CLINICAL REVIEW

Unsafe and potentially safe herbal therapies

TERESA BAILEY KLEPSER AND MICHAEL E. KLEPSER

Abstract: Unsafe and potentially safe herbal therapies are discussed.

The use of herbal therapies is on the rise in the United States, but most pharmacists are not adequately prepared educationally to meet patients' requests for information on herbal products. Pharmacists must also cope with an environment in which there is relatively little regulation of herbal therapies by FDA. Many herbs have been identified as unsafe, including borage, calamus, coltsfoot, comfrey, life root, sassafras, chaparral, germander, licorice, and ma huang. Potentially safe herbs include feverfew, garlic, ginkgo, Asian ginseng, saw palmetto, St. John's wort, and valerian. Clinical trials have been used to evaluate feverfew for migraine prevention and rheumatoid arthritis; garlic for hypertension, hyperlipidemia, and infections; ginkgo for circulatory disturbances and dementia; ginseng for fatigue and cancer prevention; and saw palmetto for benign prostatic hyperplasia. Also studied in formal trials have been St. John's wort for depression and valerian for insomnia. The clinical trial results are suggestive of efficacy of some herbal therapies for some conditions. German Commission E, a regulatory body that evaluates the safety and efficacy of herbs on the basis of clinical trials, cases, and other scientific literature, has established indications and dosage recommendations for many herbal therapies.

Pharmacists have a responsibility to educate themselves about herbal therapies in order to help patients discern the facts from the fiction, avoid harm, and gain what benefits may be available.

Index terms: Contraindications; Dosage; Drug interactions; Drugs, clinical effectiveness; Education, pharmaceutical; Mechanism of action; Patient information; Pharmacists; Plants; Toxicity

Am J Health-Syst Pharm. 1999; 56:125-38

Many of today's patients are using herbal therapies. According to Eisenberg et al.,[1] one in three people in the United States used at least one form of alternative medicine in 1990. The authors reported that use of unconventional medicine did not differ by sex or insurance status but differed by ethnic group (greatest among whites), income (more common among people with incomes greater than $35,000), age (25–49 years), and educational level (some college education). People in this country spent $3.24 billion for herbal therapies in 1997.[2]

As herbal use increased over the past decade, the number of U.S. pharmacy schools offering courses addressing herbal therapies declined. According to a 1997 publication by Miller and Murray,[3] only 9 of 77 pharmacy colleges maintained pharmacognosy as a course in their curricula. Many colleges had discontinued that course in the late 1970s in favor of more clinically oriented courses. Although many institutions eliminated pharmacognosy as a full course, 74% reported offering at least one course in which herbal therapies were addressed; however, only one third of those courses were required courses in the professional curriculum. Furthermore, the average number of credit hours for courses addressing herbal therapies was only 2.8 (range, 1–8), and only 38% of the course content was devoted to discussing herbal therapies. As a result, most pharmacists are not adequately equipped to respond to their patients' requests for information on herbal products.

Another dilemma U.S. pharmacists face regarding herbal therapies is the seeming lack of regulation and guidance by FDA. The Food, Drug, and Cosmetic Act of

TERESA BAILEY KLEPSER, PHARM.D., is Assistant Professor (Clinical) and MICHAEL E. KLEPSER, PHARM.D., is Associate Professor, Division of Clinical and Administrative Pharmacy, College of Pharmacy, The University of Iowa, Iowa City.

Address reprint requests to Dr. Teresa Bailey Klepser at the Division of Clinical and Administrative Pharmacy, College of Pharmacy, The University of Iowa, S412 Pharmacy Building, Iowa City, IA 52242, or teresa-klepser@uiowa.edu.

The assistance of C. Rosemarie Petzold with translation of non-English-language articles is acknowledged.

This is **article 204-000-99-001-H01** in the **ASHP Continuing Education System;** it qualifies for 2.0 hours of continuing-education credit. See page 139 or http://ce.ashp.org for the learning objectives, test questions, and answer sheet.

1938 and the Kefauver-Harris Drug Amendments of 1962 require that pharmaceutical companies prove their products to be safe and effective in order to be marketed. Before these regulations, herbal products were widely touted as remedies for ailments ranging from anxiety to heart failure. When these laws were enacted, some pharmaceutical companies complied with the regulations and provided scientific evidence of the safety and efficacy of their products; however, others discontinued manufacturing products, including some herbal medications. Some manufacturers began marketing herbs as nutritional supplements—a legislative loophole that allowed products with no proven efficacy to be marketed as long as no claims of efficacy were printed on the product label. Also, the Dietary Supplement Health and Education Act of 1994 (DSHEA) classifies herbal products as dietary supplements.[4] The labeling for dietary supplements cannot make any claims of therapeutic efficacy, only claims of effects on body structure or function. Under this provision, a manufacturer could claim that St. John's wort enhances mood or that Asian ginseng gives the body energy but could not claim that St. John's wort treats depression or that Asian ginseng treats chronic fatigue syndrome. If a manufacturer states a claim of therapeutic efficacy, such as treatment of a disease, the manufacturer must notify the secretary of health and human services within 30 days after making this claim. According to DSHEA, dietary supplements must include the following statements in the product labeling: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." The act allows the secretary of health and human services to remove a supplement from the market only when the product has been shown to be hazardous. The act allows the use of written material to promote products as long as the information is not false or misleading, does not promote a particular manufacturer or brand, presents a balanced view of available scientific information, appears physically separate from the product, and has no information appended to the material, such as stickers. The act also established the Office of Dietary Supplements at the National Institutes of Health and charged it with conducting scientific research on dietary supplements.

The approach of the Canadian Health Protection Branch is very similar to FDA's with respect to herbal products. The manufacturer must prove safety, efficacy, standardization, and stability to make a therapeutic claim for an herbal product or to market doses in a quantity known to be therapeutic. In Canada only one herb, feverfew, has gone through the standard process of premarket authorization in order to obtain a drug identification number.[5]

Several countries have more advanced legislative regulation of herbal products than the United States and Canada. In 1978, the German Federal Health Agency established German Commission E, a regulatory body that evaluates the safety and efficacy of herbs on the basis of clinical trials, cases, and other scientific literature. German Commission E has published more than 320 monographs on herbs; the American Botanical Council has translated those monographs into English. Many of the recommendations in this article are taken from the findings of German Commission E.

Unsafe herbs

In a national survey, a majority of interviewed consumers who used herbal therapies reported believing that herbs are just as effective, safe, and cost-efficient as nonherbal remedies.[2] The majority thought herbal therapies were as good as or better than nonherbal remedies in terms of efficacy (53%), safety (65%), and cost (58%).[2] However, the belief in safety may be false and potentially dangerous. Some herbs contain constituents that are carcinogenic or hepatotoxic.[6] Herbs considered carcinogenic include borage (*Borago officinalis*), calamus (*Acorus calamus*), coltsfoot (*Tussilago farfar*), comfrey (*Symphytum* species), life root (*Senecio aureus*), and sassafras (*Sassafras albidum*).[6] These herbs, except for calamus and sassafras, contain pyrrolizidine alkaloids that have been found to produce hepatic carcinomas in animals. The German Federal Health Agency has established regulations on the amount of pyrrolizidine alkaloids that may be contained in these herbs; however, the same is not true in the United States. Current regulations in the United States do not require that products identify the amount of pyrrolizidine alkaloids; thus, preparations containing these herbs are potentially unsafe. Safrole in sassafras and *cis*-isoasarone in calamus have shown a carcinogenic potential in animals in U.S. studies.[6]

Herbal remedies that have been reported to be hepatotoxic include chaparral (*Larrea tridentata*), germander (*Teucrium chamaedrys*), and life root.[6] There are case reports of patients developing jaundice, fatigue, pruritus, markedly elevated serum liver enzymes, severe cholestasis, hepatitis, and hepatocellular injury or necrosis documented by serial liver biopsies.[7-9] Signs and symptoms may occur three weeks to as late as seven months after ingestion.[8,9]

Licorice. Licorice (*Glycyrrhiza glabra*) is another herb that is now considered potentially harmful. When used in high dosages for long periods, licorice may cause pseudoaldosteronism, which can be manifested as headache, lethargy, sodium and water retention, hypokalemia, hypertension, heart failure, and cardiac arrest. To minimize the risk of adverse effects, German Commission E recommends that licorice be used for no longer than four to six weeks. The use of licorice is contraindicated in patients with liver cirrhosis, cholestatic liver disorders, hypertonia, kidney diseases, hypokalemia, pregnancy, and cardiovascular diseases.[10] Although licorice products are currently available in

the United States, patients should be advised to use licorice only under the supervision of a physician.

Ma huang. Ma huang (*Ephedra sinica*) is another potentially harmful herb that is available in the United States. Ma huang is considered unsafe for patients with hypertension, diabetes mellitus, or thyroid disease.

Claims have been made that ma huang is useful for the treatment of bronchial asthma, cold and flu symptoms, fever and chills, headaches and other aches, edema, and lack of perspiration.[11] Ma huang contains approximately 1% ephedrine and therefore has the potential to stimulate the central nervous system.[12] However, ephedrine is difficult to extract and purify from ma huang.

Ma huang is contraindicated in patients who have heart conditions, hypertension, diabetes, or thyroid disease or are taking a monoamine oxidase (MAO) inhibitor. Drugs interacting with ma huang may be similar to those that interact with ephedrine and include such agents as theophylline and cardiac glycosides. Patients taking ma huang should avoid caffeine-containing products. Adverse effects noted for ma huang include nervousness, insomnia, headache, dizziness, skin flushing, tingling, vomiting, palpitations, hypertension, and myocardial infarction.[6,12] Because of its stimulant properties and serious adverse-effect profile, patients should be urged to use ma huang only under medical supervision.

Ma huang may be consumed as a tea prepared by steeping 1 teaspoonful (2 g) of dried herb in 0.5 pint (240 mL) of boiling water for 10 minutes.[12,13] This tea preparation contains the equivalent of 15 to 30 mg of ephedrine. The maximum recommended ephedrine dosage is 150 mg during a 24-hour period.

Some products available without a prescription contain the combination of ma huang and St. John's wort and are marketed as "herbal phen-fen." Phen-fen received its name when phentermine and fenfluramine were used in combination for weight loss. Herbal phen-fen is touted as a natural and effective weight-loss agent that does not contain phentermine or fenfluramine. However, herbal phen-fen carries the same warnings that apply to ma huang and St. John's wort when each is used alone. Furthermore, there are no clinical studies to support the use of herbal phen-fen.

Potentially safe herbs

Potentially safe herbs discussed in this article are feverfew, garlic, ginkgo, Asian ginseng, saw palmetto, St. John's wort, and valerian.

Feverfew (*Tanacetum parthenium*)

Since feverfew is indicated by the Canadian Health Protection Branch for use in the prophylaxis of migraine headaches, in Canada manufacturers of nonprescription feverfew may make claims of its effectiveness in preventing migraines.[14] Other reported uses of feverfew include the treatment of fever, menstrual problems, asthma, dermatitis, and arthritis.

Mechanism of action. The mechanism of action of feverfew remains unknown,[15] although researchers have suggested several possibilities: inhibition of serotonin release, inhibition of prostaglandin synthesis, inhibition of platelet aggregation and secretion, inhibition of polymorphonuclear leukocyte degranulation, inhibition of phagocytosis of human neutrophils, inhibition of mast-cell release of histamine, cytotoxic activity against human tumor cells, antimicrobial activity, and an antithrombotic potential.[15,16] Feverfew may inhibit serotonin release from platelets in the same manner as does methysergide maleate, an ergot alkaloid.[17] The irreversible inhibition of prostaglandin synthesis is thought to occur through a mechanism different from that of salicylates, possibly by inhibition of cyclooxygenase and phospholipase A_2. Alpha-methylene butyrolactones found in feverfew, particularly parthenolide and epoxyartemorin, have been shown to irreversibly inhibit thromboxane B_2 and leukotriene B_4 in human leukocytes.[18] Inhibition of thromboxane B_2 and leukotriene B_4 indicates that phospholipase, possibly phospholipase A_2, is inhibited.[19] Other investigators have reported that inhibition of phagocytosis of human neutrophils may reduce tissue damage by oxygen radicals.

Clinical efficacy for prevention of migraines. Johnson[20] evaluated the efficacy of feverfew in 17 patients with a history of migraines for at least two years and no more than eight attacks a month. Patients in this double-blind study had regularly used feverfew for at least three months before being enrolled. Patients taking medications for migraine prophylaxis were enrolled if the drug regimen had been started before use of feverfew. The patients received feverfew 50 mg or placebo every morning for six months. During the study, the patients were allowed to consume acetaminophen, aspirin, or ergotamine for acute relief of a migraine. Each patient kept a diary detailing the frequency and severity of migraine symptoms. Patients in the placebo group had migraines significantly more often than patients in the feverfew group (3.4 versus 1.5 attacks per month, $p < 0.02$). The incidence of nausea and vomiting was lower in the feverfew group (42% versus 79%, $p < 0.05$). The two groups consumed similar amounts of aspirin and ergotamine; however, placebo recipients consumed more acetaminophen (no p value given). Although the severity of headaches and the incidence of nausea and vomiting were reported to be significantly greater in the placebo group compared with the feverfew group, data were not reported. Because this study involved current users of feverfew, the study may have been biased in favor of feverfew by preselecting patients who already tolerated and benefited from the herb.

Murphy et al.[21] conducted a randomized, double-blind study of feverfew for the prophylaxis of migraine

in 60 patients who had had migraines for at least two years and at least one attack a month. Patients were enrolled in the study if they were otherwise healthy. All migraine-related medications were stopped before the start of the study. The patients received one feverfew capsule (70–114 mg, with a mean of 82 mg per capsule) or placebo daily for four months. The patients kept a migraine diary. Symptoms were graded with a 4-point scale of severity; patients' global assessment of treatment efficacy was measured with a 10-cm visual-analogue scale, where 0 cm was "worst ever" and 10 cm was "best ever." The number of migraine attacks was significantly reduced by feverfew (3.6 attacks during two months for feverfew, versus 4.7 attacks for placebo, $p < 0.005$). The duration of attacks was similar between the groups and averaged 14–15 hours per attack. Headaches tended to be milder in patients taking feverfew; however, the difference was not significant. Feverfew was associated with a significantly lower incidence of nausea (39% versus 42%) and vomiting (5% versus 9%) ($p < 0.02$). The visual-analogue scale for global assessment of efficacy also showed feverfew to be superior to placebo (7.4 versus 6.0 cm, $p < 0.0001$). There were no differences in adverse effects. The most commonly reported adverse effect in both groups was mouth ulceration (10% for feverfew and 16% for placebo, no p value given).

Palevitch et al.[22] conducted a randomized, double-blind trial in 57 patients who attended an outpatient pain clinic in Israel. The severity of migraines and symptoms was determined with a questionnaire. During the first part of the trial, all patients received feverfew 100 mg daily for 60 days. In the second part, patients received feverfew (containing 0.2% parthenolide) 100 mg daily or placebo for 30 days, and in the third part, the patients were crossed over to the other treatment. Pain intensity and symptoms associated with migraines were significantly reduced when the patients took feverfew. There was no washout period before the crossover, and no patient demographics were reported.

De Weerdt et al.[23] conducted a randomized, double-blind trial in 44 patients, ages 18–64 years, who had suffered monthly migraine attacks since early youth. All prophylactic migraine medications were stopped; however, the patients could continue to use migraine-abortive medications such as acetaminophen, ergot preparations, and sumatriptan. Patients received one feverfew capsule daily for four months or placebo and were then crossed over, with no washout period. Compliance was assessed by counting pills. Patients in both treatments suffered the same number of migraines. Feverfew did not offer any benefit over placebo. The feverfew capsules were prepared from an alcoholic extract of the herb that may not have contained the same active ingredients as dry leaves.

Clinical efficacy for treatment of rheumatoid arthritis. Pattrick and colleagues[24] conducted a double-blind study of feverfew in 41 women with uncontrolled symptomatic rheumatoid arthritis. The patients were randomly assigned to receive feverfew 70–86 mg daily or placebo for six weeks and were allowed to receive an intra-articular dose of triamcinolone hexacetonide 20 mg at three weeks if symptoms persisted. Measures of efficacy included the duration of early morning stiffness, stiffness after inactivity, pain, grip strength, the Ritchie articular index, and global assessments by patients and observers. In general, patients in both groups reported similar efficacy. However, the feverfew group had significantly better grip strength (a positive effect on rheumatoid arthritis) and significantly higher concentrations of serum immunoglobulin G (a negative effect). The groups required similar numbers of corticosteroid injections. One patient taking feverfew reported minor oral mucosal ulceration and tongue soreness.

Cautions. Feverfew should be avoided in pregnancy because it may have emmenagogue activity (i.e., promote menstruation). Women who are lactating, children under the age of two years, and persons who are allergic to plants in the daisy family (Asteraceae) should also avoid feverfew.

Drug interactions. Because of its potential to inhibit cyclooxygenase and phospholipase A_2, feverfew may interact with anticoagulants and potentiate the antiplatelet effect of aspirin.

Adverse effects. The most commonly reported adverse effect of feverfew is gastric discomfort after oral consumption. Minor oral mucosal ulcerations, tongue irritation, and lip swelling may occur when fresh leaves are chewed. Heart rate was reported to increase by 26 beats/min in two patients.[11] Since there is a lack of precise information on potential long-term toxicity, the Canadian Health Protection Branch advises consumers not to take feverfew continuously for more than four months without medical advice. Discontinuation of feverfew may produce muscle and joint stiffness and nervous system reactions such as rebound of migraine symptoms, anxiety, and poor sleep patterns.[11]

Dosage. The Canadian Health Protection Branch recommends a dosage of 125 mg of feverfew daily; each dosage unit should contain at least 0.2% parthenolide.

Garlic (*Allium sativum*)

Garlic is indicated by German Commission E for use in the support of dietary measures for treating hyperlipoproteinemia and to prevent arteriosclerosis.[13] Garlic has been reported to have antiplatelet, antibacterial, antifungal, antihypertensive, antihyperlipidemic, and anti-inflammatory properties.[25]

Mechanism of action. Garlic's proven mechanisms of action include inhibition of platelet function; increased levels of two antioxidant enzymes, catalase and glutathione peroxidase; and inhibition of thiol enzymes, such as coenzyme A and 3-hydroxy-3-meth-

ylglutaryl coenzyme A (HMG-CoA) reductase. Garlic contains an inactive ingredient, alliin, which is a colorless, odorless sulfur-containing amino acid. When a garlic bulb is pressed or cut, allinase is released and converts alliin to allicin. It is allicin that gives garlic its characteristic odor. Allicin is believed to be at least one of the active ingredients in garlic and has been found to increase the levels of antioxidant enzymes.[11] Other potentially active ingredients include the organic disulfides that are found in garlic oil. These compounds inactivate thiol enzymes, such as coenzyme A and HMG-CoA reductase.[11] Garlic oil inhibits platelet function by interfering with thromboxane synthesis.[26]

Clinical efficacy for treatment of hypertension. There have been many studies evaluating the efficacy of garlic. Silagy and Neil[27] performed a meta-analysis of studies evaluating the effect of garlic on blood pressure. Only prospective, randomized studies with two or more treatment-group comparisons and a duration of at least four weeks were included in the meta-analysis. Eight studies met the predefined criteria and are summarized in Table 1.[28-35] Each of these studies included patients with an elevated blood pressure, but not necessarily hypertension, during a run-in phase of two to four weeks. Six of the studies were placebo controlled. One study compared garlic with reserpine and a diuretic, and another compared garlic with bezafibrate, an antihyperlipidemic agent. All but one[34] of the studies were described as double-blind; however, garlic's odor seems difficult to hide, and it is not known if these studies accomplished the blinding effectively. All the studies used the same dried garlic powder preparation (Kwai®) in dosages of 600–900 mg daily (equivalent to 1.8–2.7 g of fresh garlic per day) for 1–12 months. The pooled mean reduction in systolic blood pressure was 7.7 mm Hg more with garlic than with placebo (95% confidence interval [CI], 5.0–17.2 mm Hg). Likewise, the pooled mean reduction in diastolic blood pressure was 5.0 mm Hg more with garlic (95% CI, 3.4–9.6 mm Hg). Some of the studies did not describe the position (e.g., supine) of the subjects when blood pressure was measured, and none of the studies assessed compliance. Because there have not been enough trials with different garlic dosages and dosage intervals, the optimum dosage for the treatment of hypertension is difficult to determine. No significant increase in adverse effects was reported with garlic.

Clinical efficacy for treatment of hyperlipidemia. Warshafsky et al.[36] performed a meta-analysis of studies that evaluated the effect of garlic on total serum cholesterol. Studies were included if they were randomized, placebo controlled, used no other antihyperlipidemic agents as controls, reached the calculated effect size, and had at least 75% of patients with baseline total cholesterol concentrations of >200 mg/dL. Five studies met the inclusion criteria and are summarized in Table 2.[29,30,37-39] The garlic dosage was 600–1000 mg daily for 8–24 weeks. Again, although the majority of the studies were double-blind, it is unknown whether the patients and observers could smell or taste the garlic. Also, the studies evaluated the effect of garlic on total cholesterol and triglycerides but not on low-density lipoprotein cholesterol or high-density lipoprotein cholesterol. The pooled results of the meta-analysis indicated that patients treated with garlic achieved total serum cholesterol concentrations a mean of 23 mg/dL lower (95% CI, −29 to −17 mg/dL, $p < 0.001$) than patients in the placebo groups. Since the investigators used a wide range of dosage regimens, the optimum regimen for garlic could not be determined. Meta-analysis of the effect of garlic on triglycerides was not carried out.

Clinical efficacy for treatment of infections. Reports from Russia and Japan describe the use of garlic against infections caused by gram-positive and gram-negative organisms.[11] Species of *Escherichia, Proteus,*

Table 1.
Summary of Studies of Garlic for Hypertension

Ref.	Study Design[a]	*n*	Dosage Regimen	Milligrams of Allicin per Day	Change in Blood Pressure: Systolic mm Hg	Systolic %	Diastolic mm Hg	Diastolic %
28	P, DB	40	600 mg/day × 12 wk	3.6	−11	−6	−15	−15
29	P, DB	47	200 mg t.i.d. × 12 wk	3.6	−19[b]	−11	−13[c]	−12
30	P, DB	40	900 mg/day × 16 wk	5.4	−6[d]	−4	−3[b]	−3
31	P, DB	60[e]	400 mg b.i.d. × 4 wk	4.8	0	0	−7[b]	−9.5
32	P, DB	60	900 mg/day × 6 mo	5.4	−25[d]	−17	−10[d]	−11
33	P, DB	42[e]	300 mg t.i.d. × 12 wk	5.4	−1	0	1	0
34	SB	40	600 mg/day × 12 wk[f]	3.6	−16	−9	−16	−16
35	DB	94[e]	900 mg/day × 12 wk[g]	5.4	−8[b]	−6	−4[b]	−5

[a] P = placebo controlled, DB = double-blind, SB = single-blind.
[b] $p < 0.05$, change from baseline.
[c] $p < 0.01$.
[d] $p < 0.001$.
[e] None of the study enrollees had hypertension at baseline.
[f] The other treatment group received reserpine and a diuretic.
[g] The other treatment group received bezafibrate.

Table 2.
Summary of Studies of Garlic for Hyperlipidemia

Ref.	Study Design[a]	*n*	Dosage Regimen	Milligrams of Allicin per Day	Reduction in Total Cholesterol		Reduction in Triglycerides	
					mg/dL	%	mg/dL	%
37	P, DB	221	800 mg/day × 16 wk	4.8	31[b]	12	38[b]	17
30	P, DB	40	900 mg/day × 16 wk	5.4	62[b]	21	50[c]	24
38	P, DB	30	700 mg/day × 8 wk	. . .[d]	32	12	30	10
29	P, DB, CX	47	200 mg t.i.d. × 12 wk	3.6	38[e]	14	31[b]	18
39	P	27	1000 mg/day × 24 wk	. . .	44[b]	14	. . .	. . .

[a]P = placebo controlled, DB = double-blind, CX = crossover.
[b]$p < 0.001$, change from baseline.
[c]$p < 0.01$.
[d]Not reported.
[e]$p < 0.05$.

Salmonella, Providencia, Citrobacter, Klebsiella, Aeromonas, Staphylococcus, and *Bacillus* have shown in vitro susceptibility to garlic.[40] Garlic also has antifungal activity against *Candida* species in vitro; however, the effect may not be clinically important.[11,40] Garlic has been evaluated as prophylaxis against viral infections.[40]

Drug interactions. When used concurrently with anticoagulants, garlic may increase the risk of bleeding.[13]

Adverse effects. Garlic has been reported to induce gastrointestinal adverse effects, such as heartburn and flatulence; sweating; lightheadedness; allergic reactions; and menorrhagia.[11,13]

Dosage. Although the investigators in a majority of the clinical studies used either 0.6–1.2 g of dried powder containing approximately 2–5 mg of allicin daily or 2–4 g of fresh garlic, German Commission E recommends a dosage of 4 g of fresh garlic daily.[12,40] Since allicin is acid labile, enteric-coated tablets or capsules yield better absorption by bypassing the stomach and releasing their contents into the alkaline medium of the small intestine.[13]

Ginkgo (*Ginkgo biloba*)

In Germany, *Ginkgo biloba* is indicated for use in the treatment of cerebral circulatory disturbances resulting in reduced functional capacity and vigilance, such as vertigo, tinnitus, memory impairment, and mood changes.[13] Ginkgo is also recommended for peripheral arterial circulatory disturbances, such as intermittent claudication.[13] Ginkgo has been used for headaches, varicose insufficiency, dementia, asthma, cochlear deafness, colitis, chronic active hepatitis B infection, hyperlipidemia, impotence, premenstrual syndrome, senile macular degeneration, shock, stroke, and depression.[41]

Mechanism of action. *G. biloba* extract produces arterial and venous vasoactive changes that increase tissue perfusion and increase cerebral blood flow.[13] The physiological effects are attributed to the extract's ability to produce arterial vasodilation, inhibit arterial spasms, decrease blood viscosity, and reduce erythrocyte aggregation. The effects are probably due to stimulation of prostaglandin biosynthesis or to indirect vasoregulatory effects on catecholamines.[13] *G. biloba* extract has also been shown to have a superoxide anion-scavenging effect and superoxide dismutase activity.[42] Ginkgo contains many active ingredients, such as flavonoids (quercetin, kaempferol, and isorhamnetin) and terpenoids (ginkgolides A, B, and C and bilobalide).[43] Flavonoids are hypothesized to provide antioxidant activity, reduce capillary fragility, and increase the threshold of blood loss from capillaries. Ginkgolides antagonize the effect of platelet-activating factor (PAF) on platelet aggregation, neutrophil degranulation, and oxygen free-radical production. Ginkgolide B is a potent inhibitor of PAF and seryl and aspartyl proteases.[44] Bilobalide may have properties that protect nerve cells.

Clinical efficacy for treatment of cerebral and peripheral circulatory disturbances. Kleijnen and Knipschild[43,45] reviewed 40 clinical studies evaluating ginkgo's efficacy in the treatment of cerebral and peripheral insufficiency. The studies were assessed with predefined criteria for patient characteristics, sample size, randomization, description of the intervention, blinding, description of the measured effect, and checkability of analyzed results by the reader. Eight studies of the effect of ginkgo on cerebral insufficiency were considered to be of good quality and are summarized in Table 3.[46-53] Twelve symptoms of cerebral insufficiency were evaluated in a majority of the studies: difficulty in concentration, difficulty in memory, absent-mindedness, confusion, lack of energy, tiredness, decreased physical performance, depression, anxiety, dizziness, tinnitus, and headaches. In six of the eight studies, a 3-, 4-, or 5-point ordinal scale was used to assess symptoms. Seven of the trials showed statistically and clinically significant positive effects of ginkgo compared with placebo.[46-52] No serious adverse effects were reported.

Of the 15 controlled trials evaluating intermittent claudication, two were determined by Kleijnen and Knipschild[43] to be of acceptable quality. Bauer[54] performed a randomized, double-blind study in 79 patients with peripheral arteriopathy (Fontaine stage 2b). The patients received ginkgo 40 mg three times daily for six months. The ginkgo group had a significant increase in walking distance tolerated before pain ($p < 0.05$).

Table 3.
Summary of Studies of Ginkgo for Cerebral Insufficiency[a]

Ref.	Study Design[a]	*n*	Dosage Regimen	Symptoms Assessed	Improvement in Symptoms
46	DB	99	150 mg/day × 12 wk	12, by patient	70% of ginkgo-treated patients, 14% of placebo-treated patients
				12, by physician	72% of ginkgo-treated patients, 8% of placebo-treated patients
47	M, DB	209	150 mg/day × 12 wk	11, by patient	83% of ginkgo-treated patients, 53% of placebo-treated patients
				11, by physician	71% of ginkgo-treated patients, 32% of placebo-treated patients
48	DB	100	160 mg/day × 3 mo	Tinnitus, dizziness, and hearing impairment; by patient	Improvement or cure within 70 days for ginkgo-treated patients and within 119 days for placebo-treated patients
49	M, DB	166	160 mg/day × 1 yr	17, by physician	17% of ginkgo-treated patients, 8% of placebo-treated patients
50	M, DB	67	160 mg/day × 3 mo	Vertigo, by patient	75% of ginkgo-treated patients, 18% of placebo-treated patients
				Vertigo, by physician	47% of ginkgo-treated patients, 18% of placebo-treated patients
51	DB	96	112 mg/day × 12 wk	Concentration	54% of ginkgo-treated patients, 19% of placebo-treated patients
				Memory	52% of ginkgo-treated patients, 17% of placebo-treated patients
				Anxiety	48% of ginkgo-treated patients, 17% of placebo-treated patients
				Dizziness	61% of ginkgo-treated patients, 23% of placebo-treated patients
				Headaches	65% of ginkgo-treated patients, 24% of placebo-treated patients
				Tinnitus	37% of ginkgo-treated patients, 12% of placebo-treated patients
52	DB	58	160 mg/day × 6 wk	12	Significant improvement in ginkgo-treated patients
53	DB	54	120 mg/day × 12 wk	Cognitive, by physician	Significant improvement in ginkgo-treated patients
				Overall, by patient	No difference
				Overall, by physician	No difference

[a]Adapted from reference 45.
[b]DB = double-blind, M = multicenter.

Ginkgo also significantly increased the total distance walked ($p < 0.001$). Global assessments by the investigator revealed that 61% of the patients who were taking ginkgo had a good or very good response, versus 6% of the placebo group (no *p* value given). Additionally, 66% of the patients taking ginkgo believed they had a good or very good response, compared with 20% of the placebo group (no *p* value given).

In a randomized, double-blind, multicenter study, Saudreau et al.[55] evaluated 55 patients with Fontaine stage 3 chronic occlusive arterial disease of the lower limbs. Twenty-six patients received i.v. infusions of 100 mg of ginkgo in 500 mL of 0.9% sodium chloride injection twice daily for eight days; 29 patients received placebo. Vasoactive drugs, hemodilution, and antiplatelets were prohibited; anticoagulants and pentazocine were allowed. Pain was evaluated with a 100-mm visual-analogue scale, where 0 represented no pain and 100 severe pain. A patient questionnaire based on the McGill Pain Questionnaire, a qualitative and quantitative instrument, was also administered. Baseline characteristics of the groups were similar. Ginkgo-treated patients had a greater reduction in pain at rest on the visual-analogue scale for pain (ginkgo, 61 mm to 30 mm; placebo, 51 mm to 39 mm; $p < 0.05$). Ginkgo recipients made significantly fewer requests for pentazocine than placebo recipients ($p = 0.03$).

Clinical efficacy for treatment of dementia. In a randomized, double-blind study in 202 patients with Alzheimer's disease or multi-infarct dementia documented with a Mini-Mental State Examination score of 9–26, Le Bars et al.[56] evaluated the effect of ginkgo 40 mg three times daily or placebo for one year. Subjects with major medical conditions, such as cardiac disease, chronic renal failure, type 1 diabetes mellitus, and liver disease, were excluded. Cognitive impairment was assessed by the investigators using the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog), on which a score of 70 represents the worst impairment. Activities of daily living and social behavior were assessed by the caregiver using the Geriatric Evaluation by Relative's Rating Instrument (GERRI), on which a score of 1 is best and a score of 5 is worst. General psychopathology was assessed by the investi-

gators using the Clinical Global Impression of Change (CGIC). Half of the patients receiving ginkgo improved by at least 2 points on the ADAS-Cog, compared with less than one third of the placebo group ($p = 0.005$). The mean change from baseline on the ADAS-Cog also favored ginkgo, with an improvement advantage of 1.4 points ($p < 0.04$). Thirty-seven percent of the patients who received ginkgo showed appreciable improvements on the GERRI, whereas only 23% of placebo-treated patients improved ($p = 0.003$). The mean change from baseline on the GERRI also favored ginkgo, with an increase of 0.07 point for ginkgo versus a decrease of 0.07 point for placebo ($p = 0.04$). There was no difference between ginkgo and placebo on the CGIC. Although ginkgo yielded statistically significant improvements on two psychiatric rating instruments, the clinical importance of the changes is unknown. The authors concluded that ginkgo may improve cognitive and social functioning for 6–12 months. Since the trial excluded patients with major medical conditions, such as cardiac disease, chronic renal failure, type 1 diabetes mellitus, and liver disease, the safety of ginkgo in those types of patients is unknown.

Adverse effects. Ginkgo is generally safe and well tolerated; however, three people have been reported to have had episodes of spontaneous bleeding while taking ginkgo. A spontaneous hyphema developed in a 70-year-old man after he ingested ginkgo 40 mg twice daily for one week.[57] The patient's only other medication was aspirin 325 mg daily, which he had been taking for three years. Bilateral subdural hematomas developed in a 33-year-old woman after she took ginkgo 60 mg twice daily for two years.[58] She had no history of major medical problems; her other medications were acetaminophen and, briefly, ergotamine with caffeine. A left frontal subdural hematoma developed in a 72-year-old woman after she took ginkgo 50 mg three times daily for six to seven months.[59] It is not known whether these three cases are coincidental or causal.

The most commonly reported adverse effects of ginkgo are gastric disturbances, headache, dizziness, and vertigo. There is one case report of tonic–clonic seizures and loss of consciousness after 50 ginkgo seeds were ingested.[11]

Dosage. German Commission E recommends a dosage of 40 mg of ginkgo three times daily with meals for at least four to six weeks.[13] Preparations that are standardized to contain 6% terpene lactones and 24% ginkgo flavone glycosides are recommended.[41] An intravenous preparation of ginkgo that is manufactured in Europe is not available in the United States.

Asian ginseng (*Panax ginseng*)

Asian ginseng is indicated in Germany for use as a tonic to combat lassitude, debility, and lack of energy and concentration, as well as during convalescence.[60] Asian ginseng has also been used as an aphrodisiac, an adaptogen to increase resistance to stress, and a treatment for weakness, atherosclerosis, bleeding disorders, colitis, and relief of problems associated with aging and cancer.[11]

The chemical composition of ginseng products may vary with the plant extract derivative, the age of the root, the location where grown, the season when harvested, and the method of drying. The active constituents, also known as ginsenosides, are present in various quantities in different parts of the ginseng plant; the root is believed to contain the highest concentrations.[61] Cultivating the plant during autumn and allowing at least five to six years of growth yields more ginsenosides. The drying technique influences the concentration of various ginsenosides in the final product; air-drying produces white ginseng, and steam produces red ginseng.[61]

Mechanism of action. At least 28 ginsenosides have been isolated.[62] Each ginsenoside produces a unique set of pharmacologic effects on the central nervous system, the cardiovascular system, and other body systems.[11] Some ginsenosides produce biological effects in direct opposition to those produced by others.[62] For example, ginsenoside R_{b1} has been shown to have a suppressive effect on the central nervous system, whereas ginsenoside R_{g1} has a stimulatory effect. Ginsenosides R_{b1}, R_{b2}, R_c, R_d, and R_e have been reported to have antistress properties. Ginsenosides have the ability to modestly reduce blood glucose concentrations and increase blood insulin. R_{g1} stimulates DNA, protein, and lipid synthesis in rat bone marrow cells, and R_{b1} increases RNA synthesis. Analgesic and anti-inflammatory effects have been reported for some ginsenosides. Hypertensive and hypotensive effects have also been noted.[61] R_{g2} has inhibitory effects on platelet aggregation similar to those of aspirin, and R_o reportedly inhibits the conversion of fibrinogen to fibrin. The amount of ginseng administered may also influence the effects produced. In rats and mice, small doses of ginseng extract resulted in increased spontaneous motor activity, whereas larger doses had an inhibitory effect on the central nervous system.[62] There is no scientific evidence of ginseng enhancing sexual experience.

Clinical efficacy for treatment of fatigue. D'Angelo et al.[63] performed a double-blind study in 32 healthy men 20–24 years of age. These volunteers were randomly assigned to receive *Panax ginseng* extract G115 (Ginsana[b]) 100 mg or placebo twice daily for 12 weeks. Each volunteer underwent a battery of psychomotor assessments. Ginseng had a favorable effect on attention (as measured with a cancellation test), processing (mental arithmetic and logical deduction tests), integrated sensorimotor function (choice reaction-time test), and auditory reaction time. However, only the mental arithmetic scores were significantly better in the ginseng group ($p < 0.05$). No differences were detected with respect to pure motor function (tapping test), recognition (digit–symbol substitution test), and visual

reaction time. Although the sample was relatively small, the investigators did use a standardized ginseng preparation and a variety of standardized, objective psychomotor assessments.

Pieralisi et al.[64] performed one of the largest randomized, double-blind, crossover studies of the effect of ginseng on physical performance. Fifty male sports teachers, ages 21–47 years, received one ginseng capsule (Geriatric Pharmaton[c])—containing *Panax ginseng* extract G115, dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements—or placebo twice daily for six weeks and were then crossed over to the other treatment for six more weeks. The volunteers' physical performance was evaluated by treadmill exercise testing. Subjects receiving ginseng had significantly improved work capacity, supposedly resulting from improved oxygen utilization by the muscles. The investigators theorized that the subjects used energy more efficiently and had greater endurance while taking ginseng—albeit a fortified formulation.

To determine the effect of ginseng on glucose control, Sotaniemi et al.[65] performed a randomized, double-blind, multicenter study that included 36 people with type 2 diabetes mellitus. The patients were randomly assigned to receive ginseng[d] 100 mg, ginseng 200 mg, or placebo once daily for eight weeks. Ginseng at either dosage improved mood ($p < 0.001$), vigor ($p < 0.01$), and psychomotor performance ($p < 0.001$). Well-being improved with the 200-mg/day dosage ($p < 0.001$). There was no improvement in memory or sleep. Ginseng lowered fasting blood glucose levels, and the 200-mg/day dosage significantly reduced glycosylated hemoglobin levels ($p < 0.05$). Exact values for outcomes were not reported, however. Ginseng did not influence the other glucose-control indicators or the lipid profiles.

Clinical efficacy for prevention of cancer. Yun and Choi[66] evaluated the effect of Asian ginseng on various human cancers in 1987 pairs of subjects in a case–control study at a cancer center in Korea. Cases and controls completed a questionnaire designed to elicit details of ginseng consumption, such as frequency, duration, and ginseng preparation used. The authors reported that ginseng significantly decreased the risk of malignancy among ginseng users compared with nonusers. They also reported that the benefit of ginseng may be dose related. Ginseng preparations that contained fresh ginseng (less than four years old when harvested, and lacking any processing), white ginseng (four to six years old, and air-dried after peeling), and red ginseng (six years old when harvested, and steamed and dried) significantly reduced the risk of some cancers. Fresh-sliced ginseng, fresh ginseng juice, and white ginseng tea did not significantly reduce the risk. Ginseng significantly reduced the risk of cancer of the lips, oral cavity, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, lungs, and ovaries. There was no risk reduction for cancers of the female breast, uterine cervix, urinary bladder, and thyroid gland.

Cautions. It is recommended that ginseng be avoided in children and in patients with hypertension, psychological imbalances, headaches, heart palpitations, insomnia, asthma, inflammation, infections with high fever, and pregnancy.[67]

Drug interactions. Two case reports describe symptoms, including insomnia, headache, tremulousness, irritability, and visual hallucinations, when phenelzine was taken concurrently with ginseng.[68,69] A reduction in the International Normalized Ratio may occur when ginseng and warfarin are taken together.[70]

Adverse effects. Hypertension, euphoria, restlessness, nervousness, insomnia, skin eruptions, edema, and diarrhea were reported in 22 patients after long-term ginseng use at an average dosage of 3 g of ginseng root daily.[71] In that particular study, however, there was no control group, the patients used a variety of ginseng preparations, and some patients used Siberian ginseng (*Eleutherococcus senticosus*) instead of Asian ginseng. In five other subjects, blood pressure actually decreased.[72] Ginseng may exert an estrogen-like effect in postmenopausal women, resulting in diffuse mammary nodularity and vaginal bleeding.[73,74]

Dosage. German Commission E recommends that Asian ginseng be taken as 1–2 g of crude herb daily or as 100–300 mg of ginseng extract three times daily.[6,11] Ginseng may also be consumed as a tea by mixing 3 g (equivalent to 1 teaspoonful) of herb in a cup of boiling water, steeping 5–10 minutes, and drinking one cup one to three times daily.[11,75] Commercial products containing at least 4–5% ginsenosides are recommended.[67]

Saw palmetto (*Serenoa repens*)

Saw palmetto has been indicated by German Commission E for use in the treatment of difficulties in micturition associated with benign prostatic hyperplasia (BPH).[12] Folklore describes the use of saw palmetto to increase breast size, sperm production, and sexual vigor.[41]

Mechanism of action. The mechanism of action of saw palmetto is unknown but is believed to be multifaceted. In vitro data suggest two probable primary mechanisms of action: (1) inhibition of the binding of dihydrotestosterone to androgen receptors in prostate cells[76] and (2) inhibition of 5α-reductase, the enzyme responsible for converting testosterone to dihydrotestosterone.[77] Other mechanisms of action may include inhibition of prolactin binding, inhibition of 5-lipoxygenase metabolite production, inhibition of growth factors involved in prostate cell proliferation, antiestrogenic activity, and antiedemic activity.[77]

Clinical efficacy for treatment of BPH. Carraro et al.[78] performed the largest double-blind study evaluating the efficacy of saw palmetto for BPH. In this multicenter study, 1069 men with moderate BPH were randomized to receive saw palmetto (Permixon[e])—con-

taining 90% free fatty acids and 7% esterified fatty acids—160 mg twice daily or finasteride 5 mg once daily for six months. There were no significant differences between the groups in patient-rated quality-of-life scores (saw palmetto group, 69%; finasteride group, 73%) or International Prostate Symptom Scores (37% and 39%). Urinary flow rate, postmicturition residual volume, and prostate volume improved in each group; however, the finasteride recipients improved more than those given saw palmetto. Several large studies have not demonstrated a benefit of finasteride relative to placebo, however.[79,80]

Semino and colleagues[81] conducted a randomized, double-blind study comparing prazosin with saw palmetto in the treatment of 41 patients with BPH. Twenty-one patients received prazosin adjusted to 2 mg twice daily, and 20 received saw palmetto 160 mg twice daily for 12 weeks. Prazosin was marginally more effective than saw palmetto, as measured by uroflowmetry, nocturnal frequency of urination, urinary flow rate, and postmicturition residual volume. The small sample and the uncertainty of whether the saw palmetto product was standardized limit this study.

Table 4 summarizes four studies of saw palmetto (standardized to 90% free and 7% esterified fatty acids) for BPH.[78,82-84]

Saw palmetto should be avoided in women who are pregnant and in children.[11]

Drug interactions. To date there have been no reported drug interactions involving saw palmetto.

Adverse effects. Adverse effects are rare but may include headache, nausea, and upset stomach.[11,12]

Dosage. German Commission E recommends a daily dose of 1–2 g of the dried saw palmetto fruit or 320 mg of the lipophilic extract.[12,13] Dosages of the lipophilic extract used in studies have typically been 80 mg four times daily or 160 mg twice daily. A standardized extract of saw palmetto containing 85–95% sterols and fatty acids is recommended.[6] Teas prepared from saw palmetto berries are probably ineffective, because the active constituents are water insoluble. Taking saw palmetto with food may decrease gastrointestinal adverse effects.

St. John's wort (*Hypericum perforatum*)

German Commission E indicates that St. John's wort may be used in supportive treatment for anxiety and depression.[60] Also reported for St. John's wort are uses as an anti-inflammatory agent and a sedative.[41]

Mechanism of action. The mechanism of action of St. John's wort is not known.[85-87] Many active ingredients have been isolated, including hypericin, pseudohypericin, quercetin, quercitrin, isoquercitrin, hyperoside, rutin, amentoflavone, hyperin, hyperforin, ashyperforin, and xanthones. Hypericin, flavonoids, and xanthones have demonstrated irreversible inhibition of MAO types A and B in vitro; however, this is not believed to be the sole mechanism of action. It is possible that St. John's wort may also inhibit reuptake of serotonin, synaptic uptake of γ-aminobutyric acid (GABA), and binding to GABA receptors. It has been postulated that St. John's wort may reduce expression of cytokines, especially interleukin-6.

Clinical efficacy for treatment of depression. Linde et al.[88] performed a meta-analysis of 23 randomized trials—15 placebo-controlled studies and 8 studies comparing St. John's wort with other antidepressant therapies. Only randomized trials in which at least two

Table 4.
Summary of Studies of Saw Palmetto (SP) for Benign Prostatic Hyperplasia (BPH)

Ref.	Study Design[a]	*n*	Dosage Regimen	% Change in Frequency of Nocturnal Urination	% Change in Urinary Flow Rate	% Change in Postmicturition Residual Volume	% Change in Prostate Volume	% Patients with Improvement in BPH Symptoms	
								Assessed by Patient	Assessed by Physician
82	P, DB	94	SP 160 mg b.i.d. × 1 mo	−46[b]	51[b]	−42[b]		88[b]	90[b]
			Placebo	−15	5	9		68	36
83	P, DB	70	SP 160 mg b.i.d. × 12 wk	−36				36	NS[c]
			Placebo	−36				35	NS
84	R, P, DB, MC	176	SP 160 mg b.i.d. × 1 mo	−32.5[d]	28.9[e]			71.3	56.6
			Placebo	−17.7	8.5			67.5	47.2
78	R, DB, MC	1069	SP 160 mg b.i.d. × 6 mo		25[f]	15[g]	−6[b]	69	37
			Finasteride 5 mg q.d.		30	−7	−18	73	39

[a] P = placebo controlled, DB = double-blind, R = randomized, MC = multicenter.
[b] $p < 0.001$, between groups.
[c] NS = not significant.
[d] $p = 0.028$.
[e] $p = 0.038$.
[f] $p = 0.035$.
[g] $p = 0.017$.

treatment groups were compared were included. Disorders studied in the meta-analysis had to have been defined with validated depression scales. Sample sizes in the studies ranged from 30 to 162 patients. Patients had a baseline Hamilton Depression Rating Scale (HAM-D) score of 12–30. "Treatment responders" were defined as having a HAM-D score of <10, a score of <50% of the baseline score, or both. The meta-analysis indicated that hypericum extract 350–1000 mg/day (equivalent to hypericin 0.48–2.7 mg/day) for four to eight weeks was significantly more effective than placebo (55% versus 22% response rates in the treatment and placebo groups, respectively [pooled rate ratio, 2.67; 95% CI, 1.78–4.01]). In the same meta-analysis, hypericum 500–900 mg/day (hypericin 0.4–2.7 mg/day) for four to six weeks was compared with maprotiline 75 mg/day, imipramine 50–75 mg/day, amitriptyline 30 mg/day, and desipramine 100–150 mg/day. Hypericum and the antidepressant drugs had similar response rates of 64% and 58.5%, respectively (pooled rate ratio, 1.10; 95% CI, 0.93–1.31). Limitations of the meta-analysis included variable dosages and preparations of St. John's wort used, short durations of treatment and follow-up, lack of compliance information, heterogeneous patient characteristics reported among studies, analysis not based on the number of patients intended to be treated, and small samples. Although the studies stated the total daily hypericin dose, hypericin may not be the sole active component of St. John's wort.

Cautions. St. John's wort may induce photosensitivity, so fair-skinned persons should be cautioned about exposure to bright sunlight. There are reports of St. John's wort producing photodermatitis in animals.[13] St. John's wort should be avoided in pregnancy because of its emmenagogue and abortifacient properties. No negative influence on general performance or the ability to drive a car or operate heavy machinery has been reported.[85]

Drug interactions. It is unknown whether St. John's wort interacts with any other medications. Since one of the proposed mechanisms of action of St. John's wort is inhibition of MAO, the herb's drug and food interaction profiles may be similar to those of prescription MAO inhibitors. When taking a prescription MAO inhibitor with certain medications or food, a person may have symptoms of a serotonin syndrome. Serotonin syndrome occurs when serotonin-mediated neurotransmission is increased by an augmentation of serotonin synthesis, increase in serotonin release, inhibition of serotonin uptake, inhibition of serotonin metabolism, or stimulation of postsynaptic serotonin receptors.[89] Initial symptoms include changes in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever and may progress to cardiac arrest, coma, seizures, or multiple organ failure with disseminated intravascular coagulation. Prescription MAO inhibitors interact with anesthetics, antidepressants, antidiabetic agents, β-blockers, dextromethorphan, guanethidine, levodopa, meperidine, serotonin-reuptake inhibitors, sympathomimetics, and L-tryptophan. Tyramine-containing foods such as cheese, beer, wine, herring, and yeast interact with MAO inhibitors. It is not known whether St. John's wort has these drug and food interactions. Currently, there are no case reports of such herb–drug or herb–food interactions. However, patients should be warned of the potential for drug and food interactions involving St. John's wort, especially the possibility for interactions with serotonin-reuptake inhibitors.

Adverse effects. Adverse effects reported to occur with St. John's wort include gastrointestinal irritations, allergic reactions, tiredness, and restlessness.[11,85,90,91]

Dosage. German Commission E recommends a daily dose of 2–4 g of the powdered herb (0.5–3 mg of hypericin).[88] In some studies the daily dose was given in three divided doses. Pharmacokinetic data suggest that it may be reasonable to give St. John's wort as a single daily dose, since the half-lives of hypericin and pseudohypericin are 24–26.5 and 16–36 hours, respectively.[85] If St. John's wort is to be taken as a tea, 1–2 teaspoonfuls (2–4 g) of the herb may be steeped in 240 mL of boiling water for 10 minutes and consumed once daily.[13]

Valerian (*Valeriana officinalis*)

German Commission E recommends valerian for use in the management of restlessness and nervous disturbances of sleep.[60] Folklore suggests that valerian has also been used as a sedative and a spasmolytic.[25]

Mechanism of action. Valerian's mechanism of action has not been fully elucidated. Houghton[92] reviewed the literature on animal and human studies of the biological activity of valerian. Several compounds have been isolated from valerian and can be grouped into three categories: constituents of the volatile oil, iridoids (also known as the valepotriates), and alkaloids. Constituents of the volatile oil have been further subdivided into 12 monoterpenes and 17 sesquiterpenes. At least 37 valepotriates and 7 alkaloids have been isolated from valerian. It is believed that valepotriates are responsible for most of the sedative activity of valerian. Valepotriates and volatile oils of valerian, including valeranone 6, kessane derivatives 3a–3f, valerenic acid 5a, and valerenal 5b, have been reported to prolong barbiturate-induced sleeping time in rodents. Valerenic acid 5a has been shown to exert pentobarbital-like central depressant activity rather than muscle relaxant or neuroleptic effects. Valerenic acid 5a has also been found to inhibit the enzyme that catalyzes the breakdown of GABA. Some of the valepotriates have demonstrated spasmolytic properties, possibly because of effects on calcium entry or calcium binding in muscle tissue. Of the valepotriates, valtrate and isovaltrate have antidepressant properties, and didrovaltrate has a tranquilizing effect similar to that of benzodiazepines.

Clinical efficacy for treatment of insomnia. Leathwood et al.[93] conducted a double-blind, crossover study in 128 volunteers. The participants completed a preliminary questionnaire on their sleep characteristics; data collected included sex, age, good versus poor sleeper, time to onset of sleep, number of awakenings per night, coffee intake, and smoking status. No information was collected on other medication use, alcohol use, physical activity, or food intake. The subjects were given nine sachets: three sachets containing two capsules of placebo, three sachets containing two capsules of valerian aqueous extract 200 mg, and three sachets containing two capsules of valerian 200 mg and hops 100 mg (Hova[f]). On nine consecutive nights, each subject ingested a single sachet one hour before retiring. On awakening each morning, the volunteers completed a questionnaire evaluating sleep latency, sleep quality, night awakenings, dream recall, and somnolence. Compared with placebo, valerian significantly improved subjective sleep quality in habitually poor or irregular sleepers ($p < 0.05$). The valerian product with hops, however, performed no better than placebo. Similarly, valerian aqueous extract, not valerian–hops, resulted in significantly shorter sleep latency compared with placebo ($p < 0.05$). Night awakenings and dream recall were similar among the groups. Valerian–hops produced greater somnolence the next morning than placebo ($p < 0.01$) or valerian extract ($p < 0.05$). The authors were unable to explain the discrepancy in the results noted for the two valerian preparations. Objective data, such as electroencephalographic patterns, were not evaluated.

Leathwood and Chauffard[94] performed a double-blind, randomized, three-way-crossover study in eight volunteers with mild insomnia. The participants were randomized to receive valerian aqueous extract 450 or 900 mg or placebo for 12 nights. Subjective data were collected by questionnaire, and objective data were collected by wrist-worn activity meters. Valerian 450 mg offered no benefit in subjective sleep quality, sleep latency, or sleep depth compared with placebo. The 900-mg dose offered no advantage over the 450-mg dose, and patients had significantly more sleepiness the next morning compared with the placebo group. Mean sleep latency, recorded by activity meters, was significantly shorter for valerian 450 mg (9 minutes) and valerian 900 mg (11.4 minutes) than for placebo (15.8 minutes).

Cautions. Precautions for valerian may be similar to those for benzodiazepines, barbiturates, and opiates. Caution is recommended when ingesting valerian while driving or performing other tasks requiring alertness and coordination. Valerian should also be used with caution during pregnancy.

Drug interactions. No drug interactions involving valerian have been reported, but given its sedative property, valerian may potentiate the sedative effect of medications such as barbiturates, benzodiazepines, opiates, and alcohol.

Adverse effects. Valerian may cause headaches, hangover, excitability, insomnia, uneasiness, and cardiac disturbances. Ataxia, decreased sensibility, hypothermia, hallucinations, and increased muscle relaxation have also been reported.[95] Valerian appears on the U.S. list of medicinal substances generally recognized as safe (commonly known as the GRAS list).

Dosage. German Commission E recommends that 2–3 g of the dried herb or extract be given one to several times a day.[59] As a tea, 2–3 g of valerian should be used per cup one to several times a day, with 2.5 g being equivalent to one teaspoon. The recommended dosage of valerian tincture is 0.5–1 teaspoonfuls (1–3 mL) one to several times daily.

Conclusion

Pharmacists have a responsibility to educate themselves about herbal therapies in order to help patients discern the facts from the fiction, avoid harm, and gain what benefits may be available.

[a]Kwai, Lichtwer Pharma GmbH, Berlin, Germany; standardized to percent content of alliin.

[b]Ginsana, Ginsana Products Ltd., Lugano, Switzerland; standardized as G115 ginseng.

[c]Geriatric Pharmaton, Pharmaton S.A., Lugano; standardized as G115 ginseng.

[d]Ginseng, Dansk Droge, Copenhagen, Denmark.

[e]Permixon, Pierre Fabre Medicament, Castres, France; standardized to 90% free and 7% esterified fatty acids.

[f]Hova, Zyma S.A., Nyon, Switzerland; standardized to 60 mg of valerian extract and 30 mg of hop flower extract.

References

1. Eisenberg D, Kessler RC, Foster C et al. Unconventional medicine in the United States: prevalence, costs and patterns of use. *N Engl J Med.* 1993; 328:246-52.
2. Johnston BA. One-third of nation's adults use herbal remedies: market estimated at $3.24 billion. *Herbalgram.* 1997; 40:49.
3. Miller LG, Murray WJ. Herbal instruction in United States pharmacy schools. *Am J Pharm Educ.* 1997; 61:160-2.
4. U.S. Senate. S. Rep. 103-410 (103rd Cong., 2nd Sess., 1994).
5. Cottrell K. Herbal products begin to attract the attention of brand-name drug companies. *Can Med Assoc J.* 1996; 155:216-9.
6. Tyler VE. What pharmacists should know about herbal remedies. *J Am Pharm Assoc.* 1996; NS36(1):29-37.
7. Alderman S, Kailas S, Goldfarb S et al. Cholestatic hepatitis after ingestion of chaparral leaf: confirmation by endoscopic retrograde cholangiopancreatography and liver biopsy. *J Clin Gastroenterol.* 1994; 19(3):242-7.
8. Larrey D, Vial T, Pauwels A et al. Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. *Ann Intern Med.* 1992; 117: 129-32.
9. Ben Yahia M, Mavier P, Metreau JM et al. Chronic active hepatitis and cirrhosis induced by wild germander. 3 cases. *Gastroenterol Clin Biol.* 1993; 17:959-62.
10. Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am.* 1994; 23:359-77.
11. The review of natural products. St. Louis: Facts and Comparisons; 1997.

12. Foster S. Herbs for your health. Loveland, CO: Interweave; 1996.
13. Tyler VE. Herbs of choice: the therapeutic use of phytomedicinals. New York: Haworth; 1994.
14. Awang DVC. Feverfew fever—a headache for the consumer. *Herbalgram*. 1993; 29:34-6.
15. Hobbs C. Feverfew. *Herbalgram* 1989; 20:26-35.
16. Hayes NA, Foreman JC. The activity of compounds extracted from feverfew on histamine release from rat mast cells. *J Pharm Pharmacol*. 1987; 39:466-70.
17. Heptinstall S, Williamson L, White A et al. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leukocytes. *Lancet*. 1985; 1:1071-3.
18. Sumner H, Salan U, Knight DW et al. Inhibition of 5-lipoxygenase and cyclooxygenase in leukocytes by feverfew. *Biochem Pharmacol*. 1992; 43:2313-20.
19. Makheja AN, Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew (*Tanacetum parthenium*). *Prostaglandins Leukot Med*. 1982; 8:653-60.
20. Johnson ES. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J*. 1985; 291:569-73.
21. Murphy JJ, Heptinstall S, Mitchell JRA. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet*. 1988; 2:189-92.
22. Palevitch D, Earon G, Carasso R. Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: a double-blind placebo-controlled study. *Phytother Res*. 1997; 11: 508-11.
23. De Weerdt CJ, Bootsma HPR, Hendriks H. Herbal medicines in migraine prevention: randomized, double-blind placebo-controlled crossover trial of a feverfew preparation. *Phytomedicine*. 1996; 3:225-30.
24. Pattrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis*. 1989; 48:547-9.
25. Tyler VE, Foster S. Herbs and phytomedicinal products. In: Covington TR, Berardi RR, Young LL, eds. Handbook of nonprescription drugs. 11th ed. Washington, DC: American Pharmaceutical Association; 1996:695-713.
26. Ariga T, Oshiba S, Tamada T. Platelet aggregation inhibitor in garlic. *Lancet*. 1980; 1:150. Letter.
27. Silagy CA, Neil HAW. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens*. 1994; 12:463-8.
28. Kandziora J. Antihypertensive effectiveness and tolerance of a garlic medication. *Arztl Forsch*. 1988; 35(1):1-8.
29. Auer W, Eiber A, Hertkorn E et al. Hypertension and hyperlipidaemia: garlic helps in mild cases. *Br J Clin Pract Symp Suppl*. 1990; 69:3-6.
30. Vorberg G, Schneider B. Therapy with garlic: results of a placebo-controlled, double-blind study. *Br J Clin Pract Symp Suppl*. 1990; 69:7-11.
31. Kiesewetter H, Jung F, Pindur G et al. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. *Int J Clin Pharmacol*. 1991; 29:151-5.
32. Santos OS, Grunwald J. Effect of garlic powder tablets on blood lipids and blood pressure. A six month placebo-controlled double-blind study. *Br J Clin Res*. 1993; 4:37-44.
33. Jain AK, Vargas R, Gotzkowsky S et al. Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med*. 1993; 94:632-5.
34. Kandziora J. The blood pressure lowering and lipid lowering effect of a garlic preparation in combination with a diuretic. *Arztl Forsch*. 1988; 35(3):1-8.
35. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. *Arzneimittelforschung*. 1992; 42:1473-7.
36. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol: a meta-analysis. *Ann Intern Med*. 1993; 119: 599-605.
37. Mader FH. Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study. *Arzneimittelforschung*. 1990; 40:1111-6.
38. Plengvidhya C, Chinayon S, Sitprija S et al. Effects of spray dried garlic preparation on primary hyperlipoproteinemia. *J Med Assoc Thai*. 1988; 71:248-52.
39. Lau BH, Lam F, Wang-Cheng R. Effect of an odor modified garlic preparation on blood lipids. *Nutr Res*. 1987; 7:139-49.
40. Reuter HD. *Allium sativum* and *Allium ursinum*: part 2. Pharmacology and medicinal application. *Phytomedicine*. 1995; 2(1):73-91.
41. Tyler VE. The honest herbal. 3rd ed. New York: Haworth; 1993.
42. Pincemail J, Dupuis M, Nasr C et al. Superoxide anion scavenging effect and superoxide dismutase activity of *Ginkgo biloba* extract. *Experientia*. 1989; 45:708-12.
43. Kleijnen J, Knipschild P. *Ginkgo biloba*. *Lancet*. 1992; 340: 1136-9.
44. Koltai M, Hosford D, Guinot P et al. Platelet activating factor (PAF): a review of its effects, antagonists and possible future clinical implications (part I). *Drugs*. 1991; 42:9-29.
45. Kleijnen J, Knipschild P. *Ginkgo biloba* for cerebral insufficiency. *Br J Clin Pharmacol*. 1992; 34:352-8.
46. Schmidt U, Rabinovici K, Lande S. Einfluss eines *Ginkgo-biloba*-Spezialextraktes auf die Befindlichkeit bei zerebraler Insuffizienz. *Münch Med Wochenschr*. 1991; 133(suppl 1):S15-8.
47. Brüchert E, Heinrich SE, Ruf-Kohler P. Wirksamkeit von LI 1370 bei älteren Patienten mit Hirnleistungsschwäche. Multizentrische Doppelblindstudie des Fachverbandes Deutischer Allgemeinärzte. *Münch Med Wochenschr*. 1991; 133(suppl 1): S9-14.
48. Meyer B. Étude multicentrique randomisée à double insu face au placebo du traitment des acouphènes par l'extrait de *Ginkgo biloba*. *Presse Med*. 1986; 15:1562-4.
49. Taillander J, Ammar A, Rabourdin JP et al. Traitement des troubles du vieillissement cérébral par l'extrait de *Ginkgo biloba*. *Presse Med*. 1986; 15:1583-7.
50. Haguenauer JP, Cantenot F, Koskas H et al. Traitment des troubles de l'équilibre par l'extrait de *Ginkgo biloba*. Etude multicentrique à double insu face au placebo. *Presse Med*. 1986; 15:1569-72.
51. Vorberg G, Schenk N, Schmidt U. Wirksamkeit eines neuen *Ginkgo-biloba*-Extraktes bei 100 Patienten mit zerebraler Insuffizienz. *Herz Gefässe*. 1989; 9:936-41.
52. Eckmann VF. Hirnleistungsstörungern-Behandlung mit *Ginkgo-biloba*-Extrakt. *Fortschr Med*. 1990; 108:557-60.
53. Wesnes K, Simmons D, Rook M et al. A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. *Hum Psychopharmacol*. 1987; 2:159-69.
54. Bauer U. 6-Month double-blind randomised clinical trial of *Ginkgo biloba* extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittelforschung*. 1984; 34:716-20.
55. Saudreau F, Serise JM, Pillet J et al. Efficacité de l'extrait de *Ginkgo biloba* dans le traitement des artériopathies oblitérantes chroniques des membres inférieurs as stade III de la classification de fontaine. *J Mal Vasc*. 1989; 14:177-82.
56. Le Bars PL, Katz MM, Berman N et al. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA*. 1997; 278:1327-32.
57. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. *N Engl J Med*. 1997; 336:1108. Letter.
58. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology*. 1996; 46:1775-6.
59. Gilbert GJ. *Ginkgo biloba*. *Neurology*. 1997; 48:1137. Letter.
60. Bisset NG, ed. Herbal drugs and phytopharmaceuticals: a handbook for practice on a scientific basis. Boca Raton, FL: CRC; 1994.
61. Bahrke MS, Morgan WP. Evaluation of the ergogenic properties of ginseng. *Sports Med*. 1994; 18:229-48.
62. Chong SKF, Oberholzer VG. Ginseng: is there a use in clinical medicine? *Postgrad Med J*. 1988; 64:841-6.

63. D'Angelo L, Grimaldi R, Caravaggi M et al. Double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. *J Ethnopharmacol.* 1986; 16:15-22.
64. Pieralisi G, Ripari P, Vecchiet L. Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, and trace elements on physical performance during exercise. *Clin Ther.* 1991; 13:373-82.
65. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes Care.* 1995; 18:1373-5.
66. Yun TK, Choi SY. Preventive effect of ginseng intake and cancer. *Int J Epidemiol.* 1995; 19:871-86.
67. Hobbs C. Ginseng: facts and folklore. *Herbs Health.* 1997; 2:35-8.
68. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol.* 1985; 5(2):65. Editorial.
69. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *J Clin Psychopharmacol.* 1987; 7(3):201-2. Letter.
70. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health-Syst Pharm.* 1997; 54:692-3.
71. Siegel RK. Ginseng abuse syndrome: problems with the panacea. *JAMA.* 1979; 241:1614-5.
72. Siegel RK. Ginseng and high blood pressure. *JAMA.* 1980; 243:32. Letter.
73. Greenspan EM. Ginseng and vaginal bleeding. *JAMA.* 1983; 249:2018. Letter.
74. Punnonen R, Lukola A. Oestrogen-like effect of ginseng. *Br Med J.* 1980; 281:1110.
75. Leung AY. Better health with (mostly) Chinese herbs and food. Glen Rock, NJ: AYSL; 1995.
76. Carilla E, Briley M, Fauran F et al. Binding of Permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate. *J Steroid Biochem.* 1984; 20(1):521-3.
77. Plosker GL, Brogden RN. *Serenoa repens* (Permixon). A review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging.* 1996; 9:379-95.
78. Carraro JC, Raynaud JP, Koch G et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate.* 1996; 29(4):231-40.
79. Lepor H, Williford WO, Barry MJ et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med.* 1996; 335:533-9.
80. Tenover JL, Pagano GA, Morton AS et al. Efficacy and tolerability of finasteride in symptomatic benign prostatic hyperplasia: a primary care study. *Clin Ther.* 1997; 19:243-58.
81. Semino MA, Ortega JLL, Cobo EG et al. Tratamiento sintomático de la hipertrofia benigna de próstata. Estudio comparativo entre prazosin y *Serenoa repens*. *Arch Esp Urol.* 1992; 45:211-3.
82. Champault G, Patel JC, Bonnard AM. A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *Br J Clin Pharmacol.* 1984; 18:461-2.
83. Reece Smith H, Memon A, Smart CJ et al. The value of Permixon in benign prostatic hypertrophy. *Br J Urol.* 1986; 58:36-40.
84. Descotes JL, Rambeaud JJ, Deschaseaux P et al. Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Invest.* 1995; 9(5):291-7.
85. American herbal pharmacopoeia. St. John's wort: *Hypericum perforatum*. *Herbalgram.* 1997; 40:1-32.
86. Suzuki O, Katsumata Y, Oya M et al. Inhibition of monoamine oxidase by hypericin. *Planta Med.* 1984; 50:272-4.
87. Hobbs C. St. John's wort—*Hypericum perforatum*. *Herbalgram.* 1989; 18/19:24-33.
88. Linde K, Ramirez G, Mulrow CD et al. St. John's wort for depression—an overview and meta-analysis of randomised clinical trials. *BMJ.* 1996; 313:253-8.
89. Mills KC. Serotonin syndrome: a clinical update. *Crit Care Clin.* 1997; 13:763-83.
90. Woelk H, Burkard G, Grünwald J. Benefits and risks of the hypericum extract LI 160: drug monitoring study with 3250 patients. *J Geriatr Psychiatry Neurol.* 1994; 7(suppl 1):S34-8.
91. Awang DVC. Herbal medicine: St. John's wort. *Can Pharm J.* 1991; 124:33-5.
92. Houghton PJ. The biological activity of valerian and related plants. *J Ethnopharmacol.* 1988; 22:121-42.
93. Leathwood PD, Chauffard F, Heck E et al. Aqueous extract of valerian root (*Valeriana officinalis L.*) improves sleep quality in man. *Pharmacol Biochem Behav.* 1982; 17:65-71.
94. Leathwood PD, Chauffard F. Aqueous extract of valerian reduces latency to fall asleep in man. *Planta Med.* 1985; 51:144-8.
95. Hobbs C. Valerian—a literature review. *Herbalgram.* 1989; 21:19-34.