
THE USE OF HERBS FOR TREATING CARDIOVASCULAR DISEASE*

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Herbs have been an integral part of society since the beginning of human civilization and are valued for their culinary and medicinal properties. With the development of patented medicines in the early part of the 20th century, herbal medicine lost ground to the new synthetic medicines touted by scientists and physicians to be more effective and reliable. Nevertheless, herbal remedies are still popular in the United States. Herbal medicine, i.e., plant structures known as phytomedicinals or phytopharmaceuticals, have become an increasing presence and area of interest to both pharmacists and other health care professionals with the advent of the German commissioned E-monographs, reporting extensive information about the safety and efficacy of herbal preparations. In fact, herbal medicines have contributed to commercial drug preparations manufactured today, such as ephedrine from *Ephedra sinica* (ma-huang), digitoxin from *Digitalis purpurea* (foxglove), salicin (the source of aspirin) from *Salix alba* (willow bark), and reserpine from *Rauwolfia serpentina* (snakeroot).^{1,2} The discovery of the antineoplastic agent paclitaxel (Taxol) from *Taxus brevifolia* (the Pacific yew tree) stresses the role of plants as a continuing resource for modern medicine.

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REGULATIONS IN THE UNITED STATES

A number of laws exist in the United States affecting the sale and marketing of drugs, including the Food and Drug Act (1906) with its Sherley amendment (1912) and the Federal Food, Drug, and Cosmetic Act (1938) with its many amendments. The Kefauver–Harris amendments passed in 1962 required that all drugs marketed in the United States be proven both safe and effective. To evaluate the safety and efficacy of drugs, the FDA turned to the Division of Medical Sciences of the National Academy of Sciences–National Research Council, which then organized a “drug efficacy study” based on reviews of *in vitro* tests and clinical trials on patients, usually supplied by the companies interested in marketing the drugs. Since very few herbs had their active ingredients isolated or had undergone clinical trials, only a small number of herbs were evaluated and only for specific indications.

In 1990, the results of the FDA’s study on over-the-counter (OTC) medications, which included many herbs and herbal products, were released to the public. A few plant products, such as *Plantago psyllium* (plantago seed), *Cascara sagrada* (cascara bark, *Rhamnus purshiana*), and *Cassia acutifolia* (senna leaf, *Senna alexandrina*), were judged to be “both safe and effective” (category I) for their laxative actions. However, 142 herbs and herbal products were deemed “unsafe or ineffective” (category II), while there was “insufficient evidence to evaluate” (category III) another 116 herbs. Many herbs and herbal products in categories II and III had been grandfathered by the 1938 act and 1962 amendments, since they were already covered in the 1906 act. Thus they were not subject to the requirements of proving both safety and efficacy to be out on the market. However, to deal with these grandfathered OTC products, the FDA declared that any grandfathered drug with claims of efficacy on the package or in the package insert that did not concur with the FDA’s OTC study would be considered misbranded and subject to confiscation.³ Complying with the new FDA regulations meant having to remove all but the names of the herbal products from their labels and marketing them as nutritional supplements or food additives. Therefore consumers who wish to obtain factual information regarding the therapeutic use or potential harm of herbal remedies would have to obtain them from books and pamphlets,

most of which base their information on traditional reputation rather than existing scientific research. Another major problem is that the marketing of herbal products under their common names, which is usually the case in health food stores and on the internet,⁴ does not allow for proper identification, as there may be many species of herbs with the same common name. Additionally, there is a lack of dose standardization with herbal medicinals having active pharmacologic ingredients.^{5,6} These problems will remain until herbal medicinals are recognized as drugs.⁷⁻⁹

With the cost and time of developing a new drug estimated at \$231 million over 12 years (based on a 1990 report from the Center for the Study of Drug Development at Tufts University), most members of the herbal and pharmaceutical industries do not pursue the *in vitro* tests and clinical trials to prove their product safe and effective, especially with the slim chance of obtaining patent protection for the many herbs that have been in use for centuries.³ The NIH allocated \$2 million each for 1992 and 1993 and 2.4 million in 2000 for research to validate alternative medical practices; however, it is clear this grant allocation is inadequate.

HERBAL REMEDIES USED TO TREAT CARDIOVASCULAR DISEASES

The use of herbal medicine has skyrocketed over the last 5 years, with out-of-pocket costs estimated at more than \$5 billion in the United States alone. The following review of herbal medicines affecting the cardiovascular system is based on information gleaned from the scientific literature (Table 1). Most herbal medicinals have multiple cardiovascular effects.

In general, the dilution of active components in herbal medicinals results in fewer side effects and toxicities in comparison with the concentration of active components in the allopathic medicines. However, cardiovascular disease is a serious health hazard and no one should attempt to self-medicate with herbal remedies without first consulting a physician.

Congestive Heart Failure

Cardiac Glycosides

A number of herbs contain potent cardioactive glycosides that have positive inotropic effects on

TABLE 1.
Some Conditions in Which Herbal Medicines Are Used
as Cardiovascular Treatments

Conditions	Examples of Herbs Used
Congestive heart failure	<i>Digitalis purpurea</i> <i>Digitalis lanata</i> <i>Crataegus</i> species Berberine
Systolic hypertension	<i>Rauwolfia serpentina</i> <i>Stephania tetrandra</i> Veratrum alkaloids
Angina pectoris	<i>Crataegus</i> species <i>Panax notoginseng</i> <i>Salvia miltiorrhiza</i>
Atherosclerosis	Garlic
Cerebral insufficiency	<i>Ginkgo biloba</i> <i>Rosmarinus officinalis</i>
Venous insufficiency	<i>Aesculus hippocastanum</i> <i>Ruscus aculeatus</i>

the heart. The drugs digitoxin, derived from either *Digitalis purpurea* (foxglove) or *D. lanata*, and digoxin, derived from *D. lanata* alone, have been used in the treatment of congestive heart failure (CHF) 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. Treating CHF with nonstandardized herbal agents would be dangerous and foolhardy. Accidental poisonings due to cardiac glycosides in herbal remedies are abundant in the medical literature.¹⁰ 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 curassavica* (redheaded cotton bush), *Asclepias fruticosa* (balloon cotton), *Calotropis precera* (king's crown), *Carissa acokanthera* (bushman's poison), *Carissa spectabilis* (winter-sweet), *Cerbera manghas* (sea mango), *Cheiranthus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptostegia grandiflora* (rubber vine), *Helleborus niger* (black hellebore), *Helleborus viridus*, *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Selenicereus grandiflorus* (cactus grandiflorus), *Strophanthus hispidus* and *Strophanthus kombè* (strophanthus), *Thevetia peruviana* (yellow oleander), and *Urginea maritime* (squill). Even the venom glands

of the *Bufo marinus* (cane toad) contain cardiac glycosides.¹¹

Health providers should be aware of the cross-reactivity of cardiac glycosides from herbal sources with the digoxin radioimmunoassay. Treatment of intoxication with these substances is directed at controlling arrhythmias and hyperkalemia, which are the usual causes of fatalities.

Berberine

Berberine is an alkaloid distributed widely in nature and used in the Orient for the treatment of CHF; it is also reported to have antihypertensive and antiarrhythmic actions. In a recent placebo-controlled trial, patients with heart failure and significant ventricular ectopy on standard therapy received berberine 1.2 to 2.0 mg/day for up to 24 months.¹² Compared to placebo, there was a reduction in mortality and ventricular ectopy, with an improvement in quality of life.

Hypertension

Rauwolfia Serpentina

The root of *Rauwolfia serpentina* (snakeroot), the natural source of the alkaloid reserpine, has been a Hindu Ayurvedic remedy since ancient times. In 1931, Indian literature first described the use of *R. serpentina* root for the treatment of hypertension and psychoses; however, the use of rauwolfia alkaloids in Western medicine did not begin until the mid-1940s. Both standardized whole-root preparations of *R. serpentina* and its reserpine alkaloid are officially monographed in the *United States Pharmacopeia*.¹³ A 200- to 300-mg dose of powdered whole root taken orally is equivalent to 0.5 mg of reserpine.

Reserpine was one of the first drugs used on a large scale to treat systemic hypertension. It acts by 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 reserpine's sympatholytic and antihypertensive actions.

Reserpine's effects are long lasting, since recovery of sympathetic function requires synthesis of new storage vesicles, which takes days to weeks. Reserpine lowers blood pressure by decreasing cardiac output, peripheral vascular resistance, heart rate, and renin secretion. With the introduc-

tion of other antihypertensive drugs with fewer central nervous system side effects, the use of reserpine has diminished. The daily oral dose of reserpine 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 per day administered once daily or in two divided doses.

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), or an active peptic ulcer or ulcerative colitis and in those receiving electroconvulsive therapy. The most common side effects are sedation and inability to concentrate and perform complex tasks. Reserpine may cause mental depression, sometimes resulting in suicide, and must be discontinued at the first sign of depression. Reserpine's sympatholytic effect and its enhancement of parasympathetic actions account for its other well-described side effects: nasal congestion, increased secretion of gastric acid, and mild diarrhea.

Stephania Tetrandra

Stephania tetrandra is sometimes used in Traditional Chinese Medicine (TCM) to treat hypertension. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium-channel antagonist, paralleling the effects of verapamil. Tetrandrine inhibits T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-associated sites, and suppresses aldosterone production.¹⁴ A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreased mean, systolic, and diastolic blood pressures for greater than 30 min; however, an intravenous dose of 40 mg/kg 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 h without affecting plasma renin activity.¹⁵ In addition to its cardiovascular actions, tetrandrine has reported antineoplastic, immunosuppressive, and mutagenic effects.¹⁴

Tetrandrine is 90% protein-bound with an elimination half-life ($t_{1/2}$) of 88 min according to dog studies; however, rat studies have shown a sustained hypotensive effect for more than 48 h after a 25 or 50 mg oral dose. Tetrandrine causes liver necrosis in dogs orally administered 40 mg/kg of tetrandrine thrice weekly for 2 months, reversible swelling of liver cells at a 20 mg/kg dose, and no

observable changes at a 10 mg/kg dose. Given the evidence of hepatotoxicity, many more studies are necessary to establish a safe dosage of tetrandrine in humans.

Lingusticum wallichii

The root of *Lingusticum wallichii* (chuan-xiong, chuan-hsiung) is used in TCM as a circulatory stimulant, hypotensive agent, and sedative.¹⁶ Tetramethylpyrazine, the active constituent extracted from *L. wallichii*, inhibits platelet aggregation in vitro and lowers blood pressure by vasodilation in dogs. With its actions independent of the endothelium, tetramethylpyrazine's vasodilatory effect is mediated by calcium antagonism and nonselective antagonism of alpha adrenoceptors. Some evidence suggests that tetramethylpyrazine can selectively act on the pulmonary vasculature.¹⁴ Currently, there is insufficient information to evaluate the safety and efficacy of this herbal medicinal.

Uncaria Rhynchophylla

Uncaria rhynchophylla (gou-teng) is sometimes used in TCM to treat hypertension.¹⁴ Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles of *U. rhynchophylla*'s vasodilatory effect. The mechanism of *U. rhynchophylla*'s actions is unclear. Some studies point to an alteration in calcium flux in response to activation, whereas others point to hirsutine's inhibition of nicotine-induced dopamine release. One in vitro study has shown that *U. rhynchophylla* extract relaxes norepinephrine-precontracted rat aorta through endothelium-dependent and -independent mechanisms. For the endothelium-dependent component, *U. rhynchophylla* extract appears to stimulate endothelium-derived relaxing factor/nitric oxide release without involving muscarinic receptors.¹⁷ Also, in vitro and in vivo studies have shown that rhynchophylline can inhibit platelet aggregation and reduce platelet thromboses induced by collagen or adenosine diphosphate plus epinephrine.¹⁴ The safety and efficacy of this agent cannot be evaluated at present owing to a lack of clinical data.

Veratrum

Veratrum (hellebore) is a perennial herb growing in many parts of the world. Varieties include *V. viride* from Canada and the eastern United States, *V. californicum* from the western United States, *V. album* from Alaska and Europe, and *V. japoni-*

cum from Asia. All *Veratrum* plants contain poisonous veratrum alkaloids, which are known to cause vomiting, bradycardia, and hypotension. Most cases of *Veratrum* poisonings are due to misidentification with other plants. Although once a treatment for hypertension, the use of *Veratrum* alkaloids has lost favor owing to a low therapeutic index and unacceptable toxicity, as well as the introduction of safer antihypertensive drug alternatives.

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

The diagnosis of *Veratrum* toxicity is established by history, identification of the plant, and strong clinical suspicion. 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 may require the addition of pressors. Electrocardiographic changes may be reversible with atropine but are sometimes not. Seizures are a rare complication and may be treated with conventional anticonvulsants. For patients with preexisting cardiac disease, the use of beta agonists or pacing may be necessary. Nausea may be controlled with phenothiazine antiemetics. Recovery is usually within 24 to 48 h.

Angina Pectoris

Crataegus

Hawthorn, a name encompassing many *Crataegus* species (such as *C. oxyacantha* and *C. monogina* in the West and *C. pinnatifida* in China), has acquired the reputation in the modern herbal literature as an important tonic for the cardiovascular system, particularly useful for angina.¹⁸ *Crataegus* leaves, flowers, and fruits contain a number of biologically active substances such as oligomeric procyanidins, flavonoids, and catechins. From current studies, *Crataegus* extract appears to have antioxidant properties and can inhibit the formation of thromboxane A₂.¹⁹ Also, *Crataegus* extract antagonizes the increases in cholesterol, triglycerides, and phospholipids in low-density lipoprotein (LDL) and very-low-

density lipoprotein (VLDL) in rats fed a hyperlipidemic diet; thus, it may inhibit the progression of atherosclerosis.²⁰ According to one study, *Crataegus* extract in high concentrations has a cardioprotective effect on ischemic-reperfused heart without an increase in coronary blood flow.²¹ On the other hand, oral and parenteral administration of oligomeric procyanins of *Crataegus* leads to an increase in coronary blood flow in cats and dogs.^{22,23} Double-blind clinical trials have demonstrated simultaneous cardiotropic and vasodilatory actions of *Crataegus*.²⁴ In essence, *Crataegus* increases coronary perfusion, has a mild hypotensive effect, antagonizes atherosclerosis, has positive inotropic and negative chronotropic actions, and as an adjunct therapy, improves the symptoms of CHF.^{25,26} A study is in progress assessing the effects of hawthorn extract on mortality as well as on quality of life and hospitalization.²⁷ The Survival and Prognosis Investigation of Crataegus Extract WS 1442 in Congestive Heart Failure (SPICE) trial has enrolled approximately 2300 patients to evaluate the long-term effects (24 months) of a standard preparation of hawthorn extract compared with placebo on hospitalization and mortality in patients with modest heart failure and an established medical regimen.²⁷ *Crataegus* also lowers blood pressure due to its action in lowering peripheral vascular resistance. Animal studies have also indicated that peripheral and coronary blood flow increases while arterial blood pressure decreases.²⁸ Hawthorn is relatively devoid of side effects; however, concomitant use of hawthorn and digoxin can markedly enhance the activity of digitalis.² Therefore hawthorn and digitalis should not be given together.

Panax Notoginseng

Because of its resemblance to *Panax ginseng* (Asian ginseng), *P. notoginseng* (pseudoginseng; san-qui) has acquired the common name of pseudoginseng, especially since it is often an adulterant of *P. ginseng* preparations. In TCM, 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.¹⁶

Although clinical trials are lacking, in vitro studies using *P. notoginseng* do 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 activator without affect-

ing the synthesis of plasminogen activating inhibitor, thus enhancing fibrinolytic parameters.²⁹

Another study suggests that *P. notoginseng* saponins may inhibit atherogenesis by interfering with the proliferation of smooth muscle cells.³⁰ In vitro and in vivo studies using rats and rabbits have demonstrated that *P. notoginseng* may be useful as an antianginal agent, since it dilates coronary arteries in all concentrations. The role of *P. notoginseng* in the treatment of hypertension is less certain, since it causes vasodilation or vasoconstriction depending on concentration and the target vessel. The results of these in vitro and in vivo studies are encouraging; however, clinical trials will be necessary to enable more informed decisions regarding the use of *P. notoginseng*. The most common side effects reported with ginseng were insomnia, diarrhea, and skin reactions.

Salvia Miltiorrhiza

Salvia miltiorrhiza (dan-shen), a relative of the Western sage *S. officinalis*, is native to China. In TCM, the root of *S. miltiorrhiza* is used as a circulatory stimulant, sedative, and cooling agent.¹⁶ *S. miltiorrhiza* may be useful as an antianginal agent because, like *P. notoginseng*, it has been shown to dilate coronary arteries in all concentrations. Also, *S. miltiorrhiza* has variable action on other vessels, depending on its concentration, so it may not be as helpful in treating hypertension. 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 cAMP phosphodiesterase. *S. miltiorrhiza* appears to have a protective effect on ischemic myocardium, enhancing the recovery of contractile force upon reoxygenation. Qualitatively and quantitatively, a decoction of *S. miltiorrhiza* was as efficacious as the more expensive isolated tanshinones.²⁹ Clinical trials will be necessary to further evaluate the safety and efficacy of *S. miltiorrhiza*.

Atherosclerosis

Allium Sativum

In addition to its use in the culinary arts, *Allium sativum* (garlic) has been valued for centuries in many cultures for its medicinal properties. In recent decades, animal and human data have fo-

cused on garlic's use in treating atherosclerosis and hypertension.³¹ A number of studies have demonstrated garlic's effects, which include lowering blood pressure, reducing serum cholesterol and triglycerides, enhancing fibrinolytic activity, and inhibiting platelet aggregation. However, some investigators have been hesitant to endorse the routine use of garlic for cardiovascular disease outright despite positive evidence because many of the published studies had methodologic shortcomings.³¹⁻³³ For example, in one of the largest collective reviews of randomized controlled trials of garlic lasting 4 weeks or longer, the researchers concluded that the effects of garlic treatment are tainted by an inadequate definition of active constituents in the study preparations.³¹ The pharmacologic properties of garlic are extremely complex, comprising a variety of sulfur-containing compounds that include allicin, alliin, diallyl disulfide, ajoene, s-allylcysteines, and gamma-glutamylpeptides, to mention a few. Many of the previous controlled trials of garlic used different preparations containing all or some of these active pharmacologic factors. This may be the major reason for the variability and confusion found in the research.³¹ The definition and delineation of the major active garlic ingredients and their specific mechanisms of action are absolutely necessary before future trials are planned and conducted.

Intact cells of garlic bulbs contain an odorless, sulfur-containing amino acid derivative known as alliin. When garlic is crushed, alliin comes into contact with alliinase, which converts alliin to allicin. Allicin has potent antibacterial properties but is also highly odoriferous 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 physiologic activity. Fresh garlic releases allicin in the mouth during the chewing process. Dried garlic preparations lack allicin but do contain alliin and alliinase. Since alliinase is inactivated by acids in the stomach, dried garlic preparations should be enteric-coated so that they pass through the stomach into the small intestine, where alliin can be enzymatically converted to allicin. Few commercial garlic preparations are standardized for their allicin yield based on alliin content, hence making their effectiveness less certain.³ However, one double-blind, placebo-controlled study involving 261 patients over 4

months using one 800-mg tablet of garlic powder daily, standardized to 1.3% alliin content, demonstrated significant reductions in total cholesterol (12%) and triglycerides (17%).³⁴ In studies that use garlic supplements containing either no alliin or poorly bioavailable alliin, no lipid lowering was realized. Consumption of large quantities of fresh garlic (0.25 to 1 g/kg body weight or about 5 to 20 average-size 4-g cloves in a 175-lb person) does appear to produce beneficial effects. However, in a metaanalysis, it was demonstrated that garlic, in an amount approximating one-half to one clove per day, decreased total serum cholesterol by about 9% in the patients studied.³⁵ The alliin yield of each 800-mg garlic tablet is equivalent to 2.8 g of fresh garlic—less than one average-size 4-g clove; in other words, therapeutic effectiveness may be seen in doses much lower than five cloves of garlic.³ In 11 large databases collected from January 1966 through February 2000, various garlic preparations did suggest small reductions in total cholesterol, LDL, and triglyceride, but no statistically significant changes were noted in high-density lipoproteins. Significant reductions in platelet aggregation and insignificant effects on blood pressure outcomes were also observed.³¹

Aside from a garlic odor on the breath and body, moderate garlic consumption causes few adverse effects. Consumption in excess of five cloves daily may result in heartburn, flatulence, and other GI disturbances. Case reports have also described bleeding in patients ingesting large doses of garlic (average of four cloves per day). Because of its antithrombotic activity, garlic should also be used with caution in people taking oral anticoagulants.³ Some individuals have also reported allergic reactions to garlic.

Cerebral and Peripheral Arterial Disease

Ginkgo Biloba

Dating back well over 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.¹⁶ Although the root and kernels of *G. biloba* have long been used in TCM, *Ginkgo* 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 two groups of substances within *G. biloba* extract

demonstrated beneficial pharmacologic actions. The flavonoids reduce capillary permeability and fragility and serve as free-radical scavengers. The terpenes (i.e., ginkgolides) inhibit platelet activating factor, decrease vascular resistance, and improve circulatory flow without appreciably affecting blood pressure. Continuing research appears to support the primary use of *G. biloba* extract for treating cerebral insufficiency and its secondary effects on vertigo, tinnitus, memory, and mood. In a study evaluating 327 demented patients,³⁶ 120 mg of *G. biloba* extract produced improvements in dementia, similar to other studies with donepezil and tacrine. However, a more recent study showed no benefit of *G. biloba* on cognitive functioning.³⁷ In addition, *G. biloba* extract appears to be useful for treating peripheral vascular disease, including intermittent claudication and diabetic retinopathy.^{3,38} A metaanalysis of eight randomized placebo-controlled trials of *G. biloba* for intermittent claudication showed a mean improvement in pain-free walking distance of 34 meters. Maximal walking distance improved by 35 to 189 meters.³⁹

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 investigations examining the efficacy of *G. biloba* extracts used preparations such as EGb 761 or LI 1370, the bioequivalence of other *G. biloba* extract products has not been established. The recommended dose in Europe is one 40-mg tablet taken three times daily with meals (120 mg daily).³ Adverse effects of *G. biloba* extract are rare but can include GI disturbances, headache, and skin rash. Several case reports of bleeding, including subarachnoid hemorrhage, intracranial hemorrhage, and subdural hematoma have been associated with *G. biloba*.⁴⁰⁻⁴² *G. biloba* should not be used in combination with analgesic agents such as aspirin, ticlopidine, and clopidogrel or anticoagulants such as warfarin and heparin, since it undermines the effect of the platelet inhibiting factor.⁴³

Rosmarinus Officinalis

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.³

Although research on rosemary is scanty, some studies have focused on antioxidant effects of diterpenoids, especially carnosic acid and carnosol, isolated from rosemary leaves. In addition to having antineoplastic effects (especially skin), antioxidants in rosemary have been credited with stabilizing erythrocyte membranes and inhibiting superoxide generation and lipid peroxidation.^{44,45} Essential oils of rosemary have demonstrated antimicrobial, hyperglycemic, and insulin-inhibiting properties.^{46,47} Rosemary leaves contain high amounts of salicylates, and its flavonoid pigment diosmin is reported to decrease capillary permeability and fragility.⁴⁸

Despite the conclusions derived from in vitro and animal studies, the therapeutic use of rosemary for cardiovascular disorders remains questionable, as few if any clinical trials have been conducted using rosemary. Due to 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 vasodilatation from the counter-irritant properties of rosemary's essential oils, there is no evidence to support any prolonged improvement in peripheral circulation.^{3,48} While rosemary does have some carminative properties, it may also cause GI and kidney disturbances in large doses. 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

Aesculus hippocastanum

The seeds of *Aesculus hippocastanum* (horse chestnut) have long been used in Europe to treat venous disorders such as varicose veins. The medicinal qualities of horse chestnut reside mostly in its large seeds, which resemble edible chestnuts. The seeds contain a complex mixture of saponins, glycosides, and several other active ingredients. The grouping of most interest is called aesculic acid or aescin. In addition to a high level of flavonoids, horse chestnuts contain several minerals including magnesium, manganese, cobalt, and iodine.

The saponin glycoside aescin from horse chestnut extract (HCE) inhibits the activity of lysosomal enzymes, which are thought to contribute to

varicose veins by weakening vessel walls and increasing permeability, resulting in dilated veins and edema. In animal studies, HCE, in a dose-dependent fashion, increases venous tone, venous flow, and lymphatic flow. HCE also antagonizes capillary hyperpermeability induced by histamine, serotonin, or chloroform. HCE decreases edema formation of lymphatic and inflammatory origin. HCE has antiexudative properties, suppressing experimentally induced pleurisy and peritonitis by inhibiting plasma extravasation and leukocyte emigration. HCE's dose-dependent antioxidant properties can inhibit in vitro lipid peroxidation. Randomized double-blind, placebo-controlled trials using HCE show a statistically significant reduction in edema, as measured by plethysmography.⁴⁹ Although still controversial, prophylactic use of HCE does not appear to decrease the incidence of thromboembolic complications of gynecologic surgery.

Standardized HCE is prepared as an aqueous-alcohol extract of 16 to 21% triterpene glycosides, calculated as aescin. The usual initial dose is 90 to 150 mg of aescin daily, which may be reduced to 35 to 70 mg daily after improvement.³ 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 very poor aescin distribution at sites other than the skin and muscle tissues underlying the application site.⁵⁰ 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 side effects are uncommon, HCE may cause GI irritation and facial rash. Parenteral aescin has produced isolated cases of anaphylactic reactions as well as hepatic and renal toxicity.³ In the event of toxicity, aescin is completely dialyzable, with elimination dependent on protein binding.

Ruscus aculeatus

Like *A. hippocastanum*, *Ruscus aculeatus* (butcher's broom) is known for its use in treating venous insufficiency. *R. aculeatus* is a short evergreen shrub found commonly in the Mediterra-

nean region. Two steroidal saponins, ruscogenin and neurogenin, extracted from the rhizomes of *R. aculeatus* are thought to be its active components.⁴⁸ In vivo studies on hamster cheek pouch reveal that topical *Ruscus* extract dose-dependently antagonizes a histamine-induced increase in vascular permeability.⁵¹ Moreover, topical *Ruscus* extract causes dose-dependent constriction on venules without appreciably affecting arterioles.⁵² Topical *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 temperature (36.5°C), and further constrict at a higher temperature (40°C); arterioles dilate at 25°C, are unaffected at 36.5°C, and remain unaffected or constricted at 40°C depending on *Ruscus* concentration.⁵³ Based on the influence of prazosin, diltiazem, and rauwolscine, the peripheral vascular effects of *Ruscus* extract appear to be selectively mediated by effects on calcium channels and alpha-adrenergic receptors.

Several small clinical trials using topical *Ruscus* extract support its role in treating venous insufficiency. One randomized double-blind, placebo-controlled trial involving 18 volunteers⁵⁴ showed a statistically significant decrease in femoral vein diameter (median decrease of 1.25 mm) using duplex B-scan ultrasonography 2.5 h after applying 4 to 6 g of a cream containing 64 to 96 mg of *Ruscus* extract. Another small trial ($n = 18$) showed that topical *Ruscus* extract may be helpful in reducing venous dilatation during pregnancy.⁵⁵ Oral agents may be as useful as topical agents for venous insufficiency, although the evidence is less convincing.

Although capsule, tablet, ointment, and suppository (for hemorrhoids) preparations of *Ruscus* extract are available in Europe, only capsules are available in the United States. These capsules contain 75 mg of *Ruscus* extract and 2 mg of rosemary oil.⁴⁸ Aside from occasional nausea and gastritis, side effects from using *R. aculeatus* have rarely been reported, even at high doses. Nevertheless, one should be wary of any drug that has not been thoroughly tested. Although there is ample evidence to support the pharmacologic activity of *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.

TABLE 2.

Adverse Cardiovascular Reactions Observed with Herbal Medicines Used for Other Indications

Examples	Herbal Medicines
Hypertension	<i>Tussilago farfara</i> <i>Ephedra sinica</i>
Hypotension	<i>Aconitum</i> species
Digitalis toxicity	Over 20 herbal substances with activity to <i>digitalis</i> radioimmunoassay
Bradycardia	<i>Aconitum</i> species Jin-bu-huan

**NONCARDIOVASCULAR HERBS WITH ADVERSE
CARDIOVASCULAR EFFECTS**

Herbs used to treat other conditions can have adverse cardiovascular reactions (Table 2).

Tussilago Farfara

Tussilago farfara (coltsfoot, kuan-dong-hua) is a perennial herb that is grown in many parts of northern China, Europe, Africa, Siberia, and North America. Over the years, *T. farfara* has acquired a reputation as a demulcent antitussive agent due to a throat-soothing mucilage within the herb. Recently, the use of *T. farfara* has lost favor due to several studies that found senkirkine, a pyrrolizidine alkaloid known to cause hepatotoxicity, in all parts of the herb. In addition, rats fed a diet containing *T. farfara* had a high risk of developing hemangioendothelial sarcoma of the liver.⁴⁸

A diterpene isolated from *T. farfara*, named tussilagone, is shown to be a potent respiratory and cardiovascular stimulant. Administered intravenously, tussilagone produces a dose-dependent increase in the peripheral vascular resistance of dogs, cats, and rats without much effect on ventricular inotropy and chronotropy. The LD₅₀ in mice with an acute intravenous administration of tussilagone is 28.9 mg/kg.⁵⁶

Ephedra Sinica

Ephedra sinica (joint fir, ma-huang), the natural source of the alkaloid ephedrine, has been used in TCM for over 5000 years as an antiasthmatic and decongestant. *Ephedra* has gained recent notoriety stemming from several fatalities of youths

and professional athletes who took an excess of *Ephedra*, which is promoted by some as a “legal high,” weight-loss aid, energy booster, and aphrodisiac.⁵⁷⁻⁶² In a review of 140 adverse case reports submitted to the FDA between 1997 and 1999, *Ephedra* alkaloids in dietary supplements caused 10 deaths and 13 permanent disabilities. Most of these tragic events were cardiovascular (e.g., cardiac arrest, arrhythmia) or neurologic (e.g., stroke, seizure). Based on this and other experiences, the FDA has banned *ephedra* as of Spring 2004, using their powers from the 1994 Dietary Supplement Health and Education Act. Unlike drugs, which must be proven safe and effective to be marketed, herbal supplements such as *ephedra* must only be proven unsafe to get them off the market.

Ephedrine acts by releasing stored catecholamines from synaptic neurons and nonselectively stimulates alpha- and beta-adrenergic receptors. Ephedrine increases mean, systolic, and diastolic blood pressures by vasoconstriction and cardiac stimulation. Ephedrine’s bronchodilating actions may be helpful for the chronic treatment of asthma. Ephedrine enhances the contractility of skeletal muscle. It penetrates the central nervous system and can produce nervousness, excitability, and insomnia. Patients taking monoamine oxidase inhibitors or guanethidine should not be receiving any product containing ephedrine alkaloids. Patients with preexisting coronary artery disease, hypertension, and severe glaucoma should also avoid ephedrine alkaloids.⁴⁸

Commercially synthesized ephedrine in the United States is identical with the alkaloid derived from *Ephedra*. Oral preparations of ephedrine sulfate are supplied as capsules and syrups. The usual adult dose is 25 to 50 mg every 6 h; for children, the dose is 3 mg/kg every 24 h in four divided doses.

Aconitum

The roots of *Aconitum* species, such as *A. kuznezoffii* (cao-wu) and *A. carmichaeli* (chuan-wa), are sometimes used in TCM to treat rheumatism, arthritis, bruises, and fractures. In Europe, *A. napellus* (monkshood, wolfsbane) grows in the wild and is sometime cultivated as an ornamental.⁶³

Plant parts of *Aconitum* species contain diterpenoid ester alkaloids, including aconitine, which

have been linked to several deaths in Hong Kong and Australia. Death usually results from cardiovascular collapse and ventricular tachyarrhythmias induced by aconite alkaloids. These alkaloids activate sodium channels and cause widespread membrane excitation in cardiac, neural, and muscular tissues. Characteristic manifestations of aconite intoxication include nausea, vomiting, diarrhea, hypersalivation, and generalized paresthesias (especially circumoral numbness). Muscarinic activation may cause hypotension and bradyarrhythmias. Transmembrane enhancement of sodium flux during the plateau phase prolongs repolarization and induces afterdepolarizations and triggered automaticity in cardiac myocytes. Aconite-induced cardiac arrhythmias can also lead to cardiac failure in as little as 5 min to as long as 4 days.

Management of aconite intoxication consists of symptomatic relief, since no specific antidote exists. Amiodarone and flecainide may be used as antiarrhythmic agents. Intra-gastric charcoal can decrease alkaloid absorption. A fatal dose can be as little as 5 mL of aconite tincture, 2 mg of pure aconite, or 1 g of plant. Considering their low therapeutic index and unacceptable toxicity, *Aconitum* and its products are not recommended even in therapeutic doses, since an erroneous dose can be fatal.

Jin-Bu-Huan

Often misidentified as a derivative of *Polygala chinensis*, jin-bu-huan is most likely derived from the *Stephania* genus. This herbal remedy contains an active alkaloid known as levotetrahydropalmatine, which is a potent neuroactive substance that produces sedation, naloxone-resistant analgesia, and dopamine-receptor antagonism in animals. Jin-bu-huan is used as an analgesic, sedative, hypnotic, and antispasmodic agent as well as a dietary supplement. It is associated with significant cardiorespiratory toxicity, including respiratory failure and bradycardia requiring endotracheal intubation. There is no specific antidote for the treatment of acute jin-bu-huan overdose. Several cases of hepatitis have also been associated with long-term ingestion of jin-bu-huan. Although it is now banned in the United States, jin-bu-huan is still being imported illegally as jin bu huan anodyne tablets.⁶⁴

TABLE 3.
Potential and Documented Interactions of Herbs with Warfarin

Potential increase in risk of bleeding
Chamomile
Feverfew
Garlic
Ginger
Ginkgo
Horse chestnut
Licorice root
Documented reports of possible decrease in warfarin's effects
Ginseng
Green tea

DRUG-HERBAL INTERACTIONS

Increases in the use of alternative medicine in the United States have made information about potential drug-herb interactions very important, especially for medications with a narrow therapeutic index, such as warfarin and digoxin.⁶⁵ Suspected drug-herbal interactions should be reported by clinicians to the FDA's Med Watch Program. The FDA has established the Special Nutritionals Adverse Event Monitoring System, a computer database that includes information about suspected adverse effects related to dietary supplements as nutritional products.

Commonly used herbs that can interact with warfarin are listed in Table 3. There is also evidence to suggest that the herb St. John's Wort (*Hypericum perforatum*) acts as an inducer of the cytochrome p450 3A4 enzyme.⁶⁶ Cardiovascular drugs such as amiodarone, amlodipine, diltiazem, felodipine, lidocaine, losartan, lovastatin, nifedipine, propafenone, simvastatin, and verapamil are substrates of the enzyme. Patients receiving any of these medications along with St. John's Wort would be at risk for exacerbation of an arrhythmia, angina pectoris, or hypertension.³⁸ Various preparations of St. John's Wort can also reduce digoxin levels in the blood.⁶⁷

There are herbal remedies (e.g., cola, ginger, licorice) that have pharmacodynamic interactions with antihypertensive drugs that will counteract their hypotensive effects. Ginseng has been shown to increase digoxin levels.

CONCLUSION

Health practitioners, in taking clinical histories, should remember to ask patients about their alternative health practices and stay informed regarding the beneficial or harmful effects of these treatments. Continuing research is elucidating the pharmacologic activities of many alternative medicines, however, such research is lacking in the United States and will require grant support from government agencies.⁶⁸⁻⁷¹ Legal surveillance of alternative medicine practices with low safety margins should be instituted for the sake of public health.⁷² As more information becomes available regarding the safety and efficacy of alternative medicines, research-supported claims may one day appear on the labels of alternative medicinals.

The integration of proven complementary therapies with conventional treatments in heart disease will allow cardiologists to offer many additional options to their patients, possibly improving quality of life and reducing human suffering.⁷³ Choosing from among the best conventional and complementary options is the only logical and ethical thing to do.

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