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REVIEW

Adverse Cardiovascular Effects and Drug Interactions with Herbs

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ABSTRACT

Herbs are plants or products of plants used since antiquity and despite their widespread promotion, their purity, efficacy and safety are often unknown. The healthcare professionals may be asked to give advice on the use of these products, in conjunction with other medications. Thus, they can potentially interact with the cardiovascular drugs with subsequent dramatic effects on the coagulation pathways and the platelets adhesion. The administration of herbs in patients suffering from cardiovascular diseases should be done sparingly, with caution, and with thorough knowledge of their possible interactions with the already prescribed drugs.

KEY WORDS: *herbs; herbal products; vitamins; potential interactions; cardiovascular diseases; adverse effects*

INTRODUCTION

Herbal supplements have been used since ancient times, especially in the East. The ancient Greeks used herbs as a key tool in their therapeutic armamentarium. A recent resurgence in their popularity has been noted in the West. Multiple factors contribute to this growing use of complementary and alternative medicine (CAM), including the general desire of good health and wellness and the traditional belief that CAM is safer and more effective than the commonly used prescribed drugs which usually have side effects.

Herbs are plants or products of plants with widespread use. Because herbs, which constitute the largest proportion of CAM use in the United States, are regarded as food products, they are not subjected to the same scrutiny and regulations as traditional medications.

The use of herbal products is prevalent particularly among senior citizens, who are taking prescription medications and usually do not really disclose the use of CAM to their health care providers. Many of these products may have potentially harmful effects on the cardiovascular system, interacting with the commonly used well-established conventional medical therapy at a clinically significant degree. A few clinical studies have systematically assessed potential interactions between herbs and medications. However, potentially serious consequences might be avoided by obtaining a more careful history about CAM use.

In the present review, we will briefly summarize the basis of the pathogenetic mechanisms of adverse reactions on the cardiovascular system with the herbs. Also, we provide a report of their interactions with the commonly used drugs,

Abbreviations
CAM = complementary and alternative medicine
CHF = congestive heart failure
FDA = (U.S.) Food and Drug Administration
HIV = human immunodeficiency
NOACs = non-vitamin K oral anticoagulants
PAF = platelet-activating factor

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in patients with heart diseases. Finally, we suggest ways to improve their safety, so as to achieve better protection of the public from untoward effects.

HERBS AND VITAMINS

Herbal remedies and high doses of vitamins are used by over 15 million U.S. citizens.[1] The majority of the consumers are elderly, in whom the incidence of cardiovascular disease and thus the use of cardiac medications, is high. This widespread use is increasing dramatically and yet current laws allow these herbal remedies to be marketed as dietary supplements, and thus they are not subjected to the same regulations which are required for drug prescriptions.[2] The most commonly used herbs and their interactions with the cardiovascular drugs are enlisted in Table 1.[3] These interactions are especially relevant, when cardiovascular medications with a narrow therapeutic index, such as digoxin and warfarin, are co-administrated with some of the herbs.[4] These seemingly innocent formulations, cost Americans 34 billion $/year and there is an increase in their out-of-pocket money cost of 6-7% per year, mostly on weight loss formulations.[7] Herbs are plants or plant products, and they are not subject to thorough checks on safety and efficacy.[8] Some of them have a direct effect on the cardiovascular or the coagulation system, while others have indirect effects due to interactions (Table 2).[5,6] Below we discuss the most frequently used herbs which could be taken either alone or in combination, as nutritional supplements.

Balsam or sedge (St. John's wort) is one of the 10 most popular herbs. St. John's wort is the common name for *Hypericum perforatum*, a yellow flower with a long and rich history. It contains a vast array of chemical compounds. The major chemical components are naphthodianthrones, of which hypericin, pseudohypericin, and hyperforin are the most revelant biologically active compounds. St John's wort also contains quercetin, flavones and xanthoids. It is used against depression, mania, sleep disorders, common cold, herpes, human immunodeficiency virus (HIV), as local anesthetic, or as an enema for ulcerative colitis.[10] It induces the hepatic cytochrome P450, particularly the CYP3A4 enzyme [17] which is involved in the oxidative metabolism of more than half of prescribed medications (Table 3).[9,10] This combination reduces the bioavailability and the efficacy of antihypertensive and antiarrhythmic drugs. Balsam halves the concentration of cyclosporine,[14] ethinyl oestradiol and indinavir[11] and is a particular problem in heart-transplanted patients.[13] It reduces the effect of warfarin, decreases the prothrombin time and the concomitant subtherapeutic anticoagulant effect increases the risk of thromboembolism.[19] It also reduces the levels of statins,[15] induces gene product P-glycoprotein, reduces the active levels of digoxin,[16] enhances the hypoglycemic effect of antidiabetic agents and the adrenergic activity of serotonin.[20]

Hawthorn (Motherwort) is the common name for *Crataegus Oxyacantha* and is often known as May bush or Thorn apple tree. The major chemical components are proanthocyanidins, flavonoids and catechins (epicatechin). It is a herb with narcotic and spasmolytic properties. It is used for the treatment of tachycardia, arrhythmia, anxiety, insomnia and amenorrhea and it is also a diuretic drug. If administrated intravenously it has antihypertensive effect and reduces platelet aggregation and fibrinogen levels, thereby it increases the risk of bleeding.[21]

Ginseng is used in a wide variety of products, especially in multivitamin preparations.[23] It is advertised as immune adjuvant, antidiabetic and stimulant of libido. It may have hypertensive, but also hypotensive effect, due to increased synthesis of nitric oxide (NO).[22] It is reported to have a wide range of pharmacological activities, because of a diversified group of steroidal saponins called ginsenosides. The bioavailability after taking ginseng orally is low, and the metabolites of ginsenosides produced by gut microbiota may be biologically active.

In Chinese medicine it is used for myocardial infarction, congestive heart failure (CHF) and unstable angina, but recent data contradict this issue. Ginseng's overuse causes hypertension, abnormal behavior and diarrhea. It contains the nephrotoxic component of germanium that can destroy cells in the ascending limb of the loop of Henle with consequent diuretic resistance.[24] Finally, it reduces the effect of warfarin and increases the levels of digitalis.[25]

Ginkgo Bilova is one of the longest living tree species in the world, and is used for cardiovascular, cerebrovascular and peripheral vascular disease, impotence, disorders of the inner ear, retinopathy, stress, depression and dementia.[26] It increases the risk of bleeding and the anticoagulant activity after interacting with cytochrome P450.[27] Finally, it decreases the activity of nicardipine.

Garlic, since the papyrus of Ebers (1550 B.C), is used as antimicrobial, anti-inflammatory, antihypertensive and antiatherosclerotic agent.[28] A recent study showed no significant statistical difference of garlic in lowering low-density lipoprotein (LDL) and other plasma lipids, over a period of 6 months, compared with placebo.[29] In experiments in rats, dietary garlic inhibited the synthesis of lipids in the liver and increased the level of serum insulin. Also, it can increase the risk of bleeding in patients receiving anticoagulants because of the active ingredient "ajoene" that inhibits the collagen-induced platelet aggregation. Garlic preparations should be discontinued 10 days prior to selective surgery especially in patients receiving aspirin or warfarin.[30,31]

Grapefruit's juice is used as a diet formula and for the "improvement of the cardiovascular system". It is a source of vitamin C, fiber, potassium, pectin and other nutrients. The components of "naringenin" and "bergamottin" inhibit the enzyme CYP3A4 which is located in the cells of the small intestine, leading to rising levels of medications, such as calcium

TABLE 1. Common Herb–Drug Interactions

Herb	Drug or Drug Class	Interaction / Comments
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
Garlic	Aspirin, clopidogrel, warfarin, or heparinoid drugs	Increases bleeding risk
Biloba	Antidiabetes drugs	Increases hypoglycemia
	Aspirin	Increases bleeding
Ginseng	Warfarin	Inhibits PAF hemorrhage
	Antidiabetes drugs	Increases hypoglycemia
	Digoxin	Interferes with digoxin assay, leading to falsely increased levels
	Warfarin	Decreases effectiveness of warfarin
Hawthorn	Phenelzine sulfate	Headache / Irritability / Insomnia
	Digoxin	Increases effects of digoxin
Licorice	Calcium-channel blockers or nitrates	Increases vasodilatory effects
Saw palmetto	Spironolactone	Increases effects of spironolactone
Soy milk	Anticoagulant or antiplatelet agents	Increases bleeding
St. John's wort	Warfarin	Decreases effectiveness of warfarin
	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)

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

channel blockers,[32] cyclosporine, statins, midazolam, estrogen, terazosin, and thus it can result in hypotension, myopathy and hepatotoxicity respectively.[33]

Hawthorn (buckthorn) is used for angina, bradyarrhythmia and brain impairment. It has positive inotropic and vasodilatory properties and it is thought to increase myocardial

TABLE 2. Commonly Used Herbs that can Potentiate the Risk of Bleeding and Arrhythmogenesis

Bleeding	Arrhythmogenesis
Bilberry	Aloe vera
Danshen	Bitter orange
Garlic	Echinaceae
Ginko bilova	Ginko bilova
Gingeng	Gingeng
Motherwort	Hawthorn
Sawpalmetto	Licorice
Alfalfa	St John's wort
Dong qual	Guarana

TABLE 3. Common Cardiovascular Drugs Metabolized by the CYPEA4 System

Medication category	Drug name
Antiarrhythmic agents	Amiodarone, disopyramide, flecainide,* lidocaine, mexiletine, quinidine**
Angiotensin receptor antagonist	Irbesartan
b-blockers	Metoprolol,* carvedilol
Calcium-channel blocker	Amlodipine besylate, felodipine, nifedipine, diltiazem, verapamil
HMG-CoA reductase inhibitor (statins)	Atorvastatin, cerivastatin, fluvastatin, lovastatin,

*also by CYP2D6, **also by CYP2D1
HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A

perfusion and to decrease the left ventricular afterload.[34,35] Actually, it improves symptoms but does not reduce morbidity and mortality. It increases the levels of digitalis and the biosynthesis of thromboxane A2 and it may increase the risk of bleeding in patients receiving anticoagulants.

Saw palmetto (berry) is used by more than 2 million men in U.S.A for the treatment of benign prostatic hypertrophy,[37] as a diuretic, and as a urinary tract antiseptic. In vitro it inhibits the alpha1-adrenergic receptors[38] and cyclooxygenase activity, and increases the associated with warfarin bleeding.[39]

Tetrandrine is a vasoactive alkaloid which is used in Chinese medicine to treat angina and hypertension. The inhibition of the L-type calcium channels causes vasodilation and may interact with other calcium antagonists.[41] It has anti-inflammatory, immunologic and antiallergic effects. It inhibits the degranulation of mast cells. It has "quinidine-like" antiarrhythmic effect.

Aconite (wolf's bane) is a strong analgesic,[42] which has bradycardic effects due to action in brain receptors. Atrial or ventricular fibrillation can be caused by direct action on the myocardium. Even an accidental contact with the leaves or the juice of the plant, can cause poisoning due to bradycardia or fatal ventricular arrhythmia which is induced by triggered activity, and hence its appellation of the "Queen of all poisons".[43,44]

Gynura or *Gynura procumbens* is cultivated in Southeastern Asia and is used to improve microcirculation and to eliminate pain. It often has adverse effects, like hepatotoxicity in animals,[45] and inhibits angiotensin converting enzyme leading to hypotension.[46]

Danshen (salvia miltiorrhiza) or **red sage** is used for congestive heart failure (CHF) and menstrual abnormalities. It increases the risk of bleeding significantly, due to inhibition of c-AMP and increases prothrombin time. It can also increase the levels of digitalis.[47]

Echinacea is widely used to fight infections, especially the common cold and upper respiratory infections. It can increase the hepatotoxicity of statins, fibrates, niacin and amiodarone. Echinacea flavonoids may as well inhibit and induce cytochrome P450.[48]

TABLE 4. Herbal Products to be Avoided in Cardiovascular Diseases

Herb	Purpoted use	Adverse effects
Alfalfa	Arthritis, asthma, diabetes, hyperlipidemia	Increases bleeding risk with warfarin
Aloe Vera	Wounds, diabetes	Hypokalemia and digitalis toxicity, arrhythmia
Angelica (dong quai)	Dyspepsia, infection, appetite loss	Increases bleeding risk with warfarin
Bilberry	Arthritis, circulatory disorders, local inflammation	Increases bleeding risk with warfarin
Butcher's broom	circulatory disorders, inflammation, leg cramps	Decreases effects of alpha-blockers

Licorice (liquorice) is widely used as an expectorant in newer cough syrups. It can cause pseudohyperaldosteronism with concomitant hypokalemia, hypertension and edema with subsequent tolerance to antihypertension medications. Licorice- induced hypokalemia can lead to increased risk for ventricular arrhythmia, particularly torsades de pointes.[49] It can also potentiate the effects of spironolactone and digoxin, while its ability to inhibit thrombin and platelet aggregation enhances the risk of bleeding when antiplatelet and anticoagulant agents are co-administered with it.[50]

Black cohosh is used in remedies against gynecological pathology. It may inhibit estrogen and serotonins.[51] After estrogen replacement therapy, it has been shown to increase the risk of thromboembolic and cardiovascular events.[52]

Yohmbine is marketed for treatment of sexual disorders and against exhaustion. Many of these effects are attributed to its alpha2- adrenergic receptor antagonist activity.[53] Thus, it increases the release of norepinephrine, resulting in inadequate blood pressure control in patients using antihypertensive and diuretic agents. Its use is contraindicated in patients with hypotension or angina.[54]

DISCUSSION

More than 30000 herbal remedies and dietary supplements are sold and 1000 new supplements are induced annually in the U.S.[58] Nevertheless and despite the above mentioned evidence, herbs can possibly find their place in modern medical treatment.[55] From a methodological point of view however, certain disadvantages and problems are associated with their use. Most importantly, scientific data on safety and effectiveness are absent and there is no standardized control and regulatory mechanism of their use. Their metabolism is often unknown. Randomized controlled studies are the best way to determine their efficacy and safety which are not often available, not demanded by consumers and health providers, and not required by regulatory agencies. The belief of the safety of CAM products is unsubstantiated. Even when the data are available, the findings are often questionable, because of lack of consistency in research methods, lack of standardization of the investigated supplements, absence of placebo groups and the inclusion of healthy- low risk volunteers.

Another major issue is the lack of regulatory oversight. The only requirement for approval is a copy of the product label to be sent by the manufacturer to the U.S. Food and Drug Administration (FDA).

The lack of quality control is another problem. There is a wide variation in manufacturing techniques and storage methods, which require urgent attention of FDA and other regulatory agencies. Also untested and unregulated steroids are sold to the public including minors. More of 40% of the herbs fail to contain as much of their active ingredients as claimed on the labels. FDA guidelines for manufacturers advise that they should avoid contaminating products with other herbs, pesticides, heavy metals and prescription drugs.[56] Nonetheless, products have been reported to contain adulterant compounds and to put consumers at risk of side effects and drug interactions.

The unethical marketing techniques have led to misleading advertisements and public misinformation. For instance, some promoted in media herbs are claimed to be "doctor recommended" or "presented without a prescription" and this leads to an unrestricted flow of equivocal and uncontrolled information towards the public.

Another serious problem is the lack of established data about herb-drug interactions by patients and health care providers who have no thorough knowledge of the possible interactions between these substances and the well established conventional therapy. This is most important in elderly patients with significant comorbidities. Most (64%) of patients with a diagnosis of atrial fibrillation, CHF, or ischemic heart disease reported concomitant use of alternative therapies and prescription drugs.[57]

Finally, many adverse reactions or harmful interactions may either be under-recognized or under-reported by both patients and physicians. These interactions can occur in the recommended dosages of these preparations. The supplement manufacturers also rarely report serious adverse effects to the FDA despite federal requirements.[58]

CONCLUSION

Considering the wide and growing use of herbs and supplements, it is essential to introduce precise rules and guidelines to standardize their indications. Also a scientific background is required, so as to direct their use, especially in complicated cases of significant and co existing diseases, which warrant the combined prescription of multiple different and mutually interacting medications.

Evidence of the safety and efficacy of the herbal products should be obtained by clinical trials, pre-marketing approval and strict post-marketing surveillance. Herb-drug interactions are more serious when cardiovascular medications with a narrow therapeutic index, such as digoxin and warfarin, are co-administrated with herbs.[4,6] Further data are required for the possible interactions with the new oral anticoagulants.

Thus, the health care professionals should question patients about the use of herbal products. This information is important, particularly in elderly patients at a higher risk of adverse interactions. Physicians should have a good knowledge base about herbs and vitamins and have in mind the possible interactions and side effects. Finally, properly designed clinical trials should be scheduled on the safety and efficacy of the herbal remedies.

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