Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 39, No. 7, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01749-7

REVIEW ARTICLE

Benefits, Adverse Effects and Drug Interactions of Herbal Therapies With Cardiovascular Effects

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Because the use of herbal therapies in the U.S. is escalating, it is essential to be aware of clinical and adverse effects, doses and potential drug-herb interactions. A consumer poll in 1998 indicated that one-third of respondents use botanical remedies, and nearly one in five taking prescription medications also used herbs, high-dose dietary supplements or both. An estimated 15 million adults are at risk for potential adverse interactions involving prescription medications and herbs or vitamin supplements, yet most practicing physicians have little knowledge of herbal remedies or their effects. Herbal products are marketed without the proof of efficacy and safety that the Food and Drug Administration (FDA) requires of drugs. The Dietary Supplement and Health Education Act of 1994 allocates responsibility to manufacturers for ensuring safety and efficacy with no specific requirements to submit documentation. Manufacturers may state a product's physiologic effects but may not make claims for the treatment or cure of specific diseases. Consumers and practitioners have little information about product safety, contraindications, interactions or effectiveness and are reliant on manufacturers to provide accurate labeling. Recently, the growing number of foods with herbs has raised concerns at the FDA, which requires evidence that food additives are safe. Considering that the growing appeal of herbal remedies is likely to continue, physicians, particularly cardiologists, must become familiar with the available cardiovascular information on herbs. This review highlights the existing data on the efficacy, adverse effects and interactions for herbal therapies that impact on the cardiovascular system. (J Am Coll Cardiol 2002;39:1083–95) © 2002 by the American College of Cardiology Foundation

Because the use of herbs and herbal therapies in the U.S. is escalating, it is essential to be aware of clinical and adverse effects, doses and potential drug interactions. Most practicing physicians have little knowledge of herbal treatments or adverse effects (1). A consumer poll in 1998, however, indicated that nearly one-third of respondents use botanical remedies (2). Moreover, of those who take prescription medications, nearly one in five uses herbs, high-dose dietary supplements or both (3), suggesting an estimated 15 million adults are at risk for adverse interactions involving prescription medications and herbs or vitamin supplements. In addition, the growing demand for soft drinks and foods with herbal additives greatly expands public exposure. Sales of such products grew from $20 million to $700 million in the past three years (4).

BACKGROUND

Herbal products are marketed without proof of efficacy or safety that the Food and Drug Administration (FDA) requires of drugs. The Dietary Supplement and Health Education Act of 1994 assigns responsibility for ensuring safety and efficacy to manufacturers, with no requirement to submit documentation of product testing; it does not set standards for quality control nor require approval before supplements enter the market (5). Manufacturers may not make claims for treatment or cure of a disease but may state a product's physiologic effects. Consumers have little information to make decisions about safety, adverse effects, contraindications, interactions or effectiveness and must rely on manufacturers to provide ingredients that are accurately labeled (6). Recently, the increasing number of foods containing herbs has raised concerns at the FDA, which requires evidence that food additives are safe; consequently, manufacturers have been warned that the safety of herbal additives must be proven (4).

Many herbal remedies cannot be patented, and manufacturers do not expect to recoup the estimated $350 million to confirm safety and efficacy (7). The National Center for Complementary and Alternative Medicine (NCCAM), established in 1998 at the National Institutes of Health, is mandated to conduct and advocate research into complementary medicines and techniques (8). With a limited budget of $68.7 million for 2000, NCCAM pursues only a few therapies and techniques being practiced (8). Investigating the efficacy of herbal therapy is complex because many contain mixtures of compounds and exist in varied forms (7). Compounds isolated from herbs may have important pharmacologic activity, but data from isolates may understate or overstate actions of the herb, and such

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Manuscript received August 20, 2001; revised manuscript received December 27, 2001, accepted January 11, 2002.

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Abbreviations and Acronyms

CHF = congestive heart failure
CNS = central nervous system
FDA = Food and Drug Administration
HDL = high-density lipoprotein
INR = international normalized ratio
LDL = low-density lipoprotein
LV = left ventricular
MI = myocardial infarction
NCCAM = National Center for Complementary and Alternative Medicine
NYHA = New York Heart Association
PAF = platelet activating factor
PT = prothrombin time
SPICE = Survival and Prognosis Intervention of Crataegus Extract trial
TCM = traditional Chinese medicine

compounds are variably present in specific products (9–12). Resources on activity, dosages, toxicities, contraindications and drug interactions of herbal remedies are constrained by limited research and information.

Experience in other countries. In Germany, the Ministry of Health established the Commission E, a committee of doctors, pharmacists, scientists and herbalists to evaluate the safety, quality and efficacy of herbs (13). Commission E approves new remedies and publishes monographs with recommendations on dose, indications, contraindications, interactions and mechanisms (13). Physician prescriptions for herbs account for more than one-half of sales in Germany, and nearly one-quarter are for cardiovascular conditions (7). The Commission E reports are widely used in the U.S. and published by the American Botanical Council (13). The reference text *PDR for Herbal Medicines* is substantially comprised of them (14). In China, there are two parallel government-supported systems of medicine (15). Traditional Chinese medicine (TCM) comprises a variety of remedies including herbs, acupuncture, acupressure and other techniques (15). Patients seek care from TCM practitioners, or practitioners trained in Western medicine, and many institutions offer both (16). Research is supported in each system; however, controlled trials are lacking because use of a placebo is considered unethical (15).

CARDIOVASCULAR BENEFITS AND ADVERSE EFFECTS OF COMMON HERBAL THERAPIES

Several herbs offer potential for cardiovascular conditions including venous insufficiency, intermittent claudication, hyperlipidemia, hypertension and congestive heart failure (CHF) (Table 1). Varied mechanisms, including antioxidant, antiplatelet, fibrinolytic, antiatherosclerotic, antihyperlipidemic, antiarrhythmic and vasodilatory actions, are

Table 1. Herbs for Cardiovascular Indications

Herb	Indication	Evidence	Comments
Danshen	Ischemic heart disease	RCT	One small trial reported symptomatic and ECG improvements (41)
	MI	NBNRCT	Improved outcome, lower mortality (35)
	Angina pectoris	Animal studies	Dilates coronary arteries but constricts noncoronary arteries at high doses (34,42)
Dong quai	Antithrombotic	RCT	Trial in stroke subjects showed no benefit (160)
Garlic	Hyperlipidemia	RCT	Reduces serum cholesterol 5%–15% (57,64–67)
	Hypertension	RCT	Weak evidence for modest effect (72)
	Atherosclerosis	RCT	Single-trial evidence for reduction in plaque size (90)
	Claudication	RCT	No significant improvement (89)
Ginkgo	Cerebrovascular disease	RCT	Conflicting evidence for improved cognition and memory (100,103–106)
	Claudication	RCT	Modest improvements in pain-free walking distance (108)
	Antioxidation	RCT	Efficacy in vitro and animal studies (110–112) but no difference clinically (113)
Ginseng	Heart failure	NBNRCT	Improvements in cardiac function (123–125)
	Hypertension	NBNRCT	Small improvement in systolic blood pressure (126); however, hypertensive effects have also been described (127)
	Antioxidation	RCT	One trial reported improved hemodynamics (130)
Hawthorn	Heart failure	RCT	Improvement in symptoms such as fatigue and measures of cardiac function (139–141). Large trial underway to assess impact on mortality and disease progression (143)
	Hyperlipidemia	Animal studies	Lowers cholesterol levels, increases LDL receptors (137,138)
Hellebore	Hypertension	RCT	Narrow therapeutic window precludes use (168)
Horse chestnut	Venous insufficiency	RCT	Reduces lower extremity edema and symptoms (148) Efficacy comparable to compression stockings (150)
Yohimbine	Postural hypotension	RCT	Small trials investigating use in autonomic failure (189)
	Erectile dysfunction	RCT	Weak evidence of efficacy (186)

ECG = electrocardiogram; RCT = randomized, controlled clinical trial; LDL = low-density lipoprotein; MI = myocardial infarction; NBNRCT = trials that were not placebo-controlled or blinded.

Table 2. Herbs With Adverse Cardiovascular Effects

Herb	Adverse Effect	Comments
Belladonna	Tachycardia	Herbal source of atropine (92)
Danshen	Platelet dysfunction	In vitro evidence of platelet antagonism (38,39)
Dong quai	Increased bleeding tendency	Presence of natural coumarins and in vitro evidence of platelet antagonism (157,159)
Feverfew	Platelet dysfunction	In vitro evidence of platelet antagonism (50) not supported in clinical trials (46,47)
Garlic	Increased bleeding tendency	Case reports of hemorrhage (61,77). In vitro evidence of platelet dysfunction (58,73,75) but conflicting platelet and fibrinolytic evidence from clinical trials (74,78–82)
Ginger	Platelet dysfunction	Conflicting results in studies of platelet antagonism in human trials (163–165)
	Hypertension	Animal studies of specific purified ginger compounds demonstrate pressor effects (166,167)
Ginkgo	Increased bleeding tendency, platelet dysfunction	Case reports of central nervous system hemorrhage (94,95). Pharmacologic evidence of platelet antagonism; however, active compounds not present in sufficient amounts in most extracts (117,118)
Ginseng	Hypertension	An abuse syndrome involving hypertension is described in chronic users (127). However, evidence from clinical trials also supports hypotensive effects (126)
Hellebore	Hypotension, bradycardia	Accidental ingestion occurs when plant is mistaken for another, especially gentian (169,170)
Kava	Platelet dysfunction	Limited in vitro evidence (174)
Licorice	Hypertension, pulmonary edema, cardiomyopathy (rarely)	Occur as a result of decreased inactivation of cortisol causing symptoms of mineralocorticoid excess (179)
Ma huang	Stroke, myocardial infarction, arrhythmia, hypertension	Numerous case reports of serious adverse events in healthy young people (154)
	Myocarditis	Rare case report (156)
Oleander	Arrhythmia	Cardiac glycosides cause symptoms similar to digoxin toxicity (197,198). Responds to digoxin antibody treatment (196)
Yohimbine	Hypertension, arrhythmia	Increases norepinephrine levels and central sympathetic outflow via α_2 antagonism (186,188)

ascribed to herbs (17). Data from epidemiologic studies support the potential of dietary antioxidants and flavonoids (18–21) present in several herbs (22,23) to improve cardiovascular health. To date, however, clinical trials with antioxidants such as vitamin E, vitamin A and beta carotene fail to show clinical benefit (24–29). Herbal remedies may induce adverse cardiac effects including sympathomimetic activity, hypertension and arrhythmias (Table 2). Many interfere with platelet function, and patients at risk for bleeding or taking antiplatelet drugs should be cautioned about specific herbs. Physicians must be attuned to interactions between herbs and drugs with a narrow therapeutic window, such as warfarin and digoxin (Table 3). Adverse effect data is almost exclusively available as case reports and, as a result, may be vastly underreported.

Lack of regulation of quality control and of product standardization makes it difficult to establish safe doses of herbal products. Active compounds may vary 200-fold between manufacturers and batches (30). Additives and contaminants including caffeine, indomethacin and heavy metals, such as lead, mercury and arsenic, have been found in herbal remedies (31–33). Misidentification of plants has led to serious adverse events including renal failure (31). Considering that the growing appeal of herbal remedies is likely to continue, physicians, particularly cardiologists, must become familiar with the available cardiovascular information on herbs. This review highlights the existing data on the efficacy, adverse effects and interactions for herbal therapies that impact on the cardiovascular system.

Danshen *(Salvia miltiorrhiza)*. Danshen is used in TCM to promote blood flow and treat cardiovascular diseases. It is sold in over-the-counter herbal preparations, prescribed by TCM doctors and administered in Chinese hospitals for angina pectoris (34), acute myocardial infarction (MI) (35) and ischemic and thrombotic disorders (36). In vitro and animal studies suggest it may be vasoactive, scavenge free radicals (37) and inhibit platelet aggregation (38,39). The active compounds in danshen are tanshinones and phenolic compounds (34,36).

Danshen has been studied in China for acute MI and ischemic heart disease (35,40). Most studies are neither placebo-controlled nor blinded, and often use danshen

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Table 3. Important Cardiovascular Drug Interactions

Drug	Herb	Evidence for Interaction
Warfarin	Dong quai	Case reports of elevation of PT and INR in patient stable on warfarin (157). Demonstration of pharmacological interaction in rabbits (158).
	Danshen	Decreases warfarin clearance and increases bioavailability (45). Case reports of hemorrhage in subjects on warfarin (43,44).
	Garlic	Rare reports of elevation in INR in subjects previously stable on warfarin (62). No other supporting data (63).
	Ginkgo	Case report of CNS hemorrhage in patient previously stable of warfarin (97). No other supporting data (63).
	Ginseng	Case report of decreased INR in patient stable on warfarin (131). No other supporting data (63).
Antiplatelet drugs (NSAIDs, ticlopidine, others)	Dong quai	In vitro evidence of platelet antagonism (157).
	Feverfew	Potential antiplatelet effects (50). No case reports of hemorrhage.
	Garlic	Case reports of platelet dysfunction with increased bleeding time (61,77). Conflicting evidence from clinical trials of antiplatelet effects (74,78–82).
	Ginger	In vitro evidence of antiplatelet activity, but no effects seen in clinical trials and no case reports of adverse events (162–165).
	Ginkgo	Case reports of hemorrhage (94–96). In vitro evidence of antiplatelet activity but no confirmatory evidence in human trials (115–119).
	Kava	In vitro evidence of platelet antagonism (174).
Digitalis	Hawthorn	Claims of interaction but no case reports and no pharmacologic data (145).
	Herbal laxatives	Herbal laxatives such as buckthorn, cascara sagrada and senna can cause loss of potassium leading to digitalis toxicity (200).
	Oleander	Contains active cardiac glycosides (197).
	St. John's wort	Reduces serum digoxin levels (199).
	Siberian ginseng	May interfere with assay, does not cause elevated digoxin levels (132,133).
Clonidine	Yohimbine	Competitive α_2-antagonist (186).
Tricyclic antidepressants	Yohimbine	Antidepressants potentiate pressor effects (190).
Methysergide, pizotifen, other serotonin antagonists	Feverfew	Antagonizes serotonin release, may potentiate the effect of other serotonin antagonists (56).

CNS = central nervous system; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; PT = prothrombin time.

combined with other herbs. A double-blind study of 67 subjects with ischemic heart disease reported symptomatic and electrocardiographic improvement with tanshinone IIA, a compound present in danshen (41). No differences in cardiac contractility, compliance, inotropy, blood viscosity or fibrinogen were found. Danshen has been studied for coronary artery vasodilation, the mechanism underlying its use in angina (42). At low doses, it causes generalized vasodilation and decreases blood pressure (42). At higher doses, however, it causes vasoconstriction in noncoronary arteries (34,42). Case reports link danshen to warfarin potentiation (43,44). Animal studies confirm that danshen decreases warfarin clearance and increases bioavailability (45).

Feverfew *(Tanacetum parthenium)*. Feverfew is primarily used for migraine prophylaxis (46). It inhibits platelet release of serotonin (47) and may have vasoactive effects (48). The active compound in feverfew, parthenolide, is a sesquiterpene lactone. Other compounds have been investigated for biologic activity, most notably flavonoids for a potential anti-inflammatory effect (49). Feverfew is one of a few herbs for which data on the content of the active compounds in commercial preparations are available (12). Typical daily doses for migraine prophylaxis are 50 to 100 mg of whole or powdered dried leaves, corresponding to 500 μg of parthenolide (12,47).

In vitro studies demonstrate that feverfew and parthenolide inhibit platelet aggregation and platelet and leukocyte release of serotonin (46,50). In vitro vasoactive effects vary with the formulation. Chloroform extracts of fresh leaves inhibit smooth muscle contractility, but extracts of dried leaves elicit a contractile response (48,51). Because chloroform extracts of dried feverfew do not contain measurable amounts of parthenolide, other vasoactive compounds may be present (48). Vasoactive and antiplatelet actions observed in vitro have not been confirmed in clinical trials (46,47,52–55).

The most common side effect is mouth ulcers (46). Feverfew's inhibition of platelet serotonin release in vitro raises concerns about interaction with antiserotonin migraine prophylactic drugs (56) and potentiation of bleeding with antiplatelet agents. However, serious adverse events or interactions have not been reported.

Garlic *(Allium sativum)*. Estimated mass-market sales of garlic supplements in 1998 were $84 million (2). Respondents to the third National Health and Nutrition Examination Survey listed garlic more frequently than other dietary supplements (5). It is believed to thin the blood, reduce cholesterol, decrease blood pressure, inhibit atherosclerosis and improve circulation.

Randomized clinical trials have been conducted for antihypertensive, antiatherosclerotic and antiplatelet actions, and intermittent claudication. A recent summary of the data supporting garlic's potential in modifying cardiovascular

risk, while generally supporting its usefulness, also emphasized the lack of knowledge about active compounds and mechanisms of action (57). Though garlic is believed to be beneficial for conditions for which approved drugs are available, such as hyperlipidemia and hypertension, few studies compare it to pharmacologic treatments.

Studies of garlic are plagued by methodologic problems related to active compounds. The active substance is allicin, formed by the action of alliinase on alliin when garlic is crushed (58). Allinase is inactivated by acid pH, heat and extraction in organic solvents (59). Thus, garlic's effects are dependent on whether it is cooked or in aqueous, oil or organic extracts (58,59). In addition to allicin, other active compounds in garlic include methyl allyl trisulfide, diallyl trisulfide, diallyl disulfide and ajoene (58–60). Its characteristic odor (60) is associated with the active compounds, which limits blinding in clinical trials. Most studies use commercially available dried garlic powder standardized for allicin content, in doses of 300 to 900 mg/day. However, even standardized products may yield different quantities of allicin owing to differences in tablet composition (11). Few trials indicate whether placebo could be differentiated from active treatment.

Garlic is generally safe and well tolerated; however, serious adverse events, including central nervous system (CNS) bleeding (61) and skin burns from topical application (57), have been reported. Effects such as flatulence, dyspepsia, allergic dermatitis and asthma have been described (57). Increases in both the prothrombin time (PT) and international normalized ratio (INR) in subjects previously stable on warfarin have been attributed to garlic (62); however, there is little to substantiate the mechanism of the interaction (63).

HYPERLIPIDEMIA. The antihyperlipidemic effect of garlic has been extensively studied. Early trials lacked controls, adequate blinding and dietary monitoring; they were underpowered or did not analyze results based on intention to treat (57,64). Recent trials have produced negative findings, possibly resulting from preparations with reduced bioavailability of allicin (11). Several meta-analyses have summarized data from clinical trials. Each has used different inclusion criteria, yet the results are consistent across analyses: garlic modestly reduces lipids 15 to 25 mg/dl (5% to 15%) (57,64–67).

The earliest meta-analyses included studies with deficiencies (65,66). Warshafsky et al. (65) reported a reduction in serum cholesterol of 23 mg/dl (9% from baseline) (65). Silagy and Neil (66) reported lipid reduction of 12% and provided a subgroup analysis of trials that utilized nonpowder forms (i.e., raw, oil or extract). Lipids were reduced by 15% in this subgroup; however, three of five studies were not double-blind and two were not placebo-controlled. Stevinson et al. (67) selected only randomized, placebo-controlled trials of hypercholesterolemic subjects and reported a reduction of only 15.7 mg/dl (4% to 6% reduction). A subgroup analysis of studies with the highest scores for methodologic quality found no difference between garlic and placebo.

Most recently, Ackermann et al. (57) reported a comprehensive meta-analysis of garlic trials, showing a reduction in cholesterol of 17 mg/dl. Subgroup analyses of trials including only hyperlipidemic subjects and double-blind trials did not differ. In contrast to Silagy and Neil (66), subgroup analysis of trials employing standardized dried garlic powder preparations showed a slightly improved reduction in cholesterol of 19 mg/dl. This analysis also reported a dose duration effect of garlic.

A trial of garlic versus a fibrate drug for hyperlipidemia reported similar efficacy (68). Treatment with dried garlic powder tablets (900 mg/day) reduced total serum cholesterol levels from 282 mg/dl to 210 mg/dl over 12 weeks while bezafibrate (600 mg/day) reduced cholesterol from 287 mg/dl to 208 mg/dl. Both treatments produced parallel reductions in low-density lipoprotein (LDL) and increases in high-density lipoprotein (HDL) cholesterol. There was a trend toward greater reduction in serum triglycerides with bezafibrate (42% vs. 29%).

HYPERTENSION. In vitro evidence suggests garlic reduces blood pressure by inhibiting platelet nitric oxide synthase (69). Many clinical trials, however, find no significant antihypertensive effect despite form, dose or duration of treatment. Studies evaluating hypertensive subjects report a modest reduction in diastolic pressure (70–72). A small, open-label trial reported that large doses of garlic powder (2,400 mg) lowered blood pressure 7/16 mm Hg. Only the diastolic pressure decreased significantly (70). In a placebo-controlled, double-blind study of 47 hypertensive subjects only the diastolic pressure decrease (13 mm Hg) was significant (71). A meta-analysis reported a modest systolic reduction of 7.7 mm Hg and diastolic reduction of 5.0 mm Hg (72), but only two trials involved hypertensive subjects.

COAGULATION. Blood-thinning properties are attributed to enhanced fibrinolytic and antiplatelet activity. There is no consensus as to the mechanism of fibrinolytic activity. In vitro and animal studies support several mechanisms for garlic's antiplatelet effects. Diallyl disulfide and diallyl trisulfide inhibit thromboxane synthesis (58,73), possibly by inhibiting phospholipase-A and mobilizing arachidonic acid (74). Extract of raw garlic contains compounds that inhibit cyclooxygenase (75) and ajoene, a compound in alcohol extracts of garlic, may inhibit binding of fibrinogen to platelet receptors (76). Ajoene, however, is not found in most garlic preparations (59,60).

Garlic's anticoagulant properties have been linked to reports of bleeding (61,77); however, clinical trials find conflicting results (74,78–82). Dried garlic powder decreased platelet aggregation in three controlled trials (78,80,81). Conversely, no difference was found in platelet aggregation or thromboxane levels in 14 healthy men (82). Several trials describe increased fibrinolytic activity, and two

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report elevation of tissue plasminogen activator (80,83–85). However, a trial using garlic powder in patients with hyperlipoproteinemia found no change in bleeding time, fibrin split products or clot lysis time (86).

ATHEROSCLEROSIS. The antiatherosclerotic activity of garlic is attributed to cholesterol lowering, but in vitro and animal studies also support effects independent of lipid levels, possibly by inhibition of lipid peroxidation (87,88). Two clinical trials report benefits in atherosclerotic conditions. In subjects with peripheral arterial occlusive disease, pain-free walking distance improved 46 meters with garlic compared to 31 meters with placebo (81). Though the mean difference in walking distance between groups increased, change in walking distance within each group was not significant (89). Garlic administered for 48 months reduced atherosclerotic plaque at the femoral artery or carotid bifurcation by 5% to 18% (90). Notably, 23% of subjects taking garlic versus 3% on placebo withdrew owing to odor, underscoring the difficulty of blinding in garlic trials.

Ginkgo *(Ginkgo biloba)*. Ginkgo biloba, the best-selling herbal remedy in the U.S. (2), is derived from the leaves of the maidenhair tree. It is used for cognition and memory as well as cerebrovascular disease, peripheral vascular disease, sexual dysfunction, affective disorders, multiple sclerosis, retinal disorders and hearing loss. The mechanisms by which ginkgo and its constituent compounds improve vascular health include free radical scavenging, antiplatelet actions, anti-inflammatory actions, vasodilation and decreased blood viscosity. Gamma-aminobutyric acid receptor agonism and inhibition of monoamine oxidase-B have also been investigated. Active isolates of ginkgo fall into two classes: flavonoids and terpenoids. An extract standardized for flavonoid and terpenoid content, EGb761, is available. Typical doses are 120 to 160 mg/day (91). Commission E recommends 120 to 240 mg extract two to three times daily for cerebral insufficiency (92). Common side effects are nausea, dyspepsia, headache and allergic skin reactions (91,93). More serious adverse effects, including spontaneous subdural hematomas (94), intracerebral hemorrhage (95) and hyphema (96), as well as warfarin and trazodone interactions, have been described (97,98).

VASCULAR DEMENTIA. Ginkgo may benefit cerebrovascular disease by improving blood flow, reducing ischemia-reperfusion injury or inhibiting platelets (91,99,100). Most trials of ginkgo enroll patients with cognitive impairment due to diverse etiologies (101,102). Few enroll patients with only vascular dementia, and these trials report conflicting results. A double-blind, placebo-controlled trial of acute ischemic stroke showed no benefit with ginkgo (100). Similarly, there was no difference in a trial of 52 subjects with vascular dementia who underwent psychometric testing (103). A trial assessing dizziness, motor activity, speech comprehension and depression reported that only dizziness improved (104). However, two trials have demonstrated improvement in measures of cognition, including the Wechsler Adult Intelligence Scale and Sandoz Clinical Assessment-Geriatric (105,106).

INTERMITTENT CLAUDICATION. Ginkgo may improve intermittent claudication via vasoregulation, platelet antagonism and protection against postischemic oxidative damage (91,93,107). At least 11 randomized, placebo-controlled trials have been conducted. A meta-analysis of trials of ginkgo for intermittent claudication reported pain-free walking distance increased by 34 meters (93). In eight trials of 415 patients all but one favored ginkgo over placebo, although only four reported confidence intervals that did not include zero. None reported serious adverse events. A meta-analysis of pharmacologic interventions for intermittent claudication similarly concluded that ginkgo improves pain-free walking distance by 32 meters (108). However, this effect was modest compared to pentoxifylline (208 meters) and naftidrofuryl (101 meters).

ANTIOXIDANT. Evidence from in vitro and animal experiments supports antioxidant activity (91,109,110). Flavonoids constitute about 25% of EGb761 (92) and have antioxidant and free radical scavenging properties, although the exact mechanism remains unclear (22). In addition, bilobalide and ginkgolides A and B are terpenoid compounds selectively studied for protecting ischemic tissue from reperfusion injury (110–112). Pietri et al. (113) investigated whether short term pretreatment with high-dose ginkgo extract (320 mg/day for five days) decreased reperfusion injury in patients undergoing aortic valve replacement. Markers of oxidative stress and cardiac performance, including cardiac index and left ventricular (LV) stroke work, improved after operation; however, clinical outcomes did not differ.

PLATELET ANTAGONISM. Ginkgo may inhibit platelets and platelet-induced postischemic inflammatory response by antagonism of platelet activating factor (PAF), which has been implicated in reperfusion injury and cardiac dysfunction in shock (114). Ginkgolide B is a potent inhibitor of PAF in humans (115,116). Other components of ginkgo extract have been identified as inhibitors of phospholipase A_2, and thus the production of PAF as well as eicosanoids (107). However, the compounds attributed with antiplatelet effects are present in small amounts in most extracts, and may not produce the same inhibition seen in studies of isolated compounds (117,118).

No controlled trials in humans confirm ginkgo as an antiplatelet agent. A placebo-controlled trial of ginkgo reported no effect on platelet aggregation (119). However, antiplatelet effects have been cited as the mechanism underlying bleeding events. Two cases of CNS hemorrhage occurred with ginkgo, 120 to 160 mg/day (94,95). In both, PT and partial thromboplastin time were normal, but bleeding time was higher and returned to normal after ginkgo biloba was discontinued. A case of hyphema occurred after ingestion of ginkgo and aspirin; however, no

coagulation or bleeding measures were reported (96). In another patient, previously stable on warfarin, administration of ginkgo was associated with elevated PT and intracerebral hemorrhage (97).

Ginseng. Ginseng refers to the root of *Panax* species. The most commonly examined species are *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng) and *Panax japonicus* (Japanese ginseng) (120). The terms "red" and "white" refer to different methods of ginseng preparation, not different species (121). Siberian ginseng, the root of an unrelated species, *Eleutherococci*, does not contain similar compounds (122). Ginseng is believed to promote vigor, potency, well-being and longevity. In China it is utilized for angina pectoris, MI and CHF. It has been evaluated for many other indications, most notably for use as an antihyperglycemic. It is administered as a whole dried root, extract, tea or capsule. The active compounds are heterogeneous triterpene saponin glycosides, collectively termed *ginsenosides*. The exact ginsenosides vary by *Panax* species (120), root age (122) and preparation method (i.e., red or white) (122). The actions of specific ginsenosides vary, and in some instances are inconsistent. Of note, many products that claim ginseng content have no ginsenosides (9,10). Typical doses are 100 to 400 mg of ginseng extract daily. The Commission E monograph recommends a dosage of 1 to 2 g of root daily (92).

HEART FAILURE. Clinical trials in China and Korea have investigated ginseng for cardiac function, although there is no known mechanism and little data from placebo-controlled or blinded studies. An open trial evaluating CHF contrasted, 1) red ginseng, 2) digoxin, and 3) digoxin plus red ginseng, and found that hemodynamic improvement was most marked with combined therapy (123). An open trial of *Panax notoginseng* plus captopril versus captopril monotherapy in subjects with LV diastolic dysfunction reported improved diastolic relaxation with the combined medications (124). In a double-blind, placebo-controlled trial of coronary heart disease, a mixture of Chinese herbs, including ginseng, found that stroke volume index and cardiac index improved (125).

HYPERTENSION. Ginseng has been shown to have both hypertensive and hypotensive effects in animal studies trials (122). Hypotensive effects are attributed to enhanced synthesis of nitric oxide (122). An open trial of 4.5 g red ginseng daily found systolic blood pressure decreased after eight weeks (126). In contrast, a ginseng-abuse syndrome has been described wherein hypertension, behavioral changes and diarrhea occur (127,128). In an observational study of 133 chronic ginseng users, 22 developed elevated blood pressure (127). Subjects reported using a variety of preparations, including some that contained Siberian ginseng (128), which has been separately linked with hypertension (129). These conflicting effects are attributed to diverse actions of particular ginsenosides (122).

ANTIOXIDANT EFFECTS. Animal studies suggest that ginseng scavenges free radicals (122). In a placebo-controlled trial of 30 patients undergoing mitral valve surgery, ginseng and ginsenoside Rb were evaluated for protective effects in ischemia and reperfusion injury (130). Both improved postoperative cardiac function; however, ginseng provided greater benefit than the isolate ginsenoside Rb.

An interaction of ginseng with warfarin, in which the INR was reduced to subtherapeutic levels, has been reported (131). However, no mechanistic evidence for the interaction has been provided (63). Interaction with digoxin, or with the digoxin assay and Siberian ginseng (132), has been observed, though this may have been due to a contaminant (133). Some ginseng preparations have been contaminated with germanium, which has led to an account of ginseng-related diuretic resistance and renal failure (134).

Hawthorn *(Crataegus species)*. Hawthorn is a spiny shrub native to Europe and North America whose leaves, flowers and berries are used for CHF. Flavonoids and oligomeric procyanthins are the active constituents of hawthorn, and an extract standardized for these compounds, WS 1442, is available. Proposed mechanisms of action include antioxidant, inotropic, vasodilatory and antihyperlipidemic actions, as well as decreased capillary permeability (92). Hawthorn extract (160 to 900 mg two to three times a day for six weeks) is approved by Commission E for use in New York Heart Association (NYHA) functional class II CHF (92). This dose corresponds to 30 to 168.7 mg procyanidins or 3.5 to 19.8 mg flavonoids per dose (92).

Both animal and in vitro studies support several potential mechanisms of action. Hawthorn extract reduces reperfusion injury in ischemic rat hearts (135). After exposure to the extract, rat cardiomyocytes show increased inotropy and a prolonged refractory period (136). Hawthorn, in addition, decreases plasma lipids and increases hepatic LDL receptor activity in rats (137,138).

HEART FAILURE. Clinical trials of hawthorn describe decreased symptoms of CHF as well as improved cardiac performance. Several controlled clinical trials report an improved product of systolic blood pressure and heart rate measured at rest and during exercise (pressure heart rate product) (139–141). In an open trial of 1,011 subjects, the ejection fraction increased and arrhythmias decreased (142). Other reports indicate that cardiac work tolerance is enhanced (92). The first large-scale study designed to look at mortality, cardiac events and hospitalization is currently underway (143). The Survival and Prognosis Investigation of Crataegus Extract (SPICE) trial is investigating WS 1442 for CHF in NYHA functional class II and III. This randomized, placebo-controlled, double-blind, international, multicenter trial will enroll 2,300 subjects by 2002. Subjects will receive either 450 mg of WS 1442, standardized to contain 84.3 mg procyanidins, or placebo in addition to standard CHF drugs (digoxin, angiotensin-converting enzyme inhibitors and diuretics) for 24 months.

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Hawthorn has few adverse effects and no reported drug interactions (92). Toxicity of WS 1442 has been studied in animals: doses up to 100 times normal produced no toxic effects (144). The claim that hawthorn potentiates digoxin has not been substantiated (145).

Horse chestnut seed *(Aesculus hippocastanum)*. Commission E has approved horse chestnut seed extract for chronic venous insufficiency (250 to 312 mg extract twice daily) (92). The active compound, aescin, is a mixture of triterpene glycosides (92). Aescin decreases lower extremity edema by decreasing capillary permeability via inhibition of endothelial lysosomal enzymes and preservation of capillary wall glycocalyx (146), and venoconstriction via prostaglandin $F_{2\alpha}$ (147). Extracts standardized for aescin content are available, and the Commission E recommends 50 mg aescin twice daily (92).

A review of eight placebo-controlled trials for venous insufficiency reported that lower extremity circumference and volume decreased, and leg pain and pruritus improved (148). The most frequent adverse effects were gastrointestinal symptoms, dizziness, headache and pruritus. Trials that compared horse chestnut to hydroxyethylrutosides, a semisynthetic mixture of flavonoid compounds (149), found little difference between treatments (148). In a partially blind study of horse chestnut seed versus compression stockings or placebo, the volume of lower extremity edema decreased 45 ml for each active treatment compared to a 10 ml increase for placebo (150).

Side effects include pruritus, nausea, headache and dizziness (148). There is one reported case of hepatitis from a commercial preparation of horse chestnut extract, Venoplant (151). Venocuran, an herbal preparation that contained horse chestnut, plus phenopyrazone, extracts of white squill, convallaria, oleander and adonis, was removed from the market owing to a systemic lupus-like syndrome (152).

Ma huang *(Ephedra sinica)*. Ma huang is a natural source of ephedrine and has potent sympathomimetic activity. Herbal remedies and soft drinks used for energy or weight loss often contain ma huang. Its pharmacokinetics and bioavailability are similar to standard doses of ephedrine (153), but the effects are delayed in onset. Between 1997 and 1999, a total of 140 reports of adverse events were related to ma huang (154); 13 caused permanent impairment and 10 resulted in death. Many reports concern healthy young people without known cardiac disease. The majority had new-onset hypertension, and other findings included cerebrovascular accidents, arrhythmias and MI. Several reports link the adverse response of ma huang to concurrent use of caffeine, guarana (a source of caffeine and theophylline [155]) or exercise. A case report of eosinophilic myocarditis possibly associated to ma huang has also been reported (156).

Other herbs. DONG QUAI *(ANGELICAE SINENSIS)*. Dong quai, a TCM remedy for menstrual symptoms and the menopause (157), is also used for antiarrhythmic, antithrombotic, antiasthmatic and analgesic effects (157–160). In humans, dong quai has been evaluated for estrogenic effects (161). Quinidine-like effects have been reported in animals (159), but not evaluated in clinical trials. Antithrombotic effects are attributed to coumarin derivatives and ferulic acid contained in the oil of the root (157,159). Ferulic acid may cause platelet dysfunction by inhibiting production of thromboxane A_2 (157). In a controlled trial of 96 subjects with new cerebral thrombosis or embolism, there was no difference in improvement rate with dong quai (160). Case reports of warfarin potentiation have been reported, and an interaction is supported by animal studies, which demonstrate alteration of warfarin pharmacodynamics after dong quai (157,158).

GINGER (*ZINGIBER OFFICINALE*). Dried ginger powder, 500 to 1000 mg, or fresh ginger, 2 to 4 g, is used for nausea (92,162). Ginger's alleged vitalizing effect on the heart and blood is attributed to decreased platelet aggregation and inhibition of thromboxane synthesis observed in in vitro studies (162). In vitro antiplatelet activity varies by form (dried, raw, cooked or extract) (163). Clinical studies, however, using raw, cooked or dried ginger do not show an effect on bleeding time, platelet aggregation or thromboxane production (163–165). Compounds isolated from ginger, including shogaol and gingerol, have been studied for positive inotropic and pressor effects (166,167); however, no clinical trials currently support these effects. Neither adverse effects nor drug interactions have been reported (92,162).

HELLEBORE (*VERATRUM* SPECIES). A variety of hellebore species grow in North America, Europe and Asia and contain active veratrum alkaloids (168). As a source of veratrum alkaloids, hellebore's use as an antihypertensive was precluded by nausea and vomiting (168). Cardiac arrhythmias also occur, particularly in association with digitalis (168). Hellebore toxicity often results from accidental ingestion, particularly when white hellebore *(Veratrum albums)* is mistaken for gentian to produce gentian wine (169). Toxicity is associated with vomiting, hypotension and bradycardia, but is rarely fatal (169,170).

KAVA *(PIPER METHYSTICUM)*. Kava, a member of the black pepper family, is used by aboriginal peoples of the South Pacific as an anxiolytic, and it has been promoted to treat anxiety, depression and muscle tension (171). Sales of kava products in the U.S. were $8 million in 1998, having grown more than 450% from the prior year (2). Kava pyrones, the active compounds in kava (172,173), may inhibit cyclooxygenase and thromboxane synthase (174). A small observational study of an aboriginal community found that HDLs were higher in kava users (175). Adverse effects include rash, elevated hepatic enzymes, pulmonary hypertension and hepatitis (175,176). Kava may also interact with benzodiazepines, inducing coma (177).

LICORICE *(GLYCYRRHIZA GLABRA)*. Licorice, an extract of the root of *Glycyrrhiza glabra,* is used as a sweetening and

flavoring agent. It is also used as an herbal remedy for gastritis and upper respiratory tract infections (178–180). Most licorice candies in the U.S. do not contain licorice (181). The active constituent of licorice is glycyrrhizic acid. A metabolite, glycyrrhetinic acid, inhibits renal 11β-hydroxysteroid dehydrogenase and causes a state of mineralocorticoid excess by impeding the inactivation of cortisol (179). Case reports link licorice to hypertension, hypertensive encephalopathy, pulmonary edema, edema, hypokalemia, arrhythmias, CHF, muscle weakness and acute renal failure (178). Dilated cardiomyopathy resulting from excessive use of licorice and glycyrrhizin for gastritis has been reported (180). Fifty to 100 g of confectionary licorice, or 50 to 300 mg glycyrrhetinic acid, over weeks may cause adverse effects (182,183). A study of 30 healthy, normotensive volunteers reported that 100 g per day of licorice (270 mg glycyrrhizic acid) over four weeks increased systolic blood pressure 6.5 mm Hg and decreased plasma potassium 0.24 mmol/l from baseline (184). Susceptibility to licorice varies greatly; subjects with underlying hypertension and women may be more sensitive (179,184). Adverse effects may take weeks to reverse because of suppression of the renin-angiotensin-aldosterone axis and because glycyrrhetinic acid has a large volume of distribution (179).

YOHIMBINE *(PAUSINYSTALIA YOHIMBE)*. Yohimbine is isolated from yohimbe, the bark of the tree *Pausinystalia yohimbe,* and is used for erectile dysfunction (185). It is a competitive alpha$_2$-antagonist that increases central sympathetic outflow and raises blood pressure, heart rate and norepinephrine levels (186–188). As a result, it may exacerbate elevated blood pressure in hypertensive patients, as well as cause arrhythmias and tremors (186,187). Yohimbine has been evaluated for use in postural hypotension associated with autonomic dysfunction (189). As an alpha$_2$-antagonist, yohimbine opposes the effects of clonidine (186). It also interacts with tricyclic antidepressants, so that pressor effects occur at lower doses, and may potentiate the alpha-adrenergic blocking properties of phenothiazines (190). Adverse reactions include mania (191), bronchospasm (192), a systemic lupus-like syndrome (193) and agranulocytosis (194). The recommended dose is 5.4 mg three times daily; pressor effects are associated with doses of 15 to 20 mg (190).

OTHER HERBAL ADVERSE EFFECTS AND DRUG INTERACTIONS. A number of herbs, including oleander, adonis, black Indian hemp (apocynum), black hellebore, lily-of-the-valley (convallaria), squill and strophanthus, contain cardiac glycosides that can potentiate digoxin (195). There are frequent case reports of toxic ingestion of oleander, a common flowering shrub found throughout North America (196–198). Oleander toxicity has been effectively treated with digoxin-specific antibodies (196). St. John's wort *(Hypericum perforatum)* decreases serum levels of digoxin through induction of a p-glycoprotein drug transporter (199). In a single-blind, placebo-controlled study, after 10 days of St. John's wort, digoxin levels were reduced more than 25% (199). Several herbs used for a laxative effect, such as senna, cascara sagrada and buckthorn (200), may augment potassium loss and lead to toxicity in digoxin users. Belladonna, an herb used for gastrointestinal symptoms, is a source of atropine and may cause tachycardia (92).

CONCLUSIONS

The growing use of herbal remedies in the U.S. has far exceeded the increase in available information on their benefits, adverse effects and drug interactions. Coherent, easily accessible data on remedies is lacking. English translations of the collected German Commission E monographs represent one of the few references for consumers and practitioners. Such information is critical to physicians who often must counsel patients about herbal alternatives to traditional therapy and address the concern of herb-drug interactions. Although there is little existing data comparing herbal therapy to approved drugs, the SPICE trial is a landmark investigation of an herbal remedy with standard therapy. With only modest evidence-based data, physicians may opt to put off interactive questions or refrain from prescribing herbal remedies. Considering that the escalating appeal of herbal remedies is likely to continue, such a stance is impractical and potentially risky for patients. Rather, another option is that physicians and other health care providers become familiar with the data and advocate for greater research and access to information.

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