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SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

THE PRESENT AND FUTURE: REVIEW TOPIC OF THE WEEK

Herbal Medications in Cardiovascular Medicine

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ABSTRACT

Herbal medications are commonly used for clinical purposes, including the treatment of cardiovascular conditions. Compared with conventional medications, herbal medications do not require clinical studies before their marketing or formal approval from regulatory agencies, and for this reason their efficacy and safety are rarely proven. In this review, we summarize available evidence on herbal medications mostly used in cardiovascular medicine. We show that the use of these medications for the treatment of cardiovascular diseases is often not supported by scientific evidence. Despite most of these herbs showing an effect on biological mechanisms related to the cardiovascular system, data on their clinical effects are lacking. Potential relevant side effects, including increased risk of drug interactions, are described, and the possibility of contamination or substitution with other medications represents a concern. Physicians should always assess the use of herbal medications with patients and discuss the possible benefits and side effects with them.
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Historically, herbs have been used for medical purposes, but their usage continues even nowadays. It is estimated that about 25% of currently commercialized medications are derived from plants used in traditional medicine, and according to a recent survey, 1 of every 5 persons in the United States has taken some herbal or dietary supplementation during his or her life (1-3). Proportions are even higher in developing countries due to reduced accessibility to essential medications and a more marked herbalism tradition. For example, in China, 30% to 50% of medications consumption consists of traditional herbs (1).

Among the various medicine specialties, herbal medications have become more prominent in cardiovascular medicine. The effects of the most promising compounds have undergone systematic evaluations, in some cases becoming historic cornerstones in the treatment of cardiovascular diseases. This is, for example, the case for digoxin and digitoxin, derived from *Digitalis lanata* and *Digitalis purpurea*; reserpine, derived from *Rauwolfia serpentina* and originally used for the treatment of psychosis; and acetylsalicylic acid (aspirin), extracted from willow bark. However, all medications, particularly those derived from herbs, conceal some harm, which sometimes exceeds the benefits. The story of digoxin and reserpine is paradigmatic in this sense. The indications for both of these medications have been progressively reduced because of their narrow therapeutic range and adverse effects, despite their pivotal role immediately after their discovery (4,5).

The aim of this review is to describe norms regulating the use of herbal medications, assess the concerns raised by the use of such products, and summarize the evidence available on the efficacy and safety of the herbal medications most commonly used in cardiovascular medicine. We also discuss how best to approach consumers of herbal medications for the treatment of cardiovascular diseases.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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HOW ARE HERBAL MEDICATIONS REGULATED?

Several general concerns are associated with the use of herbal medications (**Table 1**). In particular, herbal medications follow a different regulatory process compared with conventional medicines and, for this reason, their efficacy and safety are often questionable.

In the United States, herbal medications are regulated by the Food and Drug Administration (FDA) under a category called dietary supplements (6). Key points of this regulation are as follows:

- Herbal medications do not need to be approved by the FDA before they enter the market, and they do not have to be proven safe or effective in the treatment of a given disease or condition.
- The FDA's role in regard to these medications relates mainly to monitoring their safety by reviewing serious adverse events reported by the manufacturer, consumers, or health care professionals through the Safety Reporting Portal.
- The FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market.
- If the FDA finds a product to be unsafe, it can take action against the manufacturer and may issue a warning or request that the product be removed from the market.

Therefore, in the United States, compared with conventional medications, herbal medications do not require clinical studies before their approval and can be found unsafe only after they have caused harm.

In the European Union, approval and marketing of herbal medications follows legislations of individual Member States, but the European Medicines Agency defined regulatory pathways as a reference point for marketing authorization or registration of herbal medicinal products. On the basis of these pathways, no clinical tests and trials on safety and efficacy are needed if the product has been used for at least 15 years within the European Union ("traditional use registration"), whereas proofs of efficacy and an "acceptable" level of safety must be documented for other herbal products (7).

REVIEW OF EVIDENCE ON HERBAL MEDICATIONS

We conducted an unsystematic, narrative review of published data to report the current knowledge on the efficacy and safety of herbal medications for the treatment of cardiovascular diseases. We selected herbal medications used for the treatment of any cardiovascular disease from the report of the National Center for Complementary Medicine of the National Institutes of Health (8). The report examines 42 herbal medications and identifies possible indications for their use. For the aim of this review, we selected herbal medications with a possible indication for the treatment of 1 or more of the following cardiovascular conditions: hypertension, heart failure, coronary artery disease, dyslipidemia, thromboembolic disorders, and peripheral artery disease. Overall, 10 of the herbal medications reviewed in the report were selected, including Asian ginseng (*Panax ginseng*), astragalus (*Astragalus membranaceus*), flaxseed oil (*Linum usitatissimum*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), grape (*Vitis vinifera*) seeds, green tea (*Camellia sinensis*), hawthorn (*Crataegus*), milk thistle (*Silybum marianum*), and soy (*Glycine max*). For each herb, we described possible indications, biological and clinical data, and safety concerns.

We searched PubMed Central (from 1966 to June 2016), the Cochrane Database of Systematic Reviews (from 1996 to June 2016), and the U.S. National Center for Complementary and Integrative Health website (accessed on June 22, 2016). Key terms included the common and Latin names of the herbs of interest, *herbal products*, *herbal medications*, and *cardiovascular diseases*. Abstracts and titles were evaluated for relevance. All published data that were deemed relevant for the discussion of the selected herbal medications for the treatment of cardiovascular disease were included.

ASIAN GINSENG (*Panax ginseng*). Possible indications. Asian ginseng is used as an adaptogen

ABBREVIATIONS AND ACRONYMS

CYP = cytochrome
DBP = diastolic blood pressure
FDA = Food and Drug Administration
GSE = grapeseed extract
HbA_{1c} = glycosylated hemoglobin
HDL = high-density lipoprotein
LDL = low-density lipoprotein
NO = nitric oxide
RCT = randomized clinical trial
SBP = systolic blood pressure

TABLE 1 Which Are the Most Common Concerns?

Concern	Description
Lack of proof of efficacy and safety	Differently from conventional medications, herbal medications do not need proof of efficacy and safety before they enter the market.
Children and pregnant women	Most herbal medications are not tested in pregnant women or children. Their use in children and in pregnant, attempting to become pregnant, or breastfeeding women should be avoided because of the increased risk of side effects, including cardiovascular events.
Contamination and substitution	Substitution of the plants listed on the labels with alternative plant species has been often reported. Contamination with conventional medications has also been described.
Active ingredient	Active ingredients for many herbal medications have not been ascertained, and if ascertained their level might vary considerably in different preparations.
Lack of antidotes	Severe side effects and organ damage might derive from the inappropriate use of herbal medications (i.e., prolonged use or overdose). No antidotes are available to counteract the effect of herbal medications.

for the body to support overall health and boost the immune system (9). Among its numerous advocated medical properties, Asian ginseng is claimed to improve blood pressure control and lower blood glucose and lipid levels.

Biological and clinical data. Preclinical data from in vitro and in vivo studies have shown that Asian ginseng contains saponins with a partial agonistic effect on steroidal receptors, known as ginsenosides, which may exert beneficial effects on the cardiovascular system by stimulating secretion of endothelial cell-derived nitric oxide (NO), modulating calcium ion channels in myocardial cells, inhibiting production of reactive oxygen species, reducing platelet adhesion, influencing autonomic neurotransmitter release, and stabilizing glucose homeostasis (10).

To date, few large, high-quality clinical trials have investigated clinical outcomes associated with the use of Asian ginseng in populations of patients with cardiovascular diseases. A very recent systematic review and meta-analysis has examined 17 randomized clinical trials (RCTs) and found no significant effect of Asian ginseng on systolic, diastolic, or mean arterial blood pressure (11). The efficacy of ginseng for the treatment of type 2 diabetes has been revised in a meta-analysis including 8 studies. No significant difference was found in glycosylated hemoglobin (HbA_{1c}) levels between the Asian ginseng supplementation and the control groups, although it appeared to improve several secondary outcomes including fasting glucose, postprandial insulin, insulin resistance, triglycerides, total cholesterol, and low-density lipoprotein (LDL) levels (12). A previous systematic review including 16 RCTs conducted in people with and without diabetes found no significant effect of this herb on HbA_{1c} levels, fasting plasma insulin, or insulin resistance (13). Thus far, there appears to be insufficient evidence to suggest a beneficial effect of Asian ginseng for cardiovascular diseases.

Safety concerns. Asian ginseng can induce enzyme activity of the cytochrome P450 (CYP450) family and, as a consequence, lower the bioavailability of a number of medications, including warfarin (14). Asian ginseng appears to be generally safe when used for a short time and at the recommended doses. Potential side effects have been described from prolonged use and include increased blood pressure, nausea, diarrhea, headache, insomnia, and allergic reactions (15).

ASTRAGALUS (*Astragalus membranaceus*). Possible indications.

Astragalus is used as a tonic to enhance the immune system and as adjunctive treatment for the common cold and upper respiratory infections. A possible effect on heart failure and coronary heart disease has also been proposed.

Biological and clinical data. Experimental evidence from in vitro and in vivo studies indicate a potential beneficial effect of astragalus on cardiomyocytes through its antioxidant and anti-inflammatory activity (16–18). It can inhibit isproterenol-induced cardiac hypertrophy in rat models (19,20), and appears to reverse angiotensin II-induced mitochondrial dysfunction in rat vascular smooth muscle cells. This effect seems to be mediated mainly by the antioxidant properties of this herb (21). Additionally, a cardioprotective effect of astragalus in viral myocarditis has also been observed in cell cultures and mouse models (22).

In clinical studies, a positive symptomatic effect of astragalus on dyspnea, chest distress, and angina, coupled with an improvement in electrocardiographic parameters and cardiac output has been described in small observational studies including patients with congestive heart failure and ischemic heart disease (23–25). However, these studies are not available in the English language. To date, data from high-quality clinical trials investigating the efficacy and safety of astragalus for the treatment of cardiovascular diseases are lacking.

Safety concerns. The safety profile of astragalus in cardiovascular patients is unknown due to the lack of adequate safety data.

FLAXSEED OIL (*Linum usitatissimum*). Possible indications.

Flaxseed is commonly used as a laxative because of its high content of soluble fiber. Potential health benefits associated with use of flaxseed and flaxseed oil include symptomatic improvement in arthritis, osteoporosis, and menopause, and cancer prevention (26). Possible beneficial effects on cardiovascular health have been claimed, including lowering blood pressure and lipid levels, reducing the progression of atherosclerosis, and preventing arrhythmias.

Biological and clinical data. Flaxseed is rich in alpha-linolenic acid, an essential n-3 polyunsaturated fatty acid, which might exert potential beneficial effects in coronary artery disease, hyperlipidemia, inflammation, and metabolic syndrome (27). Flaxseed also contains lignans, which act as both antioxidant agents and phytoestrogens, and is a source of both soluble and insoluble fiber, which are known to improve blood lipid levels by increasing fecal excretion of bile acids and interfering with endogenous cholesterol synthesis (28). Animal studies have shown that flaxseed may retard the progression and foster the regression of atherosclerotic plaques (29).

The anti-inflammatory properties of flaxseed, including the potential for decreasing platelet and endothelium reactivity and proliferation, would contribute to the reported antiatherogenic effect (30).

A meta-analysis of 11 controlled trials including 1,004 participants treated with variable doses of whole flaxseed or flaxseed-derived products for 3 to 48 weeks found a statistically significant, but slight decrease of both systolic (-1.77 mm Hg) and diastolic blood pressure (DBP) (-1.58 mm Hg) in the treatment group (31). A higher antihypertensive effect of flaxseed was found among patients with peripheral artery disease who consumed 30 g/day of flaxseed compared with placebo (32). This beneficial effect of flaxseed seems to be mostly attributable to a decrease in circulating oxylipins, which are known regulators of vascular tone and inflammation (33,34).

Flaxseed significantly reduced total and LDL cholesterol in a meta-analysis of 28 RCTs of supplementation with flaxseed or its derivatives in 1,539 adults (35). No effect of flaxseed on high-density lipoprotein (HDL) cholesterol and triglycerides was found. The included clinical studies were largely heterogeneous in terms of type of intervention, doses, populations, and methodological quality. A 15% reduction of blood LDL cholesterol levels was reported in a sample of patients with peripheral artery disease supplemented with flaxseed compared with placebo (36). In 2014, Health Canada approved a claim linking ground whole flaxseed consumed at a dose of 40 g/day to blood cholesterol lowering on the basis of the pooled results from 7 RCTs conducted in normal and hypercholesterolemic individuals (37). Although there is evidence from animal studies that flaxseed and its bioactive constituents may shorten the QT interval and the action potential duration of the heart, the effect of flaxseed on preventing ventricular arrhythmias in humans has not yet been investigated (38).

Safety concerns. Flaxseed was generally well tolerated in clinical studies. Due to its high fiber content, flaxseed may cause intestinal disorders, including constipation and diarrhea. It may interfere with the intestinal absorption of oral medications, thus leading to decreased efficacy.

GARLIC (*Allium sativum*)

Possible indications. Garlic has been known for its preventive and therapeutic properties in many medical conditions, including cardiovascular diseases, cancers, and infections. In particular, garlic has been postulated to have a beneficial effect on lowering blood pressure, reducing blood levels of cholesterol and triglycerides, and inhibiting platelet aggregation (39,40).

Biological and clinical data. It has been suggested that garlic may exert an antiatherosclerotic effect by interfering with inflammatory and oxidative pathways, and inhibiting lipid deposition in the vessels (41,42). Decreased peripheral vascular resistance, vasodilation, and smooth muscle cell relaxation could be mediated by a direct influence of garlic on several biological mechanisms involved in the pathogenesis of hypertension, including oxidative stress, and endothelial NO and hydrogen sulfide production (43,44). Furthermore, garlic has been shown to reduce both endogenous synthesis and intestinal absorption of cholesterol (45,46). Finally, a positive effect of garlic on lowering blood glucose levels has been documented in animal models with diabetes (47,48).

Numerous observational and experimental clinical studies have investigated the potential efficacy of garlic for the treatment of hypertension in humans, but the results were conflicting. A Cochrane review published in 2012 found insufficient evidence to conclude a beneficial effect of garlic, compared to placebo, on reducing cardiovascular morbidity and mortality in patients with hypertension (49).

A positive effect of garlic on blood lipids has been documented in several clinical studies in humans (50). A meta-analysis including 39 primary trials in patients with blood cholesterol levels higher than 200 mg/dl showed that administration of garlic preparations for 2 months reduced total and LDL cholesterol by 10%, with no significant effect on HDL cholesterol and triglycerides (51). RCT data did not show any effect of garlic on improving clinical outcomes in patients with arterial peripheral occlusive disease (52).

Garlic was found to reduce fasting blood glucose levels in a meta-analysis including 7 RCTs conducted in healthy individuals and diabetic patients (53). Although, this was not confirmed, in a very recent pilot study of type 2 diabetic patients, garlic supplementation neither influenced the metabolic parameters, including insulin resistance, nor resulted in improvements in endothelial function, vascular inflammation, or oxidative stress (54). To date, there is no conclusive evidence on the efficacy of garlic for the treatment of cardiovascular conditions, although some positive data are available. RCTs of garlic for the treatment of cardiovascular diseases have numerous methodological shortcomings, including small sample sizes, short durations, lack of statistical power, inadequate randomization, high heterogeneity in the preparations of garlic, and dosages.

Safety concerns. Although most studies lack an adequate assessment of the safety profile, garlic supplementation appears to be generally safe for humans. Most frequent side effects include breath

and body odor, heartburn, nausea, and vomiting (55). Due to the potential antiplatelet activity caused by garlic consumption, it should be taken with extreme caution in individuals treated with antiplatelet or anticoagulant medications (55).

GINKGO (*Ginkgo biloba*). Possible indications. Ginkgo leaf extract has been used extensively and for years in the treatment of asthma, bronchitis, fatigue, and tinnitus. Very recently, gingko has been largely studied in regard to potentially improving memory and cognition, and for possibly preventing and treating dementia and coronary heart disease.

Biological and clinical data. The main active constituents of ginkgo leaf extract including ginkgolides, bilobalides, and flavonoids, showing antioxidant, anti-inflammatory, and platelet inhibition activity (56). Gingko has been found to inhibit angiotensin-converting enzyme and to modulate endothelial NO release in animal models (57).

However, the clinical benefit of gingko in patients with hypertension has not yet been proven (58). A large RCT including over 3,000 participants followed for an average of approximately 6 years found no evidence that, compared with placebo, gingko reduced total or cardiovascular disease mortality, or cardiovascular events, including myocardial infarction, angina pectoris, and stroke (59). Moreover, a possible symptomatic improvement in patients with peripheral artery disease has been suggested in several clinical studies, although findings from more recent RCTs did not confirm such benefits to be associated with gingko (60).

Safety concerns. Several side effects from gingko have been reported in clinical studies, and include headache, nausea, diarrhea, dizziness, and skin rashes (61). An increased risk of bleeding may be attributable to the antiplatelet activity of gingko (62). Major bleeding events, including subarachnoid and intracranial hemorrhage, have been described during concomitant use of gingko with antiplatelet and anticoagulant medications (63,64).

GRAPE (*Vitis vinifera*) SEEDS. Possible indications. Grapeseed extract (GSE) is commonly believed to be of some benefit for the treatment of many cardiovascular conditions, including atherosclerosis, hypertension, hypercholesterolemia, chronic venous insufficiency, and diabetic retinopathy and neuropathy.

Biological and clinical data. Grapes are known to contain a large amount of antioxidant compounds. In particular, resveratrol is mainly found in grape skin, whereas oligomeric proanthocyanidin complexes, vitamin E, flavonoids, and linoleic acid are highly concentrated in the seeds (65,66). In addition, it has been documented that grape seeds may inhibit platelet function and platelet-dependent inflammatory responses (67,68).

A meta-analysis of 9 RCTs including 390 individuals found a significant but small effect of GSE on lowering systolic blood pressure (SBP), with no change reported for DBP, blood lipid levels, and C-reactive protein (69). More recently, GSE was found to reduce SBP by 5.6% and DBP by 4.7% after 6 weeks of treatment compared with placebo in a sample of 36 individuals with pre-hypertension (70). It has also been shown that GSE may reduce LDL cholesterol and protect it from oxidation (71,72). Given the limited data and the small effects described, as of now, there is insufficient evidence to endorse the use of grape seeds for treatment of any cardiovascular conditions.

Safety concerns. The grape seed safety profile is not sufficiently known due to the lack of adequate data to assess it. Common side effects reported in RCTs include itching, dizziness, nausea, diarrhea, headache, sore throat, and cough (69,70).

GREEN TEA (*Camellia sinensis*). Possible indications. Green tea has been used as a possible treatment for improving mental alertness and aiding in weight loss. Proposed cardiovascular effects include reduction of cholesterol levels, improved diabetes control, and prevention of cardiovascular events.

Biological and clinical data. Green tea is rich in flavonoids that are mainly present as catechins (73). It also contains large amounts of vitamins and minerals, such as folic acid, niacin, pantothenic acid, riboflavin, manganese, potassium, and magnesium (74).

Large observational studies have found that green tea may reduce cardiovascular morbidity and mortality when consumed in high doses (at least 3 cups a day) and for a long term (75). A systematic Cochrane review investigated the efficacy of tea for the primary prevention of cardiovascular disease and included 11 RCTs, 7 of which examined green tea (76). The investigators found a statistically significant effect of green tea on lowering total cholesterol, LDL cholesterol, SBP, and DBP. However, these findings were derived from a limited number of studies that were of short duration (3 to 6 months), had small sample sizes, were heterogeneous with respect to the study patients included, and tested different forms (tea extract in the form of tablets, capsules, bags, or beverages) and dosages of green tea. Additionally, regular consumption of green tea has been associated with a decreased risk of type 2 diabetes mellitus in cohort studies (77). However, the results of RCTs examining the effects of green tea on markers of glucose-insulin homeostasis have been controversial (78,79).

Safety concerns. In clinical studies, green tea appeared to be generally safe. There have been some case reports of liver damage in subjects consuming concentrated green tea extracts, but such cases were very rare and mostly associated with complete recovery after interruption of green tea ingestion (80,81). Also, green tea contains small amounts of vitamin K, which can reduce the effectiveness of anticoagulant medications, such as warfarin (76,77).

HAWTHORN *(Crataegus)*. Possible indications. Hawthorn is traditionally used for the treatment of digestive, heart, and kidney diseases. In particular, favorable effects have been claimed for hawthorn in many cardiovascular conditions, including hypertension, hyperlipidemia, arrhythmia, and congestive heart failure (82).

Biological and clinical data. Biological data have shown antioxidant properties of hawthorn at the cellular and mitochondrial levels (83,84). This herb's anti-inflammatory effect would also be related to down-regulation of the intracellular expression of inflammatory cytokines (85). In addition, hawthorn appeared to exert a positive inotropic effect by influencing the sodium-potassium (Na^+/K^+)-ATPase and enhancing calcium transport in cardiomyocytes (86). It may also exert antiarrhythmic effects through a mechanism similar to the action of class III antiarrhythmic drugs (87). A vasodilating effect of hawthorn in both the coronary and the peripheral vessels has been described, and could directly influence NO levels in the endothelium and inhibit angiotensin-converting enzyme (88). It has also been claimed that hawthorn may have an antiatherosclerotic effect, reducing endothelial barrier dysfunction (89), inhibiting smooth muscle cell migration and proliferation after vessel injury, and inhibiting platelet aggregation (90,91). In addition, it has been suggested that hawthorn can inhibit cholesterol synthesis in the liver and lipid absorption in the intestine (92,93).

Despite this large amount of biological data, there is no robust evidence to support the use of this herb for the treatment of cardiovascular diseases. Meta-analyses of RCTs have shown that hawthorn may improve some functional measures, such as maximal workload, left ventricular ejection fraction, exercise tolerance, and pressure heart rate product in patients with chronic heart failure (New York Heart Association functional class I to III) (94,95). In addition, significant recovery from symptoms, such as shortness of breath, fatigue, and palpitations, was found in those subjects receiving hawthorn compared with placebo. However, data to assess the effect of hawthorn on hard cardiac outcomes are still lacking. A positive effect of hawthorn on hypertension, especially on lowering DBP, was reported in few RCTs (96–99). However, the small sample size and potential lack of power of such studies does not allow inferences to be made regarding hawthorn's antihypertensive effect. Similarly, very few and small RCTs have indicated a favorable effect on lowering blood lipid levels, but larger clinical studies are required to adequately assess these clinical outcomes (100).

Safety concerns. Side effects in clinical studies were rare and mild, and included nausea, dizziness, gastrointestinal complaints, headache, and palpitation (101). There is also preclinical evidence for a potential interaction between hawthorn and digoxin, leading to an increase in the effect of digoxin (102).

MILK THISTLE (*Silybum marianum*). Possible indications. Milk thistle has been proposed as an herbal remedy for liver disorders and gallbladder disease. Recently a possible effect on cardiovascular disease has also been postulated.

Biological and clinical data. Silymarin, the known active ingredient of milk thistle, includes a group of flavonoids that may be responsible for its strong antioxidant and anti-inflammatory activities (103). Such properties have been extensively documented in preclinical studies (104,105). Recently, it has been claimed that silymarin may protect tissues, including the heart, against ischemia reperfusion injury, probably by influencing mechanisms of preconditioning (106).

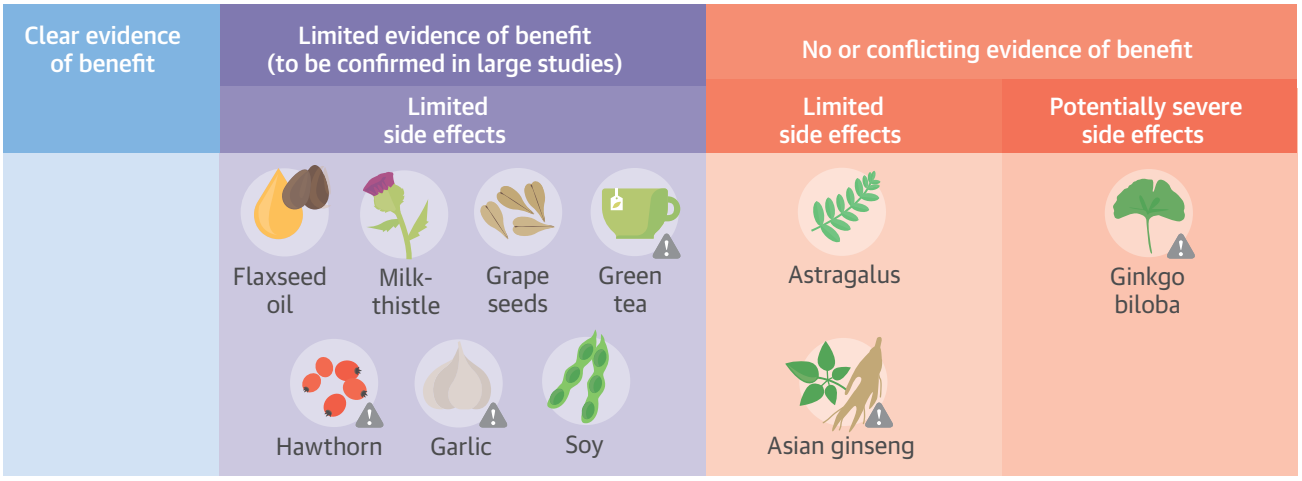
Clinical studies investigating the efficacy of milk thistle for the treatment of cardiovascular diseases in humans are lacking. The suggestion that milk thistle may be useful in reducing overall cardiovascular risk derives from clinical studies conducted among patients with type 2 diabetes mellitus (107). In a recent meta-analysis including 5 RCTs and 270 diabetic patients, silymarin produced a significant reduction in fasting blood glucose and HbA_{1c} levels, with no effect on the blood lipid profile (108). No major cardiovascular events were examined.

Safety concerns. Milk thistle was well tolerated in clinical studies. The most frequently reported side effects included allergic reactions, skin rashes, gastrointestinal complaints, diarrhea, and headache.

SOY (*Glycine max*). Possible indications. Soy is claimed to have a beneficial effect on numerous medical conditions, including menopausal symptoms, osteoporosis, cognitive disturbances, and cancer (109). It is believed to reduce the cardiovascular risk by lowering cholesterol and blood pressure (110).

Biological and clinical data. Soybeans, the seeds of the soy plant, have a high content of proteins.

CENTRAL ILLUSTRATION **An Evidence-Based Review of Herbal Medications Used in Cardiovascular (CV) Medicine**



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They also contain isoflavones, which are compounds with both estrogen-like properties and antiestrogen activity (111). Initial evidence from animal studies suggested that compared with animal proteins, soy protein reduced cholesterol levels and prevented atherosclerosis (112).

A meta-analysis of 29 RCTs found that compared with animal proteins, soy protein, at an average dietary intake of 47 g/day, significantly decreased blood LDL cholesterol and triglyceride levels, with no effect on HDL cholesterol (113). Following such findings, in 1999, the FDA issued a health claim for soy stating that, "25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease" (114). In 2006, the American Heart Association reviewed a large number of studies investigating the potential health benefits of soy and found that many of them did not confirm the previously claimed evidence (115). In these studies, a very large amount of daily soy protein (50 g/day) appeared to have a small effect on lowering LDL cholesterol. Soy also appeared not to influence levels of HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. The American Heart Association conclusive advice states that soy dietary products could be beneficial to cardiovascular health because of their high content of polyunsaturated fats, fiber, vitamins, and minerals, and low content of saturated fat. More recently, the European Food Safety Authority found that only 4 of 18 reviewed RCTs reported a significant decrease in LDL cholesterol associated with soy protein consumption (116). Therefore, despite a consistently documented slight effect of soy protein on lowering LDL cholesterol, further high-quality RCTs are needed to conclude whether any soy components have beneficial effects on cardiovascular morbidity and mortality.

Safety concerns. Soy consumption for short periods appeared generally safe in clinical studies. Commonly reported side effects included nausea, gastrointestinal complaints, and constipation. Concern exists regarding a possible association of soy and the isoflavones contained in soy with an increased risk of endometrial hyperplasia; breast, ovarian, and uterine cancer; male infertility; and thyroid dysfunction (117).

SUMMARY. In summary, evidence of positive cardiovascular effects is lacking for most of the herbal medications examined. In addition, results of studies showing a positive effect on cardiovascular conditions are limited, owing to small sample sizes or a limited effect size, and therefore need to be confirmed in larger studies (**Central Illustration**). Thus far, none of the herbal medications assessed can be recommended for treatment of cardiovascular conditions.

POSSIBLE NEGATIVE CARDIOVASCULAR EFFECTS CAUSED BY HERBAL MEDICATIONS

In addition to those mentioned earlier, other herbal medications used for treatment of noncardiovascular conditions may raise relevant cardiovascular concerns. For example, bitter orange, which is commonly

TABLE 2 Most Relevant Interactions Between Herbal Medications (Used Both for the Treatment of Cardiovascular Diseases and for Other Conditions) and Cardiovascular Medications

Herbal Medication (Ref. #)	Interacting Cardiovascular Medication(s)	Mechanism of Action	Potential Side Effect
Asian ginseng (14,123)	Warfarin	Induction of CYP2C9	↓ Effect
Cranberry (18,122)	Warfarin	Inhibition of CYP2C9	↑ Risk of bleeding
European elder (125)	Diuretics	Additive diuretic effect	↑ Diuresis
Garlic (55,124)	Aspirin and anticoagulant agents	Reduction of platelet function	↑ Risk of bleeding
Ginkgo (63,64,124)	Aspirin and anticoagulant agents	Reduction of platelet function	↑ Risk of bleeding
Goldenseal (121)	Medications metabolized by CYP2D6 and CYP3A4	Inhibition of CYP2D6 and CYP3A4	↑ Effect
Green tea (76,77)	Warfarin	Contains vitamin K	↓ Effect
Hawthorn (102)	Digoxin	Increased blood concentration of digoxin	Arrhythmias
Licorice root (126)	Loop and thiazide diuretic agents	Mineralocorticoid-like effect	Hypokalemia
Salvia miltiorrhiza (120)	Warfarin	Reduction in binding to albumin	↑ Risk of bleeding
St. John's wort (123)	Medications metabolized by CYP3A4 and CYP2C9	Induction of CYP3A4 and CYP2C9	↓ Effect

CYP = cytochrome.

used as a dietary supplement for weight loss and as an appetite suppressant, contains synephrine, an alkaloid with adrenergic properties. Synephrine has been shown in clinical studies to cause tachycardia, tachyarrhythmia, QT prolongation, ischemic stroke, angina, and myocardial infarction (118). Ephedra, a product that contains ephedrine and used to be widely used for weight loss, was banned from the market in 2004 by the FDA because of a high risk of cardiovascular events, in particular arrhythmias, heart failure, myocardial infarction, changes in blood pressure, and death. Between 1995 and 1997, the FDA received more than 900 reports of possible side effects related to this product, including stroke, myocardial infarction, and sudden death (119).

Herbal medications can also interact with cardiovascular drugs (**Table 2**) by altering the pharmacokinetics of cardiovascular medications, thus influencing their distribution and metabolism. For example, Salvia miltiorrhiza has been shown to significantly decrease the binding of warfarin to serum albumin, increasing free drug concentrations in vivo, leading to an increased risk of bleeding (120). Goldenseal, a product used as an antimicrobial agent to prevent common colds and upper respiratory tract infections, significantly inhibits CYP2D6 and CYP3A4, leading to an increase in the concentration of drugs, including atorvastatin, simvastatin, warfarin, diltiazem, verapamil, and propranolol, metabolized by these CYPs (121). Cranberries, which are used to prevent urinary tract infections in women, might inhibit the activity of CYP2C9, the primary isoenzyme involved in the metabolism of warfarin, causing elevation of the international normalized ratio and increased risk of bleeding (18,122). In contrast, St. John's wort, which has been shown in clinical studies to be effective in the treatment of depression, and Asian Ginseng can induce CYP activity, reducing the efficacy of medications metabolized by these enzymes, including warfarin. St. John's wort can also induce the activity of P-glycoprotein, 1 of the most clinically important transmembrane transporters in humans, influencing plasma concentrations of known P-glycoprotein substrates, such as digoxin. Herbal medications may antagonize the effect of cardiovascular drugs (123). For example, green tea contains small amounts of vitamin K, and therefore can antagonize the effect of warfarin (76,77). However, the effects of cardiovascular medications might be potentiated by concomitant use of herbal medications. For example, ginkgo and garlic might reduce platelet function, possibly leading to an increased risk of bleeding if taken together with aspirin or anticoagulant agents (55,63,64,124); hawthorn might increase the blood concentration of digoxin (102), raising the risk of arrhythmias; and European elder might potentiate the effect of diuretic agents (125). A final concern relates to the concomitant use of licorice and loop or thiazides diuretic agents because of an increased risk of hypokalemia (126).

Due to the lack of preclinical data and clinical studies focusing on the effects of herbal medications, most of the available evidence on the safety profiles of these medications come from post-marketing studies, which are often represented by case reports or case series. Therefore, it is not always possible to clearly establish a cause-effect link between exposure to herbal medications and potential side effects.

HOW TO APPROACH A PATIENT USING HERBAL MEDICATIONS

Physicians should be aware of the possible indications and side effects related to the use of herbal

medications (127). However, correctly identifying new signs or symptoms of herbal medications is challenging for physicians, due to a lack of knowledge on their effects and common under-reporting from patients (128). Indeed, about 70% of patients do not notify their physicians about their use of supplements (129) and, at the same time, physicians are unlikely to regularly gather correct information on their use (130,131). In fact, on the one hand patients believe that it is pointless to report the use of herbal medications, because they are reputed to be safe and are not perceived as drugs, whereas on the other hand, physicians do not give adequate weight to the clinical implications of such preparations (131). Moreover, use of herbal medications has been associated with poor adherence to conventional medications, raising significant concerns in terms of safety and effectiveness of concurrent treatments (132).

In order to deal with this issue, physicians should carry out a structured interview. Information on use of alternative preparations, herbal medications, and actual drugs should be properly recorded, and signs and symptoms must be evaluated in accordance with the clinical story. Communicating with the patient is a crucial component of the process, where the pros and cons of specific herbal medications should be explained and their risk-benefit profile properly discussed (133). Eventually, the decision to withdraw or withhold a new herbal medication should be shared with the patient.

The education of physicians is another important matter. Thus far, in most Western countries, the study of alternative medicine is not embedded in medical school syllabi, and guidelines for consultation do not exist. As a result, whether to get the necessary knowledge of the field to provide better care for their patients is solely up to the physician. Ultimately, physicians and patients may have to consult specific web portals from government and regulatory agencies that provide relatively reliable and updated sources of information that often can fill the gap left by scientific societies (6,8,134).

CONCLUSIONS

Use of herbal medications for the treatment of cardiovascular diseases is not supported by scientific evidence. Although most of the herbs demonstrate an effect on biological mechanisms associated with cardiovascular disease, available clinical studies are limited in sample size and do not show any impact on relevant clinical outcomes. Therefore, to date, available data do not provide enough evidence to recommend the use of herbal medications in clinical practice. In addition, potential relevant side effects, including increased risk of drug interactions, have been described, and the possibility of contamination or substitution with other medications is a concern. Physicians should improve their knowledge of herbal medications to adequately weigh the clinical implications related to their use, and be able to discuss with patients their possible benefits and side effects, and explain that natural does not always mean safe.

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