports between 1936 and 1973, two-thirds claimed efficacy. A new trial to reduce nicotine withdrawal symptoms using a variety of sublingual lobeline tablet doses (2.5, 5.0, or 7.5 mg) and frequencies (three, six, nine, or 12 times daily) found significant symptom reduction with increasing dosage. Maximum efficacy was noted with 7.5 mg 9-12 times per day with no clinically significant adverse effects.[31] However, a subsequent multicenter trial of 7.5 mg sublingual lobeline nine times daily with 750 subjects for six weeks found no significant differences in cessation efficacy between lobeline and placebo. There was a positive trend for lobeline among highly dependent smokers.[32]

Lobeline and other alkaloids are not the only active components in lobelia. A study in mice using a crude methanolic extract of lobelia leaves demonstrated antidepressant activity. Upon fractionation, beta-amyrin palmitate was determined to be the active component.[33] It was found to increase norepinephrine in brain synaptosomes in mice.[34] Thus, like yohimbe, lobelia effects represent more than the activity of one major alkaloid. This is reflected in the lobeline content of an average herb dose (0.76% of 100 mg = 0.76 mg) amounting to only one tenth of the therapeutic lobeline dose for smoking cessation (7.5 mg). Due to its potentially toxic effect on sensitive or compromised individuals, lobelia should not be used in full or large doses by individuals suffering from heart disease, hypertension, dyspnea, or pneumonia. Its use is best avoided by young children, pregnant women, or those having low vitality including the elderly or victims of chronic anxiety with fatigue.[35]

Most herbalists and naturopathic doctors who use lobelia combine its liquid extracts in low-to-moderate amounts with other herbal extracts, either to use topically as a muscle relaxant or internally to treat respiratory symptoms associated with infections and asthma. Like nicotine, dermal absorption of lobeline is significant and can result in nausea and vomiting when lobelia is applied externally. Certainly, clear instructions as to proper restricted dosage and warnings about symptoms of excess should accompany any product or prescription (for internal or external use) that contains lobeline in significant amounts.

4. Bitter orange (*Citrus aurantium*) peel or unripe fruit

The dried rind of bitter orange (also known as Seville or sour orange and in China as chih-shi or zhishi) traditionally has been used for its bitterness and flavor as an aromatic digestive tonic in cases of dyspepsia.[7] Due to its bitter tonic action, the dried peel should not be used in cases of gastrointestinal ulcers.[3,35] Ingestion of large amounts of orange peel reportedly have caused colic, convulsions, and even death in children. Still, the *BSH* classifies bitter orange peel as safe when used appropriately.[2] The peel has been used in Brazilian folk medicine for insomnia, anxiety, and epilepsy, and the oil from the peel has been found to be sedative, anxiolytic, and anticonvulsant in rats at 0.5-1.0 g/kg.[36] The oil derived from the fresh peel also is used internally for flatulence and as a flavoring agent.[7] This aromatic oil has photosensitizing furanocoumarin components, as do other citrus oils, that should not be applied externally less than 12 hours before ultraviolet exposure.[3]

However, it is not based on traditional uses of the peel or its oil that bitter orange has come under increased scrutiny. Bitter orange unripe fruit extracts have recently become popular components of antiobesity treatments based on their content of adrenergic amines including synephrine, octopamine, and tyramine. Octopamine and synephrine increase lipolysis and fat oxidation in insect and mammalian fat cells.[37,38] Commercial extracts are typically standardized to their synephrine content. In the fresh fruit, synephrine content is only 0.02%, but in dried fruit it rises to 0.35%. Two dried extracts each contained about 3.0% synephrine, while three other herbal products had yields of 0.25%, 0.66%, and 0.99% synephrine. The dried extracts had low levels of octopamine (0.02-0.03%) and tyramine (0.06%), while the other three herbal products had half these amounts except for one with 0.15% octopamine. The fresh and

dried fruit were below the limits of quantification for these two amines.[39] Documented efficacy and safety of such bitter orange antiobesity products remains to be published.

Concern about bitter orange arises due to the adrenergic cardiovascular effects of these bioamines, especially synephrine. A study in rats using a "special extract" of bitter orange standardized to 6% synephrine found that a daily oral dose of 2.5-20 mg/kg for 28 days led to weight loss and reduced food intake. However, there was a dose-dependent mortality of 10-50% due to ventricular dysrhythmias but no blood pressure abnormalities.[40] Synephrine (at 0.1, 0.2, and 0.4 mg/kg/min) and the traditional Chinese digestant preparation, an aqueous extract of bitter orange unripe fruit with 1.25% synephrine (at 1.25, 2.5, and 5.0 mg/kg/min), were each administered intravenously to rats. Both increased mean arterial pressure in a dose-dependent manner.[41] In China, a synthetic mixture of bitter orange bioamines (synephrine and N-methyltyrosamine) has been shown to increase cardiac output and constrict dilated microvessels in dogs with endotoxic shock. It was used by injection to treat 50 children with septic shock with 96% efficacy.[42] Synephrine (also called oxedrine) delivered intravenously to 12 healthy men at 4 mg/min increased systolic and mean arterial blood pressure along with left ventricular contractility while reducing peripheral vascular resistance, but did not affect heart rate.[43]

The juice from bitter orange contains 57 mcg/mL synephrine but no measurable octopamine. In a crossover trial with normal subjects 8 oz of the juice (13.7 mg synephrine) did not change heart rate, systolic and diastolic blood pressure, or mean arterial pressure. Yet based on the potential effects of its synephrine content, it is considered contraindicated for individuals with tachyarrhythmias, severe hypertension, narrow-angle glaucoma, and MAO inhibitor recipients.[44] Based on results of consumption by two individuals of 8 oz of the juice containing 6,7-dihydroxybergamottin, drug substrates of cytochrome P450 (CYP) 3A4 may be better absorbed and and have increased activity due to the reduction of enterocyte content of CYP3A4 by 40%.[45] However, a bitter orange product lacking the compound 6,7-dihydroxybergamottin failed to alter bioavailability of 3A4 substrate midazolam in 12 humans after four weeks.[46]

A recent case report of a serious cardiovascular event made note of the use of a bitter orange antiobesity extract. A 55-year-old white woman developed chest pain and an aching shoulder. An arteriogram displayed a lesion in her left main coronary artery, and she was diagnosed as having an acute lateral wall myocardial infarction (MI). For a year she had been ingesting a multicomponent dietary supplement (Edita's Skinny Pill) for weight loss that contained 300 mg of bitter orange extract. She smoked but did not have a history of hypertension, coronary disease, or hyperlipidemia. Though this case did not establish bitter orange or synephrine as the cause of her MI, this was suspected due to similar cases associated with ephedra.[47] According to a major meta-analysis of ephedra and ephedrine safety, these agents are associated with increased risk of cardiac, psychiatric, gastrointestinal, and autonomic symptoms, though the majority of adverse event case reports are not documented sufficiently to allow for a meaningful assessment.[48] The actual risk with bitter orange extracts appears small compared to ephedra preparations. However, the safety of using ephedra or bitter orange extract is complicated by the combination of these products with sources of caffeine and other ingredients such as diuretics.[48,49]

Concentrated synephrine extracts of bitter orange do not only concentrate this one alkaloid. N-methyltyramine, similar in structure and activity to synephrine, is possibly available in higher amounts than found in the peel. In addition, the flavonoid compounds methyhesperidin and its derivatives are present in small amounts in the fruit, but in higher amounts can produce cardiac effects similar to the extract.

The tendency to abuse natural substances promoted to enhance weight loss by taking larger amounts than recommended is an issue for some individuals. The risk is further increased when pharmacologically potent substances in plants are specifically concentrated in extracts, even though bitter orange and other botanicals may be safe when normal doses are used in their whole form or as a traditional extract such as a tea.

In China, decoctions of 3-10 g of the peel are used for digestive complaints. This would provide about 7.5-22.5 mg synephrine or 0.11-0.33 mg/kg for someone with 70 kg body weight. Bitter orange should be avoided in pregnancy.[50] The dose approved by the German Commission E for loss of appetite or dyspepsia is 4-6 g of the dried peel made into a tea or 2-3 mL of tincture with no specified contraindications.[51]

Unlikely hazardous

1. Skullcap (*Scutellaria lateriflora*) plant

Skullcap, also called blue skullcap, is a native American plant that has a long history of use as a mild sedative and antispasmodic for insomnia, restlessness, and skeletal muscle spasms. The infusion is prepared by steeping one teaspoon in a cup of water for 30 minutes and can be taken three to four times daily. The tincture

can be effective in doses as low as 3-12 drops and is best taken in hot water.[7] A recent placebo-controlled, double-blind study in healthy volunteers showed that encapsulated freeze-dried skullcap herb and its freeze-dried extract are both effective anxiolytic agents compared to placebo.[52] Skullcap is designated in the *BSH* as an herb "that can be safely consumed when used appropriately." However, this book acknowledges a controversy about reports of hepatotoxicity associated with skullcap. In all likelihood, these reports appear to associated with products that had been adulterated with a species of *Teucrium*.[2] *[On the issue of the hepatotoxicity of germander (*Teucrium chamaedrys*), see Part 1 of this article in the August 2004 issue of* Alternative Medicine Alert.*]*

Four cases of hepatotoxicity in Great Britain were reported in the late 1980s in association with herbal products that purportedly contained skullcap. The symptoms of jaundice, dark urine, and/or pale stools in each case followed use of tablets labeled as containing skullcap and/or valerian. Consumption occurred over three days, three weeks in two cases, or two months. It took from two to 13 months for liver function tests to return to normal.[53] Reports of other cases of products containing skullcap with or without other herbs such as valerian or mistletoe were noted. No experimental data support the hepatotoxicity of valerian, mistletoe, or skullcap.[53,54] On examining commercial sedative preparations in Great Britain, it was found that the skullcap was not a *Scutellaria* species but rather from the genus *Teucrium*.[55] Several other cases of liver damage were reported in Norway with patients using skullcap alone or with several other herbal remedies. No positive identification of the hepatotoxic agents was reported.[6]

A case report in America also followed the use of skullcap (six capsules daily for six months) and a separate product labeled as pau d'arco at an unspecified dosage. This resulted in fatal hepatic failure, but the liver demonstrated evidence of hepatic veno-occlusive disease typical of pyrrolizidine alkaloid toxicity rather than typical toxic hepatitis.[56] *[On the issue of hepatotoxicity of pyrrolizidine alkaloids, see the section on comfrey in Part 1.]* Substitution of *Teucrum* species for *Scutellaria* also has reportedly occurred in America.[57] Although some skullcap is grown commercially, most is wild-harvested. The wholesale supply of blue skullcap labeled as *S. lateriflora* may include other indigenous *Scutellaria* species as well. However, "pink skullcap," also known as wild germander (*Teucrium canadense*) is available at a lower wholesale price. It has been known as an adulterant to commercial supplies of skullcap.[58] Although the morphological features of the two generally are distinct, once powdered, the microscopic characteristics are similar. A simple thin layer chromatogram produces an identifiable fingerprint of the flavonoids that allows for easy detection of substitution. A standard high performance liquid chromatogram also can readily distinguish between *Scutellaria* and *Teucrium* species because of the 6-hydroxy flavones without a B ring that are detected as constituents of *Scutellaria* only. Each genus has characteristic patterns that differ distinctly from the other.[59]

There is suspicion but no solid evidence to indicate that skullcap is a likely hazardous herbal supplement. Reports of hepatotoxicity in Europe associated with its use in most cases involve consumption of other herbal products as well, at a time when other herbs now known as hepatotoxins had not been removed from the commercial market. The few cases in which a skullcap product was reportedly used alone failed to document that the product actually contained skullcap. Subsequent analysis of commercial skullcap products indicates that germander species were substituted. Since the source for wholesale skullcap is largely wild-harvested plants from North America where wild germander is sold as pink skullcap, the cause for confusion, though unacceptable, is understandable. The situation is analogous to the Belgium use of a toxic *Aristolochia* species because of similarities between common Chinese names. *[On the issue of this mistaken herbal identity, see the section on aristolochic acid in Part 1.]* What is required is the establishment of good manufacturing regulations that assure product identity and accurate commercial labeling, beginning with correct labeling of wholesale herbs according to their scientific nomenclature, not just their common names.

2. Organ/glandular extracts

The *CR* inclusion of these animal products encompasses an extremely long list of possible products that the *CR* article summarizes as "brain/adrenal/pituitary/placenta/other gland" substance or concentrate. The basis for the inclusion of such products on their list as likely hazardous is due to a "theoretical risk of mad cow disease, particularly from brain extracts." However, *CR* also notes that in January 2004, the FDA banned from use in foods and supplements all high-risk bovine materials from older cows. Organ tissues from cows younger than 30 months of age are still permitted.[1] The ban recently was extended to cosmetic products such as lipstick and hairspray. The excluded high-risk material from cattle 30 months or older includes the skull, brain, eyes, and spinal cord. The tonsils and small intestine are prohibited from cattle of all ages, as well as tallow rendered with a concentration of impurities greater than

0.15%. This follows the first case of mad cow disease, or bovine spongiform encephalopathy, reported in the United States in December 2003, to prevent its spread to humans, which may result in the fatal variant Creutzfeldt-Jakob disease. The reason for the distinction in cattle age is that animals older than age 30 months can harbor prions, the misshapen proteins associated with the wasting away of brain tissue.[60]

Animal products typically carry a risk of contamination with infectious material that supercedes that of dried plants or their extracts. Since government regulations banning tissues that can harbor mad cow disease apply to foods, supplements, and cosmetics, the "likely hazardous" designation would seem to apply equally to these different types of products that contain FDA-approved bovine parts. Nonetheless, those dietary supplements that specifically utilize bovine material should clearly indicate compliance with these standards on the label. For the sake of consumer confidence, all dietary supplements that contain animal products of any sort should specifically indicate on the label the animal source, part, and country and date of origin. Such label information acknowledges the personal importance of dietary and cultural/religious preferences and taboos by allowing customers to make informed choices. It also provides a means of assessing product safety in the wake of future unforeseen issues of contamination.

Safety Through Moderation, Good Manufacturing, and Proper Labeling

Obvious dangers exist when dietary supplements, including herbs but especially herbal concentrated extracts, are indiscriminately consumed. In the case of pennyroyal oil, the content delivered in the whole herb or its traditional water extracts make an acute, unintentional over-exposure unlikely. However, the purified aromatic distillate, or large doses of an alcoholic extract, dramatically increase the potential risk of acute toxicity. In the case of yohimbe products, authentic extracts with significant levels of yohimbine can result in anxiety, high blood pressure, and other complications, especially for those using psychogenic or cardiovascular medications. Thus, its contraindication for iatrogenic impotence secondary to antidepressant or antihypertensive use should be clearly stated. Lobelia is a reliable bronchodilator whose usefulness is limited by its obvious emetic effect when used in large doses. However, this activity helps prevent absorption of amounts that could have seriously detrimental outcomes. Bitter orange extracts that are manufactured to concentrate synephrine content for the purposes of weight loss have a potential for abuse similar to ephedra products. The less potent activity of synephrine in comparison to ephedrine likely lessens both its effectiveness and risk when taken for obesity. The traditional use of its decoction as a digestive tonic is regarded as safe. With moderate consumption of traditional forms of these herbs the documented adverse effects associated with acute overdosage can be avoided.

The issue of misidentification has left its mark on the reputation of skullcap. Strict labeling requirements that assure proper identification of product contents is necessary to avoid toxicity from spurious herbs with similar common names or appearances. Requirements for appropriate sources and clear labeling of animal-derived dietary supplement material is warranted, especially in the case of bovine organ material. The implementation of good manufacturing practices, including record keeping to document sourcing and processing, is vital to public and professional assurance of safety for all dietary supplements. While absolute safety in health products may be an impossible goal, appropriate efforts need to be made to establish procedures that provide reliable products. It is inherently imperative that dietary supplements and their instructional labeling serve to enhance and improve, rather than threaten, the public's health and well-being. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

Ginseng and Warfarin

Source: Yuan CS, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients. *Ann Intern Med* 2004;141:23-27.

Goal: To evaluate whether American ginseng interacts with warfarin.

Design: Randomized, double-blind, placebo-controlled study completed over four weeks.

Subjects: Twenty healthy subjects (nine men and 11 nonpregnant women, 10 Caucasians) each paid $250 at study's end.

Methods: After initial screening, subjects received oral warfarin 5 mg daily for the first three days of week 1. During the second week, participants were randomly selected to receive either 2 g of American ginseng orally, or placebo, daily for three consecutive weeks. During the first three days of the last week of the study, all subjects were again given 5 mg warfarin daily. Participants recorded their food intake and filled out a questionnaire each week. Blood was drawn for International Normalized Ratio (INR) and plasma warfarin levels on days 1, 3, 4, 5, and 7 of the first and last week of the study. The primary endpoint was change in peak INR from week 1 to week 4.

Results: A small, but statistically significant, reduction in peak INR occurred in those subjects using American ginseng as compared to the placebo group. Lower results were likewise obtained in the ginseng group for INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC. Peak INR was correlated with peak plasma warfarin level.

Conclusion: American ginseng lessens the anticoagulant effect of warfarin.

Study strengths: All subjects completed the trial; close follow-up and laboratory evaluation; standardized dose of ginseng.

Study weaknesses: Small sample size; lack of generalizability (subjects were all healthy, while patients receiving warfarin generally are not); atypical dosing schedule.

Of note: Ginseng is one of the best-selling herbs in the country, but three different plants with varied medicinal activities are commonly sold as ginseng: *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Eleutherococcus senticosus* (known as Eleuthero or Siberian ginseng, although not technically a ginseng); ginseng is classified as an adaptogen or a restorative tonic that balances bodily functions; subjects maintained a consistent dietary intake of vitamin K throughout the study and did not use other medications; all ginseng used in the study came from the same lot with

an acceptable ginsenoside content (5.19%); 12 subjects were randomized to receive ginseng, while eight ingested the placebo; the researchers used a dose of American ginseng at the high end of the recommended range.

We knew that: Approximately 16% of people in the United States using prescription drugs are also using botanicals, meaning that upwards of 15 million people are at risk for herb-drug interactions; warfarin acts by impairing production of vitamin K-dependent coagulation factors in the liver; ginsenosides (triterpenoid saponins) appear to be the major active constituents of ginseng.

Clinical import: As the authors point out, warfarin possesses a narrow therapeutic index and its use is associated with risk of bleeding. Taking additional agents that may lessen warfarin's anticoagulant activity may place patients at risk in the opposite fashion, by leaving them with an INR in the sub-therapeutic range. One published report cites decreased anticoagulant activity in a patient previously stabilized on warfarin therapy after using Asian ginseng, and now we have suggestion of American ginseng use potentially causing the same problem, albeit in healthy subjects using an unusual dosing schedule. That stated, the effect of American ginseng on the INR noted in this study is clinically very small (the decrease in peak INR with ginseng compared to placebo at study's end was 0.19). Still, it is prudent to inquire about botanical medicine use, including use of American ginseng, in patients taking warfarin, especially those with whom there is difficulty maintaining a therapeutic INR.

What to do with this article: Keep a copy of the abstract on your computer. ❖

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

42. Essential oils should not be used:
a. in or near the eyes.
b. around the noses of children younger than age 5.
c. orally in those weighing less than 45 lbs.
d. topically in those younger than age 2.
e. All of the above

43. The *Botanical Safety Handbook* notes that yohimbe is contraindicated in:
a. liver disease.
b. kidney disease.
c. chronic inflammation of sexual organs or the prostate gland.
d. All of the above

44. Due to the rapic induction of vomiting when ingested in large doses, the absorption of fatal amounts of lobeline is unlikely under normal circumstances.
a. True
b. False

45. Concern about bitter orange arises due to the adrenergic cardiovascular effects of:
a. octopamine.
b. synephrine.
c. tyramine.
d. All of the above

46. Reports of hepatotoxicity associated with skullcap appear to involve products that had been adulterated with a species of *Teucrium*.
a. True
b. False

Answers: 42. e, 43. d, 44. a, 45. b, 46. a.

In Future Issues:

Acupuncture for the Treatment of Insomnia

Creatine to Increase Muscle Strength

Probiotics for Gastrointestinal Disorders and Antibiotic-Associated Diarrhea in Children

CAM Therapies and End-of-Life Care

Supplement to *Alternative Medicine Alert*
October 2004

ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

Patient Handout: Herbal Supplements—Safety

HERBAL SUPPLEMENTS ARE A TYPE OF DIETARY SUPPLEMENT *(SEE SIDEBAR BELOW)* THAT contain herbs, either singly or in mixtures. An herb (also called a botanical) is a plant or plant part used for its scent, flavor, and/or therapeutic properties.

Herbs have a long history of use and of claimed health benefits. If prepared and used correctly, the safety of herb use has generally been good; however, problems have been reported. This fact sheet contains points you should consider for your safety if you use, or are thinking about using, herbs for health purposes.

Key points

- It's important to know that just because an herbal supplement is labeled "natural" does not automatically mean it is safe or without any harmful effects. For example, the herbs chaparral and comfrey have been linked to serious liver damage.
- Herbal supplements can have drug-like effects. Therefore, they can cause medical problems if not used correctly or if taken in large amounts. In some cases, people have experienced negative effects even though they followed the instructions on a supplement label.
- Women who are pregnant or nursing should be especially cautious about using herbal supplements, because these products have not been tested in pregnant and nursing women and their effects are not known. This caution also applies to treating children with herbal supplements.
- It is important to consult your health care provider before using an herbal supplement, especially if you are taking any medications (whether prescription or over-the-counter). Some herbal supplements are known to interact with medications in ways that cause health problems. Even if your provider does not know about a particular supplement, he can access the latest medical guidance on its uses, risks, and interactions.

About Dietary Supplements

Dietary supplements were defined in a law passed by Congress in 1994. A dietary supplement must meet all of the following conditions:

- It is a product (other than tobacco) intended to supplement the diet, which contains one or more of the following: vitamins; minerals; herbs or other botanicals; amino acids; or any combination of the above ingredients.
- It is intended to be taken in tablet, capsule, powder, softgel, gelcap, or liquid form.
- It is not represented for use as a conventional food or as a sole item of a meal or the diet.
- It is labeled as being a dietary supplement.

- If you use herbal supplements, it is best to do so under the guidance of a medical professional who has been properly trained in herbal medicine. This is especially important for herbs that are part of an alternative medical system, such as the traditional medicines of China, Japan, or India. (Alternative medical systems are built upon complete systems of theory and practice, and have often evolved apart from and earlier than the conventional medicine that is practiced in the United States.)
- In the United States, herbal and other dietary supplements are regulated by the Food and Drug Administration (FDA) as foods. This means that they do not have to meet the same standards as drugs and over-the-counter medications for proof of safety and effectiveness. Although many dietary supplement companies manufacture products according to strict quality standards, the FDA has proposed new Good Manufacturing Practices for dietary supplements that will take effect soon.
- The active ingredient(s) in many herbs and herbal supplements are not known. There may be dozens, even hundreds, of such compounds in an herbal supplement. Scientists are currently working to identify these ingredients and analyze products. Identifying the active ingredients in herbs and understanding how herbs affect the body are important research areas for the National Center for Complementary and Alternative Medicine (NCCAM).
- Published analyses of herbal supplements have found differences between what is listed on the label and what is in the bottle. This means that you may be taking less—or more—of the supplement than what the label indicates. Also, the word "standardized" on a product label is no guarantee of higher product quality. Because of this variability, if you find a product that works for you, you should stick with it.
- Some herbal supplements have been found to be contaminated with metals, unlabeled prescription drugs, micro-organisms, or other substances.
- There has been an increase in the number of web sites that sell and promote herbal supplements on the Internet. The Federal Government has taken legal action against a number of company sites for posting incorrect or deceptive claims.

For more information

It is important to know how to evaluate dietary supplements claims. Some sources are listed below.

NCCAM Clearinghouse
P.O. Box 7923
Gaithersburg, MD 20898-7923
Telephone: (888) 644-6226
Fax-on-demand service: (888) 644-6226
E-mail: info@nccam.nih.gov
Web site: nccam.nih.gov

The NCCAM Clearinghouse provides information on complementary and alternative medicine and on NCCAM. Services include fact sheets, other publications, and searches of federal databases of scientific and medical literature. The Clearinghouse does not provide medical advice, treatment recommendations, or referrals to practitioners.

U.S. Food and Drug Administration (FDA)
Center for Food Safety and Applied Nutrition
Telephone: (888) 723-3366
Web site: www.cfsan.fda.gov

Information includes "Tips for the Savvy Supplement User: Making Informed Decisions and Evaluating Information" and updated safety information on supplements. If you have experienced an adverse effect from a supplement, you can report it to the FDA's MedWatch program, which collects and monitors such information, at (800) FDA-1088 or www.fda.gov/medwatch.

Office of Dietary Supplements (ODS)
Web site: ods.od.nih.gov

The Office's information, offered via its web site only, includes the International Bibliographic Information on Dietary Supplements (IBIDS), a searchable database of citations to peer-reviewed scientific literature on dietary supplements (go to dietary-supplements.info.nih.gov, select "Health Information").

CAM on PubMed
Web site: www.nlm.nih.gov/nccam/camonpubmed.html

CAM on PubMed, a database developed jointly by NCCAM and the National Library of Medicine, offers citations to articles in science-based, peer-reviewed journals on complementary and alternative medicine. Most citations include abstracts, and many link to the full text of articles.

Adapted from: National Center for Complementary and Alternative Medicine, National Institutes of Health. Available at: http://nccam.nih.gov/health/supplement-safety/.