Herbal Medicine for the Treatment of Cardiovascular Disease

Clinical Considerations

Nick H. Mashour, MD; George I. Lin, MD; William H. Frishman, MD

Herbs have been used as medical treatments since the beginning of civilization and some derivatives (eg, aspirin, reserpine, and digitalis) have become mainstays of human pharmacotherapy. For cardiovascular diseases, herbal treatments have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia. However, many herbal remedies used today have not undergone careful scientific assessment, and some have the potential to cause serious toxic effects and major drug-to-drug interactions. With the high prevalence of herbal use in the United States today, clinicians must inquire about such health practices for cardiac disease and be informed about the potential for benefit and harm. Continuing research is necessary to elucidate the pharmacological activities of the many herbal remedies now being used to treat cardiovascular diseases.
This review examines herbal medicines that affect the cardiovascular system both in terms of efficacy and safety as gleaned from the scientific literature that is available. These herbs are categorized under the primary diseases they treat. However, most herbal medicines have multiple cardiovascular effects that frequently overlap. The purpose of this organization is to simplify, not to pigeonhole herbs under specific diseases. In general, the dilution of active components in herbal medicines results in fewer adverse and toxic effects in comparison with the concentration of active components in the allopathic medicines. However, these adverse effects and drug interactions should not be overlooked; cardiovascular disease is a serious health hazard and no herbal remedy regimen should be initiated without careful consideration of its potential impact (Table).

**CONGESTIVE HEART FAILURE**

A number of herbs contain potent cardioactive glycosides, which have positive inotropic actions on the heart. The drugs digoxin, derived from either *D. purpurea* (foxglove) or *Digitalis lanata*, and digoxin, derived from *D. lanata* alone, have been used in the treatment of congestive heart failure for many decades. Cardiac glycosides have a low therapeutic index, and the dose must be adjusted to the needs of each patient. The only way to control dosage is to use standardized powdered digitalis, digitoxin, or digoxin. When 12 different strains of *D. lanata* plants were cultured and examined, their total cardenolide yield ranged from 30 to almost 1000 nmol/1 g. As is evident, treating congestive heart failure with nonstandardized herbal drugs would be dangerous and foolhardy.

Some common plant sources of cardiac glycosides include *D. purpurea* (foxglove, already mentioned), *Adonis microcarpa* and *Adonis vernalis* (adonis), *Apocynum cannabinum* (black Indian hemp), *Asclepias incarnata* (redheaded cotton bush), *Asclepias friticosa* (balloon cotton), *Calotropis procera* (king’s crown), *Carissa spectabilis* (wintersweet), *Cerebra manghas* (sea mango), *Cheiranthus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptogedia grandiflora* (rubber vine), *Helleborus niger* (black hellebore), *Helleborus viridis*, *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Selenicereus grandiflorus* (cactus grandiflorus), *Strophampus hispidus* and *Strophantus kombe* (strophampus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill). Even the venom glands of the animal *Bufo marinus* (cane toad) contain cardiac glycosides. Recently, the digitalislike steroid in the venom of the *B. marinus* toad was identified as a previously described steroid, marinobufagenin. Marinobufagenin demonstrated high digoxinlike immuno-reactivity and was antagonized with an antidigoxin antibody.

Accidental poisonings and even suicide attempts with ingestion of cardiac glycosides are abundant in the medical literature. Some herbal remedies (eg, Siberian ginseng) can elevate synthetic digoxin drug levels and cause toxic effects. In the United States, there are about 15000 intoxications due to accidental or intentional ingestion of poisonous plants annually. In 1993, 2388 toxic exposures in the United States were reported to be due to plant glycosides. Of these, the largest percentage were attributed to oleander (ie, 25%). In the case of oleander, all plant tissues, including the seeds, roots, stems, leaves, berries, and blossoms, are considered extremely toxic. In fact, death in humans has been reported following ingestion of as little as 1 oleander leaf. The clinical manifestations of oleander intoxication, as well as other natural glycosides, is virtually identical to digoxin overdose. Morbidity and mortality are mainly related to cardiotoxic adverse effects that usually include life-threatening ventricular tachyarrhythmias, bradycardia, and heart block. The diagnosis should rely on the clinical presentation of unexplained hyperkalemia, and cardiac, neurologic, and gastrointestinal symptoms.

The diagnosis can be further supported by the detection of the substance digoxin in a radioimmunoassay for digoxin. However, the extent of cross-reactivity between the cardiac glycosides from herbal sources and antibodies used in the radioimmunoassays has not been clearly defined. For this reason, digoxin assays may serve to confirm the suspected diagnosis but not to quantify the severity. Once the diagnosis has been established, the use of digoxin-specific Fab antibody fragments may be helpful in the treatment of severe intoxication. Other modalities, such as dialysis, cannot be easily facilitated because, like digoxin, natural glycosides are distributed extensively into peripheral tissues.

### **HERBS FOR CARDIOVASCULAR CONDITIONS WITH SEVERE ADVERSE REACTIONS OR NOTABLE DRUG INTERACTIONS**

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* A-V indicates arteriovenous anastomosis; ECG, electrocardiographic; and NA, data not applicable.
mid 1940s. Both standardized whole root preparations of \textit{R. serpen
tina} and its reserine alkaloid are officially monographed in the United States Pharmacopeia. A powdered whole root of 200 to 300 mg orally is equivalent to 0.5 mg of reserine.

Reserine was one of the first drugs used on a large scale to treat systemic hypertension. It acts irreversibly blocking the uptake of biogenic amines (norepinephrine, dopamine, and serotonin) in the storage vesicles of central and peripheral adrenergic neurons, thus leaving the catecholamines to be destroyed by the intraneuronal monoamine oxidase in the cytoplasm. The depletion of catecholamines accounts for reserine's sympatholytic and antihypertensive actions. Reserine's effects are long lasting, since recovery of sympathetic function requires synthesis of new storage vesicles, which takes days to weeks. Reserine lowers blood pressure by decreasing cardiac output, peripheral vascular resistance, heart rate, and renin secretion. With the introduction of other antihypertensive drugs with fewer central nervous system adverse effects, the use of reserine has diminished. The daily oral dose of reserine should be 0.25 mg or less, and as little as 0.05 mg if given with a diuretic. Using the whole root, the usual adult dose is 50 to 200 mg administered once daily or in 2 divided doses.

\textit{Rauwolfia} alkaloids are contraindicated for use in patients with previously demonstrated hypersensitivity to these substances, in patients with a history of mental depression (especially with suicidal tendencies), in patients with active peptic ulcer disease or ulcerative colitis, and in patients receiving electroconvulsive therapy. The most common adverse effects are sedation and inability to concentrate and perform complex tasks. Reserine may cause mental depression, sometimes resulting in suicide, and its use must be discontinued at the first sign of depression. Reserine's sympatholytic effect and its enhancement of parasympathetic actions account for its well-described adverse effects: nasal congestion, increased gastric secretion, and mild diarrhea.

\textit{Stephania tetrandra} is an herb sometimes used in traditional Chinese medicine to treat hypertension. Tetrandrine, an alkaloid extract of \textit{S. tetrandra}, has been shown to be a calcium channel antagonist, paralleling the effects of verapamil. Tetrandrine blocks T and L calcium channels, interferes with the binding of dihydralazine and methoxyverapamil at calcium-channel binding sites, and suppresses aldosterone production. A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreases mean, systolic, and diastolic blood pressures for more than 30 minutes; however, an intravenous 40-mg/kg dose killed the rats by myocardial depression. In stroke-prone hypertensive rats, an oral dose of 25 or 50 mg/kg produced a gradual and sustained hypotensive effect after 48 hours without affecting plasma renin activity. In addition to its cardiovascular actions, tetrandrine has reported antineoplastic, immunosuppressive, and mutagenic effects.

Tetrandrine is 90% protein-bound with an elimination half-life of 88 minutes, according to dog studies; however, rat studies have shown a sustained hypotensive effect for more than 48 hours after a 25- or 50-mg oral dose. Tetrandrine causes liver necrosis in dogs orally administered 40 mg/kg of tetrandrine 3 times weekly for 2 months, reversible swelling of liver cells with a 20-mg/kg dose, and no observable changes with a 10-mg/kg dose. Given the evidence of hepatotoxicity, many more studies are necessary to establish a safe dosage of tetrandrine in humans.

More recently, tetrandrine has been implicated in an outbreak of rapidly progressive renal failure, termed Chinese herb nephropathy. Numerous individuals developed the condition after using a combination of several Chinese herbs as part of a dieting regimen. It has been hypothesized that the cause may be attributed to misidentification of \textit{S. tetrandra}; nonetheless, questions still remain as to the role of tetrandrine in the development of this serious toxic effect.

The root of \textit{Linguisticum wallichii}, inhibits platelet aggregation in vitro and lowers blood pressure by vasodilation in dogs. With its actions independent of the endothelium, tetramethylpyr-
azine's vasodilatory effect is mediated by calcium channel antagonism and nonselective antagonism of \alpha-adrenergic receptors. Some evidence suggests that tetramethylpyrazine acts on the pulmonary vasculature. Currently, there is insufficient information to evaluate the safety and efficacy of this herbal medicinal.

\textit{Uncaria rhynchophylla} is sometimes used in traditional Chinese medicine to treat hypertension. Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles of \textit{U. rhynchophylla}'s vasodilatory effect. The mechanism of \textit{U. rhynchophylla}'s actions is unclear. Some studies point to an alteration in calcium ion flux in response to activation, whereas others point to hirsutine's inhibition of nicotine-induced dopamine release. One in vitro study has shown \textit{U. rhynchophylla} extract relaxes nor
epinephrine-precontracted rat aorta through endothelium-dependent and -independent mechanisms. For the endothelium-dependent component, \textit{U. rhynchophylla} extract appears to stimulate endothelium- derived relaxing factor and/or nitric oxide release without involving muscarinic receptors. Also, in vitro and in vivo studies have shown that rhynchophylline can inhibit platelet aggregation and reduce platelet thromboses induced with collagen or adenosine diphosphate plus epinephrine. Safety and efficacy cannot be evaluated at this time because of a lack of clinical data.

\textit{Veratrum} (hellebore) is a perennial herb grown in many parts of the world. Varieties include \textit{V. viride} from Canada and the eastern United States, \textit{V. califor
nicum} from the western United States, \textit{V. album} from Alaska and Europe, and \textit{V. japoni
cum} from Asia. All \textit{V.} plants contain poisonous alkaloids known to cause vomiting, bradycardia, and hypotension. Most cases of \textit{V.} poisonings are due to mis
dentification with other plants. Although once a treatment for hyperten
sion, the use of \textit{V.} al-
kaloids has lost favor owing to a low therapeutic index and unacceptable toxicity, as well as the introduction of safer antihypertensive drug alternatives.40

Veratrum alkaloids enhance nerve and muscle excitability by increasing sodium ion conductivity. They act on the posterior wall of the left ventricle and the coronary sinus baroreceptors, causing reflex hypertension and bradycardia via the vagus nerve (Bezold-Jarisch reflex). Nausea and vomiting are secondary to the alkaloids’ actions on the nodose ganglion.30

The diagnosis of Veratrum toxicity is established by history, identification of the plant, and strong clinical suspicion. Clinical symptoms usually occur quickly, often within 30 minutes.41 Treatment is mainly supportive and directed at controlling bradycardia and hypotension. Veratrum-induced bradycardia usually responds to treatment with atropine; however, the blood pressure response to atropine is more variable and requires the addition of pressors. Other electrocardiographic changes, such as atrioventricular dissociation, may also be reversible with atropine.42 Seizures are a rare complication and may be treated with conventional anticonvulsants. For patients with pre-existing cardiac disease, the use of β-agonists or pacing may be necessary. Nausea may be controlled with pharmacological therapy as well as suppressing cholesterol biosynthesis.47

According to another study, Crataegus extract, in high concentrations, has a cardioprotective effect on ischemic-reperfused hearts without causing an increase in coronary blood flow.48 On the other hand, oral and parenteral administration of oligomeric procyanins of Crataegus has been shown to lead to an increase in coronary blood flow in both cats and dogs.49,50 Double-blind clinical trials have demonstrated simultaneous cardioprotective and vasodilatory actions of Crataegus.51 In essence, Crataegus increases coronary perfusion, has a mild hypotensive effect, antagonizes atherogenesis, and has positive inotropic and negative chronotropic actions.52

In a recent multicenter, placebo-controlled, double-blind study, an extract of Craetaegus was shown to clearly improve the cardiac performance of patients with New York Heart Association class II heart failure. In this study, the primary parameter analyzed was the heart rate product (systolic blood pressure × heart rate).53 Recent studies have suggested that the mechanism of cardiac action for Crataegus species may be due to the inhibition of the 3’, 5’-cyclic adenosine monophosphate phosphodiesterase.54

Hawthorn is relatively devoid of adverse effects. In fact, in comparison with other inotropic drugs such as epinephrine, amrinone, milrinone, and digoxin, Crataegus has a potentially reduced arrhythmogenic risk because of its ability to prolong the effective refractory period, while the other drugs mentioned previously all shorten this parameter.55,56 Also, it should be noted that concomitant use of hawthorn with digitalis can markedly enhance the activity of digitalis.57

Because of its resemblance to Panax ginseng (Asian ginseng), Panax notoginseng has acquired the common name of pseudoginseng, especially since it is often an adulterant of P ginseng preparations. In traditional Chinese medicine, the root of P notoginseng is used for analgesia and hemostasis. It is also often used in the treatment of patients with angina and coronary artery disease.30 Panax notoginseng has been described as a calcium channel antagonist in vascular tissue. More specifically, its pharmacological action may be as a novel and selective calcium ion antagonist that does not interact with the L-type calcium ion channel but rather may interact with the receptor-operated calcium ion channel.58

Although clinical trials are lacking, in vitro studies using P notoginseng suggest possible cardiovascular effects. One study that used purified notoginsenoside R1, extracted from P notoginseng, on human umbilical vein endothelial cells showed a dose- and time-dependent synthesis of tissue-type plasminogen activating factor without affecting the synthesis of plasminogen activating inhibitor. Thus, fibrinolytic parameters were enhanced.59 Another study suggests that P notoginseng saponins may inhibit atherogenesis by interfering with the proliferation of smooth muscle cells.60 In vitro and in vivo studies using rats and rabbits demonstrate that P notoginseng may be useful as an antianginal drug, since it dilates coronary arteries in all concentrations. The role of P notoginseng in the treatment of hypertension is less certain, since P notoginseng causes vasodilation or vasoconstriction depending on the concentration and target vessel.61 The results of these in vitro and in vivo studies are encouraging; however, clinical trials will be necessary to make a more

ANGINA PECTORIS

Crataegus hawthorn, a name encompassing many Crataegus species (such as Crataegus oxyacantha and Crataegus monogyna in the West and Crataegus pinnatifida in China) has acquired the reputation in modern herbal literature as an important tonic for the cardiovascular system that is particularly useful for angina. Crataegus leaves, flowers, and fruits contain a number of biologically active substances, such as oligomeric procyanins, flavonoids, and catechins. From current studies, Crataegus extract appears to have antioxidant properties and can inhibit the formation of thromboxane as well.44,45

Also, Crataegus extract antagonizes the increases in cholesterol, triglyceride, and phospholipid levels in low-density lipoprotein (LDL) and very low-density lipoprotein in rats fed a hyperlipidemic diet; thus, it may inhibit the progression of atherosclerosis.46 This hypocholesterolemic action may be due to an upregulation of hepatic LDL receptors resulting in greater influx of plasma cholesterol into the liver. Crataegus also prevents cholesterol accumulation in the liver by enhancing cholesterol degradation to bile acids, as well as suppressing cholesterol biosynthesis.47

Veratrum am份a (wu-chu-yu) is a Chinese herbal drug that has been used as a treatment for hypertension. It contains an active vasorelaxant component called rutacearpne that can cause endothelium-dependent vasodilation in experimental models.43

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In traditional Chinese medicine, the Salvia officinalis (dan-shen), a relative of the Western sage Salvia officinalis, is native to China. In traditional Chinese medicine, the root of S miltiorrhiza is used as a circulatory stimulant, sedative, and cooling drug.38 Salvia miltiorrhiza may be useful as an antianginal drug because it has been shown to dilate coronary arteries in all concentrations, similar to P notoginseng. Also, S miltiorrhiza has variable action on other vessels depending on its concentration, so it may not be as helpful in treating hypertension.61 In vitro, S miltiorrhiza, in a dose-dependent fashion, inhibits platelet aggregation and serotonin release induced by either adenosine diphosphate or epinephrine, which is thought to be mediated by an increase in platelet cyclic adenosine monophosphate caused by S miltiorrhiza’s inhibition of cyclic adenosine monophosphate phosphodiesterase.62 Salvia miltiorrhiza appears to have a protective action on ischemic myocardium, enhancing the recovery of contractile force on reoxygenation.63 More recently, S miltiorrhiza has been shown to protect myocardial mitochondrial membranes from ischemia-reperfusion injury and lipid peroxidation because of its free radical–scavenging effects.64 Qualitatively and quantitatively, a decoction of S miltiorrhiza was as efficacious as the more expensive isolated tanshinones.59

Clinical trials will be necessary to evaluate the safety and efficacy of S miltiorrhiza. Of note, it has been observed clinically that when S miltiorrhiza and warfarin sodium are coadministered, there is an increased incidence in warfarin-related adverse effects; in rats S miltiorrhiza was shown to increase the plasma concentrations of warfarin as well as the prothrombin time.65

**ATHEROSCLEROSIS**

In addition to its use in the culinary arts, garlic (Allium sativum) has been valued for centuries for its medicinal properties. Garlic is one of the herbal medicines that has been examined more closely by the scientific community. In recent decades, research has focused on garlic’s use in preventing atherosclerosis. Garlic, like many of the other herbal medicines discussed previously, has demonstrated multiple beneficial cardiovascular effects. A number of studies have demonstrated these effects that include lowering blood pressure, inhibiting platelet aggregation, enhancing fibrinolytic activity, reducing serum cholesterol and triglyceride levels, and protecting the elastic properties of the aorta.

Consumption of large quantities of fresh garlic (0.25 to 1.0 g/kg or about 5–20 average sized 4-g cloves in a person weighing 78.7 kg) has been shown to produce the beneficial effects mentioned earlier.58 In support of this, a recent double-blind cross-over study was conducted on moderately hypercholesterolemic men that compared the effects of 7.2 g of aged garlic extract with placebo on blood lipid levels. This study found that there was a maximal reduction of 6.1% in total serum cholesterol levels and 4.6% in LDL cholesterol levels with garlic compared with placebo.65

However, despite positive evidence from numerous trials, some investigators have been hesitant to outright endorse the routine use of garlic for cardiovascular disease because many of the published studies had methodological shortcomings, perhaps because constituent trials were small, lacking statistical power. Also, inappropriate methods of randomization, lack of dietary run-in period, short duration, or failure to undertake intention-to-treat analysis may explain the cautious acceptance of previous meta-analyses.73 In fact, one recent study found no demonstrable effect of garlic ingestion on lipid and lipoprotein levels. This study used a cross-over design protected by a washout period to reduce between-subject variability as well as close assessment and reporting of dietary behavior, which had been lacking in previous trials.74 Another study found no effect of garlic on cholesterol absorption, cholesterol synthesis, or cholesterol metabolism.73 As is evident, the precise extent of garlic’s impact on atherosclerosis remains controversial; larger, more rigorously designed trials may be necessary to better determine its utility in preventing cardiovascular disease.

Garlic has also been studied in hypertensive patients as a blood pressure–lowering agent. Similar to its lipid effects, no conclusive studies have been conducted and many methodological shortcomings exist in study designs. The results of one meta-analysis that considered 8 different trials suggest some clinical use for patients with mild hypertension, but there is insufficient evidence to recommend its use as routine clinical therapy.68 Garlic has also been shown to possess antiplatelet activity. In the past, this action was mostly documented in vitro.75 A new study examined the effect of the consumption of a fresh clove of garlic on platelet thromboxane production and showed that after 26 weeks, serum thromboxane levels were reduced about 80%.76 This may prove to be beneficial in the prevention of thrombosis in the future. Recently, the effect of long-term garlic intake on the elastic properties of the aorta was also studied. Participants in the trial (limited to those aged 50–80 years) consumed 300 mg/d of standardized garlic powder for more than 2 years. The results showed that the pulse-wave velocity and standardized elastic vascular resistance of the aorta were lower in the garlic group than in the control group. Consequently, long-term garlic powder intake may have a protective effect on the elastic properties of the aorta related to aging.77 In these ways, garlic has shown numerous beneficial cardiovascular effects that need to be investigated further to determine its therapeutic utility.

Intact cells of garlic bulbs include an odorless, sulfur-containing amino acid known as allinin. When garlic is crushed, allinin comes into contact with allinase, which converts allinin to allicin. Allicin has potent antibacterial properties, but it is also highly odorous and unstable. Ajoenes, self-condensation products of allicin, appear to be responsible for garlic’s antithrombotic activity. Most authorities now agree that allicin and its derivatives are the active constituents of garlic’s physiological ac-
tivity. Fresh garlic releases allicin in the mouth during the chewing process. Dried garlic preparations lack allicin but contain allin and allinase. Since allinase is inactivated in the stomach, dried garlic preparations should be coated with enteric so that they pass through the stomach into the small intestine where allin can be enzymatically converted to allicin. Few commercial garlic preparations are standardized for their allicin yield based on allin content, hence making their effectiveness less certain.5 However, one double-blind, placebo-controlled study involving 261 patients for 4 months using one 800-mg tablet of garlic powder daily, standardized to 1.3% allin content, demonstrated significant reductions in total cholesterol (12%) and triglyceride levels (17%).78

Aside from a garlic odor on the breath and body, moderate garlic consumption causes few adverse effects. However, consumption in excess of 5 cloves daily may result in heartburn, flatulence, and other gastrointestinal disturbances. Some people have reported allergic reactions to garlic, most commonly allergic contact dermatitis. Patch testing with 1% diallyl disulfide is recommended when garlic allergy is suspected.79 Because of its antithrombotic activity, garlic should be used with caution in people taking oral anticoagulants concomitantly.5,80

The resin of Commiphora mukul (gugulipid), a small, thorny tree native to India, has long been used in Ayurvedic medicine to treat lipid disorders. The primary mechanism of action of gugulipid is through an increase in the uptake and metabolism of LDL cholesterol by the liver.81 In a double-blind, cross-over study completed in 125 patients taking gugulipid compared with 108 patients taking clofibrate, the average decrease in serum cholesterol and triglyceride levels was 11% and 16.8%, respectively, with gugulipid compared with 10% and 21.6%, respectively, with clofibrate. In general, hypercholesterolemic patients responded more favorably to gugulipid therapy than hypertriglycerideemic patients.82 Moreover, it was shown in another randomized, double-blind trial that C mukul also decreased LDL cholesterol levels by 12.5% and the total cholesterol–high-density lipoprotein cholesterol ratio by 11.1%, whereas the levels were unchanged in the placebo group.83

Besides being potentially as effective in lowering blood lipid levels as modern hyperlipidemic drugs, gugulipid may even be safer. In the trial mentioned previously, compliance was greater than 96%, with only the adverse effects of headache, mild nausea, and hiccups noted.84 However, it has been shown that gugulipid may affect the bioavailability of other cardiovascular drugs, namely, propranolol hydrochloride and diltiazem hydrochloride. Gugulipid significantly reduced the peak plasma concentration and area under the curve of both these drugs, which may lead to diminished efficacy or nonresponsiveness.85 Undoubtedly, gugulipid is a natural lipid-lowering drug with potential for therapeutic use, but rigorous, larger clinical trials will be necessary to further evaluate its safety and efficacy before it can be endorsed as an alternative therapy for hyperlipidemia and prevention of atherosclerosis.

Maharishi amrit kalash-4 and Maharishi amrit kalash-5 are 2 complex herbal mixtures with significant antioxidant properties that have been shown to inhibit LDL oxidation in patients with hyperlipidemia. In experimental studies, the herbal mixtures have also been shown to inhibit enzymatic- and nonenzymatic-induced microsomal lipid peroxidation and platelet aggregation.85

**CEREBRAL AND PERIPHERAL VASCULAR DISEASE**

Having existed for more than 200 million years, Ginkgo biloba (maidenhair tree) was apparently saved from extinction by human intervention, surviving in Far Eastern temple gardens while disappearing for centuries in the West. It was reintroduced to Europe in 1730 and became a favorite ornamental tree.86 Although the root and kernels of G biloba have long been used in traditional Chinese medicine, the tree gained attention in the West during the 20th century for its medicinal value after a concentrated extract of G biloba leaves was developed in the 1960s. At least 2 groups of substances within G biloba extract (GBE) demonstrate beneficial pharmacological actions. The flavonoids reduce capillary permeability as well as fragility and serve as free radical scavengers. The terpenes (ie, ginkgolides) inhibit platelet-activating factor, decrease vascular resistance, and improve circulatory flow without appreciably affecting blood pressure.87 Continuing research appears to support the primary use of GBE for treating cerebral insufficiency and its secondary effects on vertigo, tinnitus, memory, and mood; also, GBE appears to be useful for treating peripheral vascular disease, including diabetic retinopathy and intermittent claudication.5,57,87-91

In a randomized, placebo-controlled, double-blind study, EGb 761, which is a standardized extract of G biloba with respect to its flavonol glycoside and terpene lactone content, was shown to significantly decrease the areas of ischemia as measured by transcutaneous partial pressure of oxygen during exercise. Because of its rapid antiischemic action, EGb 761 may be valuable in the treatment of intermittent claudication and peripheral artery disease in general.92

Also, studies have been examining the cardioprotective efficacy of EGB 761 in regard to its anti-free radical action in myocardial ischemia–reperfusion injury. In vitro studies with animal models have shown that this compound may exert such an effect.93,94 A clinical study of 15 patients undergoing coronary bypass surgery demonstrated that oral EGB 761 therapy may limit free radical–induced oxidative stress occurring in the systemic circulation and at the level of the myocardium during these operations.95 It remains to be studied whether extracts of G biloba may be used as pharmacological adjuvants to limit tissue damage and metabolic alterations following coronary bypass surgery, coronary angioplasty for acute myocardial infarctions, or even in managing coronary thrombosis. Although approved as a drug in Europe, Ginkgo is not approved in the United States and is instead marketed as a food supplement, usually supplied as 40-mg tablets.
of extract. Since most of the investigations examining the efficacy of GBEs used preparations such as EGb 761 or LI 1370, the bioequivalence of other GBE products has not been established. The recommended dosage in Europe is one 40-mg tablet taken 3 times daily with meals (120 mg/d).5,87 Adverse effects due to GBE are rare but can include gastrointestinal disturbances, headache, and allergic skin rash.5,87

Known mostly as a culinary spice and flavoring agent, Rosmarinus officinalis (rosemary) is listed in many herbal sources as a tonic and all-around stimulant. Traditionally, rosemary leaves are said to enhance circulation, aid digestion, elevate mood, and boost energy. When applied externally, the volatile oils are supposedly useful for arthritic conditions and baldness.5

Although research on rosemary is scant, some studies have focused on antioxidant effects of dipterpenoids, especially carnosic acid and carnosol, isolated from rosemary leaves. In addition to having antineoplastic effects, antioxidants in rosemary have been credited with stabilizing erythrocyte membranes and inhibiting superoxide generation and lipid peroxidation.96,97 Essential oils of rosemary have demonstrated antimicrobial, hyperglycemic, and insulin-inhibiting properties.98,99 Rosemary leaves contain high amounts of salicylates, and its flavonoid pigment diosmin is reported to decrease capillary permeability and fragility.57,100,101

Despite the conclusions derived from in vitro and animal studies, the therapeutic use of rosemary for cardiovascular disorders remains questionable, because few, if any, clinical trials have been conducted using rosemary. Because of the lack of studies, no conclusions can be reached regarding the use of the antioxidants of rosemary in inhibiting atherosclerosis. Although external application may cause cutaneous vasodilation from the counterirritant properties of rosemary’s essential oils, there is no evidence to support any prolonged improvement in peripheral circulation.5 While rosemary does have some carminative properties, it may also cause gastrointestinal and kidney disturbances in large doses.5,101 Until more studies are done, rosemary should probably be limited to its use as a culinary spice and flavoring agent rather than as a medicine.

VENOUS INSUFFICIENCY

The seeds of horse chestnut, Aesculus hippocastanum, have long been used in Europe to treat venous disorders such as varicose veins. The saponin glycoside aescin from horse chestnut extract (HCE) inhibits the activity of lysosomal enzymes thought to contribute to varicose veins by weakening vessel walls and increasing permeability, which result in dilated veins and edema.5 In fact, recent research has shown that A hippocastanum inhibits only against hyaluronidase but not elastase, and this activity is linked mainly to the saponin escin.102 In animal studies, HCE, in a dose-dependent fashion, increases venous tone, venous flow, and lymphatic flow. It also antagonizes capillary hyperpermeability induced by histamine, serotonin, or chloroform. This extract has been shown to decrease edema formation of lymphatic and inflammatory origin. Horse chestnut extract has antiexudative properties, suppressing experimentally induced pleurisy and peritonitis by inhibiting plasma extravasation and leukocyte emigration, and its dose-dependent antioxidant properties can inhibit in vitro lipid peroxidation.103,104 Randomized, double-blind, placebo-controlled trials with HCE show are eduction in edema, measured using plethysmography.105,106

In another recent randomized, placebo-controlled study, the efficacy and safety of class 2 compression stockings and dried HCE were compared. Both HCE and the compression stockings decreased lower leg edema after 12 weeks of therapy; the results showed an average 43.8-mL reduction with HCE and 46.7-mL with compression stockings, while the placebo group showed an increase of 9.8 mL. Both HCE and compression therapy were well tolerated, with no serious adverse effects. This study may indicate that both of these modalities are reasonable alternatives for the effective treatment of patients with chronic venous insufficiency.107 Also, HCE has been shown to markedly improve other symptoms associated with chronic venous insufficiency, such as pain, tiredness, itching, and tension in the swollen leg, in a case-observation study.108 Aside from effects on venous insufficiency, prophylactic use of HCE has been thought to decrease the incidence of thromboembolic complications of gynecological surgery. However, since this issue is still controversial,109 this does not appear to be the case.109

Standardized HCE is prepared as an aqueous alcohol extract of 16% to 21% of triterpene glycosides, calculated as aescin. The usual initial dosage is 90 to 150 mg/d of aescin, which may be reduced to 35 to 70 mg/d if clinical benefit is seen.5 Standardized HCE preparations are not available in the United States, but nonstandardized products may be available.

Some manufacturers promote the use of topical preparations of HCE for treatment of varicose veins as well as hemorrhoids; however, at least one study has demonstrated poor aescin distribution at sites other than the skin and muscle tissues underlying the application site.110 Moreover, the involvement of arterioles and veins in the pathophysiology of hemorrhoids makes the effectiveness of HCE doubtful, since HCE has no known effects on the arterial circulation. For now, research studies have yet to confirm any clinical effectiveness of topical HCE preparations.

Although adverse effects are uncommon, HCE may cause gastrointestinal irritation. Parenteral aescin has produced isolated cases of anaphylactic reactions, as well as hepatic and renal toxic effects.5,111-113 In the event of toxicity, aescin can be eliminated via dialysis, with elimination dependent on protein-binding.114 Horse chestnut extract is also one of the components of venocuran, a drug marketed as a treatment for venous disorders. In 1975, venocuran was determined to cause a pseudolupus syndrome characterized by recurrent fever, myalgia, arthralgia, pleuritis, pulmonary infiltrates, pericarditis, myocarditis, and mitochondrial antibodies in the absence of nuclear antibodies after pro-
longed treatment.\textsuperscript{115,116} Venocuran has since been withdrawn from the market; however, the nature of its pathophysiologic action is still unknown.

Like \textit{A hippocastanum}, \textit{Ruscus aculeatus} (butcher’s broom) is also known for its use in treating venous insufficiency. \textit{Ruscus aculeatus} is a short evergreen shrub found commonly in the Mediterranean region. Two steroidal saponins, ruscogenin and neurogenin, extracted from the rhizomes of \textit{R aculeatus} are thought to be its active components.\textsuperscript{103} In vivo studies on hamster cheek pouch reveal that topical \textit{Ruscus} extract dose dependently antagonizes histamine-induced increases in vascular permeability.\textsuperscript{117} Moreover, topical \textit{Ruscus} extract causes dose-dependent constriction of venules without appreciably affecting arterioles.\textsuperscript{118} Topical \textit{Ruscus} extract’s vascular effects are also temperature dependent and appear to counter the sympathetic nervous system’s temperature-sensitive vascular regulation: venules dilate at a lower temperature (25°C), constrict at near physiologic temperatures (36.5°C), and further constrict at higher temperatures (40°C); arterioles dilate at 25°C, are unaffected at 36.5°C, and remain unaffected or constrict at 40°C, depending on \textit{Ruscus} concentration.\textsuperscript{119} Based on the influence of prazosin, diltiazem, and rauwolscine, the peripheral vascular effects of \textit{Ruscus} extract appear to be selectively mediated by effects on calcium channels and \(\alpha_1\)-adrenergic receptors with less activity at \(\alpha_2\)-adrenergic receptors.\textsuperscript{117,118} Also, \textit{R aculeatus} exhibits strong antielastase activity and has little effect on hyaluronidase in direct contrast to \textit{A hippocastanum}. This activity may contribute to their efficacy in the treatment of venous insufficiency since these enzyme systems are involved in the turnover of the main components of the perivascular amorphous substance.\textsuperscript{102}

Several small clinical trials using topical \textit{Ruscus} extract support its role in treating venous insufficiency. One randomized, double-blind, placebo-controlled trial involving 18 volunteers showed a beneficial decrease in femoral vein diameter (median decrease, 1.25 mm) using duplex B-scan ultrasonography. The decrease was measured 2.5 hours after applying 4 to 6 g of a cream containing 64 to 96 mg of \textit{Ruscus} extract.\textsuperscript{120} In another small trial (\(N = 18\)) it was shown that topical \textit{Ruscus} extract may be helpful in reducing venous dilation during pregnancy.\textsuperscript{121} Oral agents may be useful as topical drugs for venous insufficiency, although the evidence is less convincing.\textsuperscript{122}

Although capsule, tablet, ointment, and suppository (for hemorrhoids) preparations of \textit{Ruscus} extract are available in Europe, only capsules are available in the United States. These capsules contain 75 mg of \textit{Ruscus} extract and 2 mg of rosemary oil.\textsuperscript{101} Aside from occasional nausea and gastritis, adverse effects from using \textit{Raculeatus} have rarely been reported, even in high doses.\textsuperscript{72} Nevertheless, one should be wary of any drug that has not been thoroughly tested. Although there is ample evidence to support the pharmacological activity of \textit{R aculeatus}, there is still a relative deficiency of clinical data to establish its actual safety and efficacy. Until more studies are completed, no recommendations regarding dosage can be offered.

ARRHYTHMIA

In traditional Chinese medicine, arrhythmias are categorized by the characteristic symptoms of palpitations and abnormal pulse. Numerous Chinese herbal medicines are identified to have antiarrhythmic effects, such as xin bao, ci zhu wan, bu xin dan, and several others.\textsuperscript{123} However, few clinical trials have been conducted to study their effects and safety. Xin bao is one agent that has begun to be examined. The mechanism of action of xin bao is thought to be through its stimulation and increased excitability of the sinusatrial node.\textsuperscript{124} In one observational study, the effects of xin bao were documented in 87 patients with sick sinus syndrome. Xin bao was administered orally 2 to 3 times per day for 2 months. Patients with major symptoms of sick sinus syndrome, which included dizziness, palpitations, and chest pressure, improved significantly after treatment.\textsuperscript{124} No serious adverse effects were noted. This study suggests a possible role of xin bao in the treatment of sick sinus syndrome. However, more scientific research on xin bao and other antiarrhythmic Chinese herbs mentioned previously are necessary before any recommendations can be made for their routine use in patients with sick sinus syndrome or other arrhythmias.

COMMENT

With the high prevalence of herbal medicine use in the United States, health practitioners should remember to inquire about such health practices when taking clinical histories and remain informed of the beneficial or harmful effects of these treatments. Continuing research is necessary to elucidate the pharmacological activities of the many cardiopotent herbal medicines and to stimulate future pharmaceutical development of therapeutically beneficial herbal drugs. However, such research is currently lacking in the United States and requires more support from government agencies before the full potential of these types of treatments can be determined. At the same time, legal surveillance of herbal medicine use with low safety margins should be instituted for the sake of public health; this is especially imperative for those herbs with adverse cardiovascular reactions\textsuperscript{125} and drug interactions. As more information becomes available regarding the safety and efficacy of herbal medicines through new clinical trials, research-supported claims may one day become available to consumers and physicians in a manner similar to the allopathic medicines.

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