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STATE-OF-THE-ART PAPER

Use of Herbal Products and Potential Interactions in Patients With Cardiovascular Diseases

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More than 15 million people in the U.S. consume herbal remedies or high-dose vitamins. The number of visits to providers of complementary and alternative medicine exceeds those to primary care physicians, for annual out-of-pocket costs of \$30 billion. Use of herbal products forms the bulk of treatments, particularly by elderly people who also consume multiple prescription medications for comorbid conditions, which increases the risk of adverse herb-drug-disease interactions. Despite the paucity of scientific evidence supporting the safety or efficacy of herbal products, their widespread promotion in the popular media and the unsubstantiated health care claims about their efficacy drive consumer demand. In this review, we highlight commonly used herbs and their interactions with cardiovascular drugs. We also discuss health-related issues of herbal products and suggest ways to improve their safety to better protect the public from untoward effects. (J Am Coll Cardiol 2010;55:515-25)

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Herbal supplements have been used for thousands of years in the East and have had a recent resurgence in popularity among consumers in the West. More than 15 million people in the U.S. consume herbal remedies or high-dose vitamins, and the total number of visits to complementary and alternative medicine (CAM) providers far exceeds those to primary physicians (Fig. 1A), amounting to more than \$34 billion out-of-pocket costs for CAM annually (1) (Fig. 1B). Of the \$37.1 billion spent for weight-loss products in 2001, \$17.7 billion was for dietary and herbal weight-loss supplements, a number projected to increase by 6% to 7% per year (2). Multiple factors contribute to the increased use of CAM, including the obesity epidemic, the prevalence of chronic disorders and pain syndromes, anxiety, depression (Fig. 1C), the general desire for good health and wellness, disease prevention, the increasing cost of conventional medicines, and the traditional belief that CAM is safer and more effective than prescription drugs that commonly have adverse effects.

Herbs, generally defined as any form of plant or plant product, constitute the largest proportion of CAM use in the U.S. (Fig. 2). Because herbs are regarded as food products, they are not subject to the same scrutiny and regulation as traditional medications. As a result, manufac-

turers are exempt from pre-market safety and efficacy testing before the release of an herbal product and from any post-marketing surveillance. Although herbal remedies are perceived as being natural and therefore safe, many have adverse effects that can sometimes produce life-threatening consequences.

Despite the paucity of scientific evidence about the safety or efficacy of herbal products, widespread promotion of CAM products in the popular media and unsubstantiated health care claims seem to be driving their demand and forcing even conventional medical practitioners to incorporate CAM therapies into their practices. In 2 nationwide surveys conducted in 1990 and 1997, Eisenberg et al. (1,3) found an increased number of visits to CAM providers from 427 million to 629 million, whereas the number of visits to primary physicians remained, in essence, unchanged (Fig. 1A). Millions of people are therefore exposed to the risk of these potential adverse interactions, especially with products that contain several herbs.

The use of herbal supplements is prevalent among patients who are taking prescription medications, particularly senior citizens (4). Yet few clinical studies have systematically assessed potential interactions between herbs and medications (5). Most patients do not readily disclose their use of CAM to their health care providers (1), and physicians may not routinely ask about such use. As a result, dangerous herb-drug interactions may be missed. However, potentially serious consequences might be avoided by obtaining a more careful history about CAM use. In this review, we highlight some common herbal remedies used, their adverse cardiovascular effects, and their potential interactions with cardiovascular drugs. We also discuss

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Abbreviations and Acronyms

- BPH** = benign prostatic hypertrophy
- CAM** = complementary and alternative medicine
- CHF** = congestive heart failure
- FDA** = U.S. Food and Drug Administration

issues about the use of herbal products and suggest ways to improve their safety.

Search Strategy and Selection Criteria

A search of the PubMed and Medline databases was performed for the years 1966 to 2008 using the search terms cardiovascular agents, complementary therapies, herb–drug interaction, and cardiovascular disease interactions to identify citations, abstracts, and articles on herbs and cardiovascular disease.

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Cardiovascular Adverse Effects of Herbal Remedies

Patients are increasingly using herbal products for purportedly preventive and therapeutic purposes (6). Some products have direct effects on the cardiovascular or hemostatic system, whereas others have indirect effects through inter-

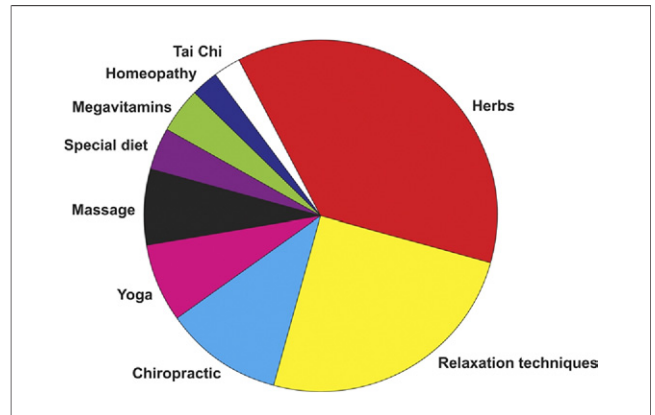


Figure 2 Types of Complementary and Alternative Medicine Used by U.S. Consumers

Data from Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997–2002. *Altern Ther Health Med* 2005;11:42–9.

actions with medications that could lead to serious consequences (4). Common herbal remedies that produce adverse effects on the cardiovascular system include St. John’s wort,

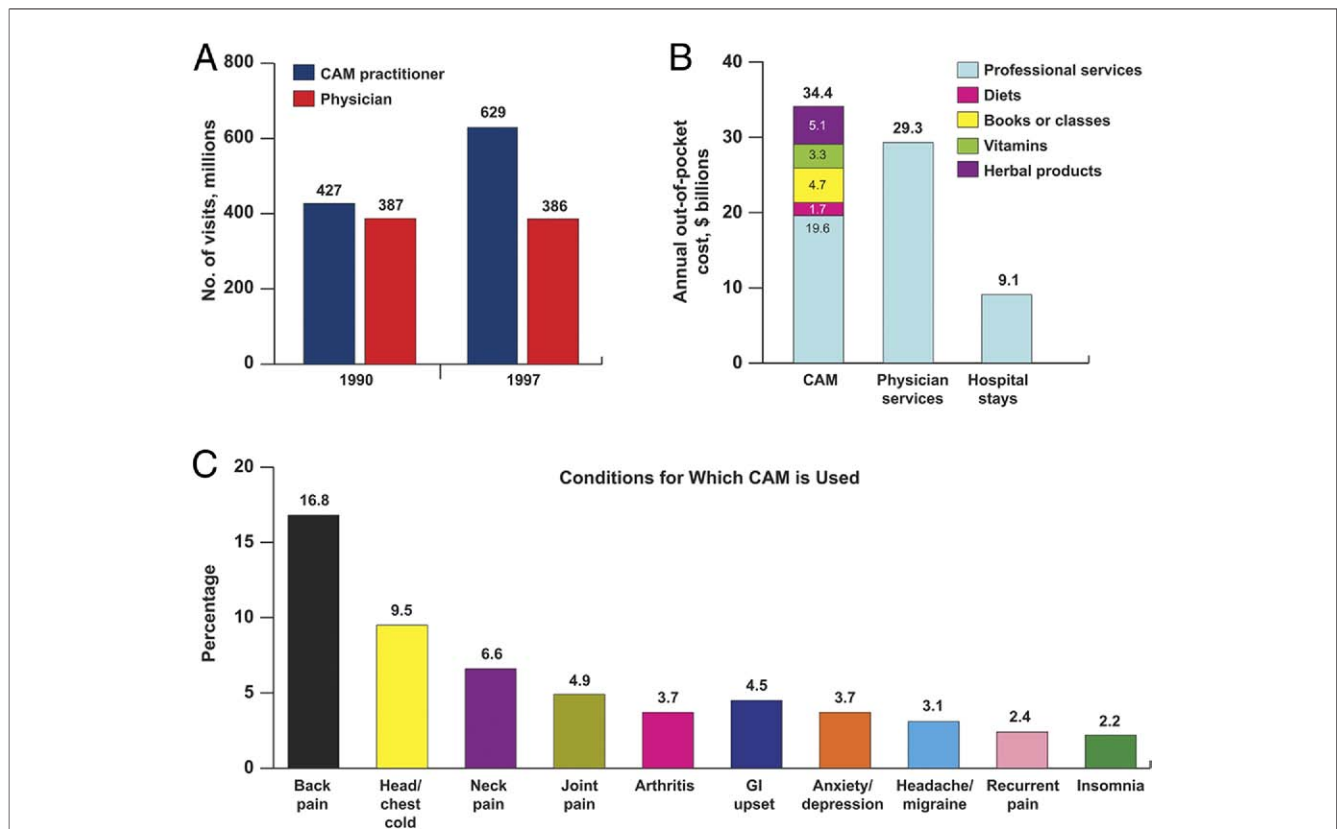


Figure 1 Comparison of Number of Visits, Costs, and Conditions Treated Medically or by CAM

(A) Annual visits to physicians versus those to complementary and alternative medicine (CAM) practitioners. Adapted, with permission, from Eisenberg et al. (1). (B) The costs of CAM services by type compared with the costs of physician services and hospitalizations. Adapted, with permission, from Eisenberg et al. (1). (C) The most common conditions for which CAM therapies are used in the U.S. Data from Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Advance data from vital and health statistics*; no 343. Hyattsville, MD: National Center for Health Statistics, 2004. GI = gastrointestinal.

Table 1 Herbal Products to Avoid in Patients With Cardiovascular Diseases*

Herb	Purported Use	Cardiac Adverse Effect of Interaction
Alfalfa	Arthritis, asthma, dyspepsia, hyperlipidemia, diabetes	Increases bleeding risk with warfarin
Aloe vera	Wounds (topical), diabetes (oral)	Hypokalemia causing digitalis toxicity and arrhythmia
Angelica (dong quai)	Appetite loss, dyspepsia, infection	Increases bleeding risk with warfarin
Bilberry	Circulatory disorders, local inflammation, skin conditions, diarrhea, arthritis	Increases bleeding risk with warfarin
Butcher's broom	Circulatory disorders, inflammation, leg cramps	Decreases effects of alpha-blockers
Capsicum	Shingles, trigeminal and diabetic neuralgia	Increases blood pressure (with MAOI)
Fenugreek	High cholesterol	Increases bleeding risk with warfarin, hypoglycemia
Fumitory	Infection, edema, hypertension, constipation	Increases effects of beta-blockers, calcium-channel blockers, cardiac glycosides
Garlic	High cholesterol, hypertension, heart disease	Increases bleeding risk with warfarin
Ginger	High cholesterol, motion sickness, indigestion, antioxidant	Increases bleeding risk with warfarin
Ginkgo	Poor circulation, cognitive disorder	Increases bleeding risk with warfarin, aspirin, or COX-2 inhibitors Potential risk of seizures
Ginseng	Aging, diminished immunity, improves mental and physical capacity and stress tolerance	Increases blood pressure Decreases effects of warfarin Hypoglycemia
Gossypol	Male contraceptive	Increases effects of diuretics Hypokalemia
Grapefruit juice	Weight loss, to promote cardiovascular health	Increases effects of statins, calcium-channel blockers, or cyclosporines
Green tea	Improve cognitive performance, mental alertness, weight loss, diuretic	Decreases effects of warfarin (contains vitamin K)
Hawthorn	CHF, hypertension	Potentiates action of cardiac glycosides and nitrates
Irish moss	Ulcers, gastritis	Increases effects of antihypertensives
Kelp	Cancer, obesity	Increases effects of antihypertensive and anticoagulant agents
Khella	Muscle spasms	Increases effects of anticoagulant agents and calcium-channel blockers
Licorice	Ulcer, cirrhosis, cough, sore throat, infections	Increases blood pressure Hypokalemia May potentiate digoxin toxicity
Lily of the valley	CHF	Increases effects of beta-blockers, calcium-channel blockers, digitalis, quinidine, steroids
Ma-huang (ephedra)	Obesity, cough	Increases heart rate and blood pressure
Night-blooming cereus	CHF	Increases effects of angiotensin-converting enzyme inhibitors, antiarrhythmics, beta-blockers, calcium-channel blockers, cardiac glycosides
Oleander	Muscle cramps, asthma, cancer, CHF, hepatitis, psoriasis, arthritis	Heart block Hyperkalemia Arrhythmia Death
St. John's wort	Depression	Increases heart rate and blood pressure (with MAOI) Decreases digoxin concentration
Storphanthus	CHF	Increases effects of cardiac glycosides
Yohimbine	Impotence	Increases heart rate Increases or decreases blood pressure

*Only major indications, adverse effects, and interactions are listed; thus, the list is not all inclusive.
CHF = congestive heart failure; COX = cyclooxygenase; MAOI = monoamine oxidase inhibitor.

motherwort, ginseng, ginkgo biloba, garlic, grapefruit juice, hawthorn, saw palmetto, danshen, echinacea, tetrandrine, aconite, yohimbine, gynura, licorice, and black cohosh (Table 1).

St. John's wort. St. John's wort is one of the top 10 best-selling herbs in the U.S. (7). It is typically used to treat depression, anxiety, sleep disorders, the common cold, herpes, and the human immunodeficiency virus. It is used as a topical analgesic, and even as an enema for ulcerative colitis.

Use of St. John's wort could potentially result in serious adverse reactions because of its effect on drug metabolism; it induces the hepatic cytochrome P450 system (8), particularly CYP3A4, an enzyme involved in oxidative metabolism

of more than 50% of all prescription medications (Table 2) (9). Therefore, coadministration of this herb and drugs metabolized by CYP3A4 (Table 2) should be avoided, as it may result in reduced bioavailability and effectiveness with subsequent recurrence of arrhythmia, hypertension, or other undesirable effects (9).

Reduced drug levels of ethinyl estradiol (10), indinavir (11), and cyclosporine (12,13) have been reported in patients using St. John's wort. In 1 study of organ transplant patients, St. John's wort caused a decrease of almost 50% in the concentration of cyclosporine (14). A similar experience was reported in renal and cardiac transplant patients who had a reduction in the efficacy of immunosuppressants taken with St. John's wort, with consequent transplant rejection (9,14).

Table 2 Common Drugs Metabolized by the CYP3A4 System*

Medication Class	Drug Names
Antiarrhythmic	Amiodarone, disopyramide, flecainide†, lidocaine, mexiletine, quinidine‡
Angiotensin receptor antagonist	Irbesartan
Antihistamine	Loratidine, fexofenadine
Antibiotic or antimicrobial	Macrolides (erythromycins), floxacins (ciprofloxacin), azoles (itraconazole, ketoconazole), protease inhibitors (indinavir sulfate, ritonavir, saquinavir, nelfinavir mesylate)
Beta-adrenergic blocker	Metoprolol,† carvedilol
Calcium-channel blocker	Amlodipine besylate, felodipine, nifedipine, diltiazem, verapamil
Chemotherapeutic	Cyclophosphamide, docetaxel, doxorubicin, etoposide, ifosfamide, paclitaxel, tamoxifen citrate, teniposide, vinblastine sulfate, vindesine sulfate, gefitinib
Immunosuppressant	Cyclosporine, tacrolimus, sirolimus
Psychotropic	Benzodiazepines (alprazolam, clonazepam, flunitrazepam, midazolam, triazolam; tricyclic antidepressants (amitriptyline, clomipramine, imipramine); SSRIs (citalopram, fluoxetine, norfluoxetine, sertraline)
HMG-CoA reductase inhibitor (statins)	Atorvastatin, cerivastatin, fluvastatin, lovastatin, simvastatin
Other	Cisapride, cortisol, ethinyl estradiol, progesterone, sildenafil, terazocin, warfarin§

*List is not all inclusive. †Also by CYP2D6. ‡Also by CYP2D1. §Also by CYP2D9.
HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; SSRI = selective serotonin reuptake inhibitor.

Concomitant use of warfarin with St. John’s wort decreases prothrombin time, which may result in subtherapeutic anticoagulation and increased risk of thromboembolism (9,10). People taking warfarin who have a history of stroke, thrombosis, atrial fibrillation, or prosthetic cardiac valves should avoid the use of St. John’s wort (Table 3). Reduced concentrations of statins may increase the risk of cardiovascular events (15). St. John’s wort can induce the multidrug resistance gene product P-glycoprotein, which may reduce the blood levels and efficacy of drugs such as digoxin, which is normally excreted by this glycoprotein (16). Hypoglycemia may occur with concomitant use of antidiabetes agents (17). Serotonin syndrome, a potentially life-threatening adverse drug reaction caused by excess serotonergic activity in the central and peripheral nervous system, has also been reported with concomitant use of antidepressants (18–20). **Motherwort.** Motherwort has a long history of use in both European and Asian traditional medicine because of its purported sedative and antispasmodic properties. Traditionally, it has been used for “cardiac debility,” tachycardia, anxiety, insomnia, and amenorrhea. It is also used as a hypotensive and a diuretic. When administered intravenously, motherwort reduces platelet aggregation and fibrinogen levels (21). It potentiates antithrombotic and antiplatelet effects and increases the risk of bleeding (Table 3).

Taken with benzodiazepines, motherwort can have a synergistic sedative effect and may result in coma.

Ginseng. The origin of the ginseng root and its manner of extraction can produce wide variations in ginseng products. Ginseng is advertised as an immune system stimulant that increases vigor, sexual potency, and longevity, and for use as an antidiabetes agent (9). Ginseng has both hypertensive and hypotensive effects, the latter caused by the enhanced synthesis of nitric oxide (22). In Chinese medicine, ginseng is used for myocardial infarction, congestive heart failure (CHF), and angina pectoris; however, current evidence does not support its use for cardiovascular conditions.

Ginseng abuse syndrome causes hypertension, behavioral changes, and diarrhea (23). A nephrotoxic contaminant, germanium, may damage cells of the thick ascending limb of the loop of Henle, thereby diminishing responsiveness to loop diuretics (24). When administered with warfarin, ginseng resulted in reduced prothrombin time (25). The inconsistency of ginseng in lowering blood glucose may be related to the type of preparation. Ginseng can produce effects similar to those of estrogen because its active components, ginsenosides, have a chemical structure similar to that of testosterone, estrogen, and glucocorticoids (26). Ginseng should not be used by women who are pregnant or receiving hormone replacement therapy. Neonatal death has been related to maternal use (27). Increased levels of digoxin are associated with Siberian ginseng, which interferes with the digoxin assay (Table 4).

Table 3 Commonly Used Herbs That Can Potentiate the Risk of Bleeding or Arrhythmogenesis

Bleeding
Alfalfa
Bilberry
Danshen
Dong quai
Fenugreek
Garlic
Ginkgo biloba
Ginseng
Motherwort
Saw palmetto
Arrhythmogenesis (QT prolongation)
Aloe vera
Bitter orange
Echinacea
Ginkgo biloba
Ginseng
Guarana
Hawthorn
Horny goat weed
Licorice
Lily of the valley
Night-blooming cereus
Oleander
Rhodiola
St. John’s wort

Table 4 Herbal Products That May Interfere With Digoxin Level and Assays

Herb	Extent of Interference	Comments
Chan su	High	Active components (e.g., bufalin) cross-react with digoxin assay Monitoring free digoxin eliminates interference
Danshen	Moderate	Falsely increases (FPIA) or falsely decreases low levels (MEIA) of digoxin Monitoring free digoxin eliminates interference
Asian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin level Monitoring free digoxin does not eliminate interference
Siberian ginseng	Moderate	Falsely increases elevated (FPIA) or falsely decreases low (MEIA) digoxin Monitoring free digoxin does not eliminate interference
Uzara root (diuretic)	NA	Increases effect with digoxin Interferes with digoxin assay

Adapted and reprinted, with permission, from Dasgupta A. Review of abnormal laboratory test results and toxic effects due to use of herbal medicines. *Am J Clin Pathol* 2003;120:127-37.

FPIA = fluorescence polarization immunoassay; MEIA = microparticle enzyme immunoassay; NA = not available.

Ginkgo. Ginkgo biloba is one of the world's oldest living tree species, dating back to the Permian period. Purported indications include conditions such as cardiovascular disease, cerebrovascular or peripheral vascular insufficiency, impotence, inner ear dysfunction, retinopathy, pre-menstrual syndrome, stress, depression, and dementia. Ginkgo is one of the best-selling herbal remedies in the U.S. for cognitive impairment (7). However, early trials that suggested it had beneficial effects on cognition were limited by inadequate methods, low numbers of patients, absence of hard end points, and publication bias (28). Recent randomized trials showed no difference between ginkgo and placebo (28,29). A large clinical trial of ginkgo for prevention of dementia, supported by the National Center for Complementary and Alternative Medicine, is underway.

The concurrent use of ginkgo with antiplatelet, anticoagulant, or antithrombotic agents increases the risk of bleeding. Hyphema, subphrenic hematoma, and intracranial hemorrhage have been reported (9). In clinical trials, ginkgo has also been shown to reduce the effectiveness of nicardipine by interacting with the cytochrome P450 system (9).

Garlic. Garlic has been mentioned in medicinal texts since the Ebers papyrus (circa 1550 BC). It has been used for treatment of infectious conditions because of its presumed antimicrobial and immune-enhancing properties. Garlic is thought to have cholesterol-lowering and other antiatherosclerotic and antihypertensive effects and is used for prevention of cardiovascular disease (30). Despite such claims, a recent study concluded that raw, powdered, or aged garlic extract versus placebo for 6 months had no significant effect on low-density lipoprotein cholesterol or other plasma lipids in adults with moderate hypercholesterolemia (31). The active component ajoene in garlic inhibits collagen-induced

platelet aggregation (32), and garlic is used for its antiplatelet and fibrinolytic effects in patients with cardiovascular disease. However, the risk of bleeding in people using anticoagulant or antiplatelet agents increases, so its concomitant use should be avoided (33,34). Garlic supplements should be discontinued about 10 days before elective surgical procedures, especially by patients taking aspirin or warfarin (33).

Grapefruit juice. Grapefruit is used as a dietary intervention to lose weight and improve cardiovascular health. Its constituents of naringenin and bergamottin inhibit the CYP3A4 enzyme in small-intestine enterocytes, which increases blood levels of CYP3A4 substrate drugs, including calcium-channel blockers, cyclosporine, statins, midazolam, estrogen, and terazosin (Table 2). The action of these medications is potentiated by their increased bioavailability (35-38), which potentially can result in dangerous hypotension, myopathy, or liver toxicity. In post-menopausal women taking estrogen, grapefruit juice may increase the risk of breast cancer by inhibiting estrogen metabolism by CYP3A4 (39). These potential interactions should be discussed with patients taking medications metabolized by the CYP3A4 system, and they should be advised to avoid grapefruit consumption.

Hawthorn. Hawthorn extract is commonly used by herbalists for treatment of angina, CHF, bradyarrhythmia, and cerebral insufficiency. Hawthorn has positive inotropic and vasodilatory effects and is thought to increase myocardial perfusion and reduce afterload. As an adjunct treatment for CHF, hawthorn has been reported to have beneficial effects on symptom control and physiologic outcomes (40,41), but the efficacy and safety of its supposed inotropic activity and effect on morbidity and mortality have not been systematically assessed (40). Hawthorn enhances the activity of digitalis (42), and its concomitant use should be monitored carefully for potential toxic effects. Hawthorn also inhibits the biosynthesis of thromboxane A₂, and it could potentially increase the risk of bleeding in patients taking antiplatelet or anticoagulant agents (9,43). Without additional data on safety and efficacy, clinicians should discourage unsupervised use of hawthorn in patients with CHF who are taking heart failure medications.

Saw palmetto. Saw palmetto is used by more than 2 million men for treatment of benign prostatic hypertrophy (BPH) (7). It is also used as a diuretic and a urinary antiseptic. The exact biologic mechanism of action of saw palmetto is not clear. In vitro, it potently inhibits alpha₁-adrenergic receptors (44). Despite claims that saw palmetto helps relieve BPH symptoms, recent clinical trials did not demonstrate any beneficial effects on BPH symptoms or post-void residual bladder volume (45). Additional prospective studies are needed to establish the role of herbal extracts in alleviating BPH symptoms.

Saw palmetto inhibits cyclooxygenase and increases bleeding with warfarin (46). In addition, its unsupervised use can result in cholestatic hepatitis, acute pancreatitis (47), and intraoper-

Table 5 Common Herb–Drug Interactions

Herb	Drug or Drug Class	Interaction or Other Comments	
Comfrey	Phenobarbital	Increases metabolism of comfrey, producing a lethal metabolite from pyrrolizidine that results in severe hepatotoxicity	
Danshen	Anticoagulant or antiplatelet agents	Increases bleeding due to additive effects	
	Digoxin	Increases side effects of digoxin	
Echinacea	Amiodarone or ibutilide	Increases QT interval	
	Statins, fibrates, niacin	Increases risk of hepatotoxic effects	
Ephedra	Antidiabetes drugs	Increases blood glucose Decreases effectiveness of oral hypoglycemic agents	
	Class IA and class III antiarrhythmics	Increases QT interval	
	Beta-blockers	Decreases effects of beta-blockers, leading to hypertension and tachycardia	
	Monoamine oxidase inhibitors	Hypertension	
Evening primrose oil	Phenobarbital	Decreases seizure threshold	
Garlic	Aspirin, clopidogrel, warfarin, or heparinoid drugs	Increases bleeding risk	
Ginkgo biloba	Antidiabetes drugs	Increases hypoglycemia	
	Aspirin	Increases bleeding	
	Warfarin	Inhibits PAF hemorrhage	
Ginseng	Antidiabetes drugs	Increases hypoglycemia	
	Digoxin	Interferes with digoxin assay, leading to falsely increased levels	
	Warfarin	Decreases effectiveness of warfarin	
	Phenelzine sulfate	Headache Irritability Insomnia	
Hawthorn	Digoxin	Increases effects of digoxin	
	Calcium-channel blockers or nitrates	Increases vasodilatory effects	
Kava	Alprazolam	Increases CNS depression Increases effects of alcohol	
Licorice	Spiroonolactone	Increases effects of spiroonolactone	
Saw palmetto	Anticoagulant or antiplatelet agents	Increases bleeding	
Soy milk	Warfarin	Decreases effectiveness of warfarin	
St. John's wort	Digoxin	Decreases serum digoxin concentration	
	Clopidogrel	Increases activity of clopidogrel Increases bleeding	
	Warfarin	Decreases warfarin bioavailability and effectiveness	
	Simvastatin	Decreases effectiveness of simvastatin	
	Paroxetine	Nausea Lethargy Incoherence	
		Class IA and III antiarrhythmic agents	Decreases effectiveness (precipitating arrhythmias)
		Cyclosporine	Decreases cyclosporine concentration due to increased clearance (transplant rejection)
	Theophylline	Decreases serum concentration	
	Indinavir	Decreases serum concentration (treatment failure in HIV patients)	
Yohimbine	Clonidine, Guanabenz	Decreases blood pressure reduction effect of centrally active agents	
	CNS stimulants (e.g., amphetamines)	Risk of hypertensive crisis due to its monoamine oxidase inhibitor activity	
	ACE inhibitors	Decreases effectiveness of ACE inhibitors Hypertension	
	Beta-blockers	Decreases effectiveness of beta-blockers Hypertension Increases heart rate	

ACE = angiotensin-converting enzyme; CNS = central nervous system; HIV = human immunodeficiency virus; PAF = platelet-activating factor.

ative floppy iris syndrome during cataract removal because of loss of iris tone (48). Ophthalmologists should be aware of this important association so that they can take the necessary steps to prevent surgical complications.

Danshen. Danshen is used in traditional Chinese medicine for treatment of coronary artery disease and menstrual abnormalities. Danshen reduces elimination of warfarin and inhibits cyclic adenosine monophosphate phosphodiesterase, which results in

additive antiplatelet effects and risk of bleeding (Table 5). Concomitant use with warfarin increases prothrombin time (49). Danshen may also interfere with digoxin assay (Table 4); in the absence of signs or symptoms of digoxin toxicity, the possibility of a false elevation of digoxin concentration should be explored.

Echinacea. Echinacea is popularly believed to stimulate the immune system and prevent infections. The evidence is still

insufficient to support clear therapeutic recommendations. The results of a controlled double-blind study indicated that echinacea had no clinically significant effects on rhinovirus infection (50). Persistent use may result in or potentiate the hepatotoxic effects of other medications (e.g., statins, fibrates, niacins, or amiodarone). Side effects include nausea, dizziness, dyspnea, rash, and dermatitis. Flavonoids from echinacea may inhibit or induce cytochrome P450 enzymes, depending on their structure and assay conditions (9).

Tetrandrine. Tetrandrine is a vasoactive alkaloid used in Chinese medicine to treat hypertension and angina. Its vasodilative effect is due to inhibition of the L-type calcium channels (51) and possible competition with other calcium-channel blockers (52). Tetrandrine lowers plasma glucose and causes hepatotoxicity and renal toxicity (53).

Aconite. Traditional Chinese practitioners use aconite for pain relief caused by trigeminal and intercostal neuralgia, rheumatism, migraine, and general debilitation. Aconite initially stimulates and then paralyzes nerves that communicate pain, touch, and temperature, producing anesthesia mediated by numerous different alkaloids blocking sodium current (54). It is also used as a mild diaphoretic and to slow pulse rate by its effect on brainstem centers. Atrial or ventricular fibrillation, however, may result from the direct effect of aconite on the myocardium. Side effects occur even after contact with leaves or sap from *Aconitum* plants (or monkshood), and can range from bradycardia and hypotension to fatal ventricular arrhythmia induced by triggered activity (55,56).

Yohimbine. Yohimbine is marketed for treatment of sexual disorders and exhaustion. Many of its effects are attributed to its α_2 -adrenergic receptor antagonist activity. Yohimbine increases the release of norepinephrine, resulting in inadequate blood pressure control in people also using antihypertensive and diuretic agents (57) (Table 5). Use of yohimbine is contraindicated in patients with hypertension, angina, and renal impairment.

Gynura. Widely used in Chinese folk medicine, gynura purportedly improves microcirculation and relieves pain; however, it has been associated with hepatic toxicity (58–61). Resultant conditions include hepatic veno-occlusive disease, which is characterized by painful hepatomegaly, fluid avidity, weight gain, and jaundice (58–60). In animals, gynura has been shown to inhibit angiotensin-converting enzyme activity, resulting in hypotension (62).

Licorice. Licorice is used as an expectorant. Modern cough syrups often include licorice extract. It can result in pseudoaldosteronism with concomitant hypokalemia, hypertension, and edema that may reduce the effectiveness of antihypertensive drugs (63). Licorice-induced hypokalemia can lead to increased risk for ventricular arrhythmia, particularly torsades de pointes (64,65) (Table 3). It can also potentiate the effects of spironolactone and digoxin (Tables 1 and 5), and can cause hyperglycemia, rendering antidiabetes agents less effective. Its ability to inhibit thrombin and platelet aggregation

enhances the risk of bleeding with antiplatelet and anticoagulant agents.

Black cohosh. Black cohosh contains triterpene glycosides and has been used in remedies for relief of symptoms of menopause, pre-menstrual tension, and other gynecologic problems. The mechanism of action is unclear. It may bind to estrogen and serotonin receptors (66). After estrogen replacement therapy was shown to increase the risk of thromboembolic and cardiovascular events and breast cancer, sales of black cohosh supplements soared (\$79 million in 2003) (67,68). In 2006, a clinical trial supported by the National Center for Complementary and Alternative Medicine failed to show that treatments containing black cohosh relieved menopause-associated symptoms (67). Commercially available dietary supplements made from black cohosh inhibit CYP3A4 and potentially increase the risk of adverse effects from some drugs (Table 2). Hepatotoxicity has been reported (66,69), and black cohosh should not be used during pregnancy or lactation (9).

Problems Related to the Use of Herbal Products

The use of herbal products is complicated by numerous problems, as summarized below.

Lack of scientific evidence of safety and efficacy. Most herbal products have not been scientifically evaluated; thus, information is limited about their pharmacokinetics, pharmacodynamics, efficacy, and safety. Randomized controlled trials are the best way to determine efficacy and safety; however, controlled trials for most herbal products are not available, not demanded by consumers or health care practitioners, and not required by regulatory agencies. Belief in the safety of CAM products remains unsubstantiated, and even when data are available, findings are often questionable because of a lack of consistency in research methods, small number of subjects, absence of placebo groups, inclusion of healthy volunteers or low-risk populations without comorbid conditions, lack of standardization of supplements being investigated, and absence of data about drug-herb interactions. Thus, findings for specific herbal products are often of limited usefulness for making decisions about efficacy or safety.

Lack of regulatory oversight. Despite the lack of scientific evidence about the efficacy and safety of herbal products, more than 30,000 dietary supplements are sold in the U.S., with an additional 1,000 new supplements introduced annually. Most patients believe that the government oversees the safety of CAM; but the fact is that the only requirement is for the manufacturer to send a copy of the product label to the U.S. Food and Drug Administration (FDA). A new dietary supplement or new formulation can be introduced and marketed overnight, without significant restriction, despite containing new, experimental, and unregulated herbal ingredients. The Dietary Supplement Health and Education Act of 1994 provides some oversight but nonetheless allows untested herbal products on the

market without safety testing (70). Unfortunately, many supplements contain ingredients or contaminants with adverse effects or interactions. If these supplements were subject to pre-market safety testing, many would no doubt be banned.

The FDA has identified several supplements, including ephedra, chaparral, comfrey, lobelia, and yohimbe, that have caused serious harm, yet it took 9 years to get ephedra alone removed from the market (71). The other products are still available for sale in stores and over the Internet. Restricting a specific substance or group of substances is not particularly helpful because manufacturers can simply introduce new formulations. From 1995 to 1997, hundreds of cases of ephedra toxicity were reported to the FDA as causing stroke, myocardial infarction, seizure, and death from cardiac arrhythmia (72). Side effects occurred in otherwise healthy young adults who used ephedra for energy boost and weight loss (72). As a result, ephedra was eventually banned by the FDA, but other structurally related sympathomimetic amines emerged to take its place in weight-loss and energy-enhancement products, such as synephrine, which is now the most popular ephedra replacement. It has a similar pharmacology and structure. Internet resources describe synephrine as an herbal supplement that stimulates fat metabolism, suppresses appetite, and boosts caloric expenditure without side effects. Synephrine inhibits intestinal cytochrome P450 and increases blood levels of many drugs (Table 2). Like ephedra and caffeine, the combination of synephrine and caffeine produces arrhythmogenesis, stroke, CHF, and seizures (73).

The general public regards herbal products as natural. Thus, there is a widespread yet false perception that herbal products are safe. According to a 2002 nationwide Harris interactive poll of more than 1,000 adults, 60% of respondents believed that supplements were approved by a governmental agency before they could be sold, that warning labels were required to list potential side effects, and that supplement manufacturers could not make safety claims without solid scientific evidence (74).

Lack of quality control. The wide variations in herbal supplement manufacturing techniques, storage methods, and lot-to-lot variability require urgent attention from the FDA and other regulatory agencies. The U.S. Pharmacopeia has been developing quality control standards, but supplement manufacturers are not required to follow these guidelines. Such latitude allows cheaply manufactured and even expired herbal products to be sold without restriction. The variation in herbal sources and the inconsistent labeling of ingredients continue to be of major concern. More than 40% of all herbal products fail to contain as much of their active ingredients as claimed on their labels (75) or substitute cheaper ingredients for more expensive ones (23).

Contamination with heavy metals, adulteration with pharmaceuticals, and prohibited animal and plant ingredients are repeatedly found in herbal products (76,77). Intentional and unintentional adulteration with antibiotics, non-

steroidal anti-inflammatory drugs, hormones, and heavy metals is common. Untested and unregulated steroids are sold to the public, including minors (78). In 2007, the FDA issued 9 safety alerts warning consumers to stop using 13 brands marketed as dietary supplements because testing identified undocumented prescription medications in them (78). Nine contained erectile dysfunction drugs such as sildenafil or tadalafil, 3 contained lovastatin, and 1 contained the weight-loss drug sibutramine.

The ramifications of using herbal supplements are sometimes discerned through subsequent medical tests or treatment. For example, colchicine has been found in the placenta of women taking ginkgo (79). Aristolochic acid nephropathy has been reported in patients who took herbal supplements without knowing that the manufacturer had substituted *Aristolochia* for another herb (80,81). In addition to being a renal toxin, aristolochic acid is on the World Health Organization's list of human carcinogens. It is banned from use in several European countries, but is still readily available in the U.S. (78,81).

The FDA guidelines for manufacturers mandate that they avoid contaminating products with other herbs, pesticides, heavy metals, or prescription drugs (82). Nonetheless, products have been repeatedly reported to contain adulterant compounds and to put unknowing consumers at risk of adverse side effects and drug interactions.

Public misinformation. Unethical marketing techniques have led to false advertisements about the safety and efficacy of the herbs reaching the public today, more so than at any other time. Herbal products are promoted in magazines, newspapers, and books, on radio and television, and through the Internet. Herbs are advocated for treatment on the basis of unproven, word-of-mouth traditions and beliefs. Some promotional materials even claim that the featured product is doctor recommended, the world's most powerful, patented, or now presented without a prescription (even if it had never been prescribed). In a study of Internet marketing of herbal products, Morris and Avorn (30) found that at least 81% of Internet sites made 1 or more health claims; with more than 50% claiming to treat, prevent, diagnose, or cure specific diseases despite regulations barring such statements (30). The sale of herbal supplements can be halted only if the product has been proven dangerous and documentary proof has been submitted to the Secretary of the Department of Health and Human Services. However, the FDA does not routinely test food supplements, and has to demonstrate that a dietary supplement is "unsafe," before it can take action to restrict the product's use or removal from the marketplace (83). The burden of proof for demonstrating that a supplement is safe must be placed on manufacturers rather than the government or consumers, and consumer protection laws must be instituted.

Lack of knowledge about herb-drug interactions by patients and health care providers. Devastating effects due to a lack of understanding about adverse herb-drug interactions can occur in vulnerable populations, including

elderly persons, children, pregnant women, immunocompromised people (e.g., those with human immunodeficiency virus or transplant recipients), and those with hepatic or renal dysfunction. Most (64%) of the patients with a diagnosis of atrial fibrillation, CHF, or ischemic heart disease who were attending a cardiovascular clinic reported concomitant use of alternative therapies and prescription drugs (84). More than one-half (58%) took supplements that had potential interactions with warfarin, amiodarone, sotalol, or digoxin. In a geriatric clinic, 46% of the patients were taking supplements with anticoagulation properties. Most (73%) were also taking a prescription anticoagulant and were unaware of potential interactions. Findings from another study indicated that 1 in 6 adults taking conventional prescription medications reported concomitant use of at least 1 CAM product during the preceding week (37). More than 40% of the respondents said that taking herbal medicine along with prescription medication was more useful than taking either alone (85).

Under-reporting of adverse drug reactions. Most consumers are unlikely to attribute health problems to a supplement that they assume is safe and natural, and are reluctant to report an adverse effect from a self-medicated substance. Supplement manufacturers also rarely report serious adverse effects to the FDA despite federal requirements. Between 1990 and 1994, fewer than 10 of more than 2,500 reports of adverse effects made to the FDA came from an herbal product manufacturer. A report from the inspector general of the Department of Health and Human Services revealed that <1% of adverse reactions caused by dietary supplements are reported to the FDA (86) (Fig. 3). Recent FDA post-marketing guidance for the supplement industry mandates the reporting of all serious adverse events to the FDA within 15 days (87).

Conclusions

The use of herbal remedies in the U.S. is widespread and increasing dramatically, yet current laws allow these herbal remedies to be marketed as dietary supplements not subject to the same regulations required for prescription drugs. Thus the purity, efficacy, and safety of herbal products are often unknown, and individual products may not even contain the amount of active ingredients listed on the label. In addition, manufacturers seldom report adverse events to the FDA. Manufacturers should be required to register with the FDA and to provide evidence of good manufacturing practices (i.e., standardization, storage, preparation techniques, and manufacturing sites). Evidence of the safety and efficacy of the herbal product should be obtained by well-designed clinical trials, pre-marketing approval regarding safety, and strict post-marketing surveillance.

Herb-drug interactions are especially relevant when cardiovascular medications with a narrow therapeutic index, such as digoxin and warfarin, are coadministered with herbs that can potentiate or reduce pharmacologic effects (4,6). Thus, health care professionals should carefully question patients about their use of herbal products. Treating physicians are often unaware of patients' use of such products because patients are not routinely asked about it. Collecting such information is important, particularly in elderly patients at higher risk of adverse interactions. Physicians should therefore have a good knowledge base about herbal remedies and should inquire about their use, discuss adverse effects, and monitor and identify possible herb-drug interactions. In addition, properly designed clinical trials are needed to assess the safety and efficacy of herbal remedies, including potential interactions with concurrently used medications.

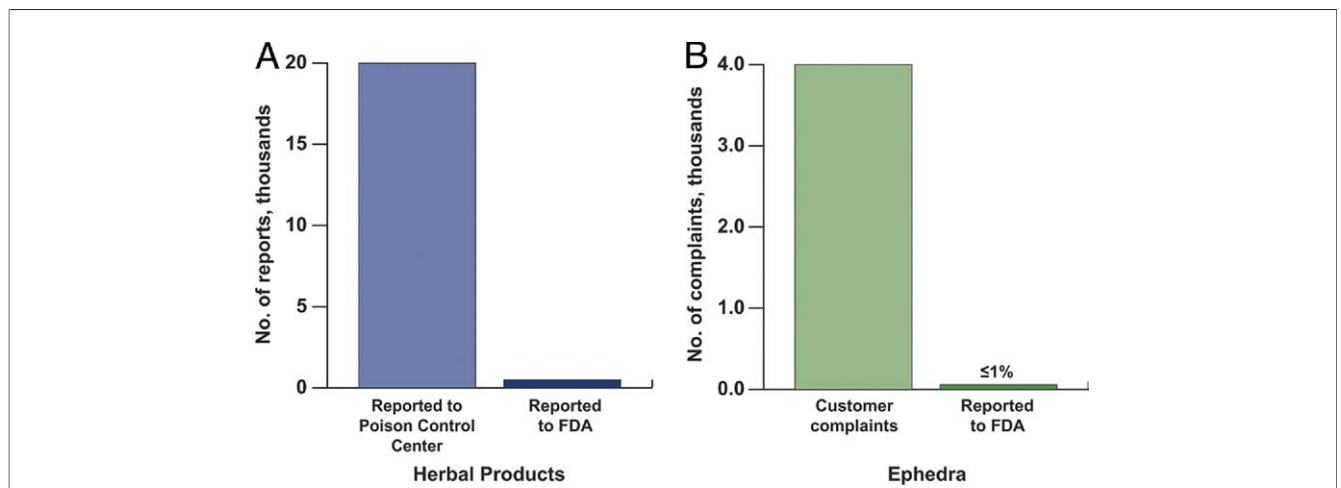


Figure 3 Adverse Effects of Herbal Products

Adverse effects of (A) herbal products and (B) ephedra are underreported to the U.S. Food and Drug Administration. Data from Litovitz TL, Klein-Schwartz W, Rodgers GC Jr., et al. 2001 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002;20:391-452.

There is a clear need for better public and physician understanding of herbal products through health education, early detection and management of herbal toxicities, scientific scrutiny of their use, and research on their safety and effectiveness. Regulatory policies are also needed to protect people from untoward effects on their health and finances. The principles and standards of evidence for safety and efficacy of drugs used in conventional medicine should also apply to herbal and other CAM products, with decisions about their use based on the results of scientific inquiry rather than on long-held but untested belief systems or traditions (88).

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Key Words: cardiovascular agents ■ complementary therapies ■ drug approval ■ herbal medicine ■ herb-drug interaction.

**Use of Herbal Products and Potential Interactions in Patients With
Cardiovascular Diseases**

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