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Review Article

**HERBAL MEDICINE USED IN TRADITIONAL CARDIOVASCULAR  
DISEASE-A REVIEW****M. Harish Reddy<sup>1,\*</sup>, K. Sambasivarao<sup>2</sup>**

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**ABSTRACT**

The cardiovascular diseases (CVDs) have been the major cause of morbidity and mortality in developed countries over the last several decades, and developing countries are rapidly catching up with this epidemic. The underlying pathology is athermanous vascular disease, resulting in coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease, and the subsequent development of heart failure and cardiac arrhythmias. The major risk factors for these disorders were recognized over many years, and they include high levels of low-density lipoprotein (LDL) cholesterol, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, insufficient consumption of fruits and vegetables, excess consumption of alcohol, and lack of regular physical activity. There has been continued research to help define more precisely the cardiovascular risk of an individual with respect to genetic factors, more complex lipid traits, and inflammatory markers, but it was reconfirmed in the INTERHEART study that the conventional risk factors accounted for over 90% of the population attributable risk for myocardial infarction. There is extensive evidence to show that drug treatment of conventional risk factors is effective in reducing cardiovascular events. Many large clinical trials with the HMG CoA reductase inhibitors (statins) have showed that lowering of LDL cholesterol with these agents decreases coronary and cerebrovascular events and that the target for LDL cholesterol becomes lower with each new set of guidelines and the availability of more potent drugs. Likewise, more effective treatment of hypertension with various classes of antihypertensive drugs has been associated with greater benefits but some recent studies suggest we may be reaching the optimal level of treated blood pressure in some patient groups. Apart from the treatment of cardiovascular risk factors with pharmacological agents and the use of antithrombotic drugs, there is growing awareness of the role of dietary factors and herbal medicines in the prevention of CVD and the possibility of their use in treatment.

A wide variety of plant extracts have been used in traditional medicine over the centuries and some, such as digoxin, have been adopted in conventional medicine. In this section, we concentrate on those plants and herbs for which there is some evidence, if not final proof, supporting their value in the prevention or treatment of CVD. More detailed reviews can be found elsewhere in the literature.

**Key Words:** *Cardiovascular, Cholesterol.*

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**Herbal medicinal species****HAWTHORN (CRATAEGUS SPECIES)**

*Crataegus* encompasses many species believed to be valuable in treating CVDs, particularly angina, heart failure, and hyperlipidemia. The leaves, flowers, and fruits of *Crataegus* species contain varying amounts of a number of biologically active substances, such as oligomeric procyanins, flavonoids, and catechins. The extract is suggested to have antioxidant properties, and inhibits the formation of thromboxane. In traditional Chinese medicine (TCM), the fruit of the hawthorn (usually *Crataegus pinnatifida*; known as *shanzha*) is widely used for many indications, including digestive disorders and for lowering cholesterol and blood pressure[1,2].

The use of *Crataegus* in CVD may seem promising, but more studies are needed to confirm the efficacy and safety of hawthorn extracts.

**GARLIC (ALLIUM SATIVUM)**

For centuries, garlic has been valued for its medicinal properties. As an herbal medicine, it has been more closely examined than many other herbs. Research focuses on garlic for preventing atherosclerosis. Multiple beneficial cardiovascular effects have been found, including lowering of blood pressure, inhibition of platelet aggregation, enhancement of fibrinolytic activity, lowering of cholesterol and triglyceride levels, and protection of the elastic properties of the aorta.

The intact cells of garlic bulbs contain an odorless sulfur-containing amino acid, allinin. When garlic is crushed, allinin comes into contact with allinase, which converts allinin to allicin[3].

Dried garlic preparations lack allicin but contain both allinin and allinase.

The consumption of large quantities of fresh garlic (0.25-1.0 g/kg or about 5-20 average-sized 4 g cloves) has been found to produce the aforementioned beneficial effects. In support of this, a double-blind, crossover study of moderately hypercholesterolemic men, which compared the effects of 7.2 g of aged garlic extract with placebo on blood lipid levels, found a maximal decrease of 6.1% in total serum cholesterol levels and 4.6% in LDL cholesterol levels with garlic[4,5]. One more recent meta-analysis concludes that garlic decreases total cholesterol to a modest extent, an effect driven mostly by the modest decreases in triglycerides, with no appreciable effect on LDL or HDL cholesterol.

Garlic has been reported to show antiplatelet stickiness activity. This has been documented in vitro and another study examined the effect of consuming a clove of fresh garlic on platelet thromboxane production. After 26 weeks, serum thromboxane levels were lowered by about 80% thus, garlic may prove to be of benefit in the prevention of thrombosis. Another trial showed that long-term intake of

standardized garlic powder at 300 mg daily for more than 2 years improved the elastic properties of the aorta. In these ways, garlic is beneficial to cardiovascular health, and these effects need further study.

**DANSHEN (SALVIA MILTIORRHIZA)**

The dried root of *S. miltiorrhiza*, known as *danshen* in TCM, is widely used in China for the treatment of angina pectoris, hyperlipidemia, and acute ischemic stroke. It has a range of potentially beneficial effects, including improving microcirculation, causing coronary vasodilatation, suppressing the formation of thromboxane, inhibiting platelet adhesion and aggregation, and protecting against myocardial ischemia. Danshen is widely used either alone or in combination with other herbal ingredients for patients with CAD and other CVDs. Clinical studies in ischemic stroke have various methodological problems and, therefore, reliable conclusions cannot be drawn from them. Further high-quality randomized controlled trials should be performed[6,7].

**LINGZHI (GANODERMA LUCIDUM)**

*G. lucidum*, or lingzhi, is a woody mushroom and a popular medicinal herb that is widely used in China and many other Asian countries to promote good health and longevity. Many potential beneficial effects, including immunomodulation and anticancer activity, have been attributed to lingzhi. The active constituents include polysaccharides and oxygenated triterpenoids, which have a broad range of biological activities and pharmacological functions. Although it is not typically used for treating CVD, it does appear to have some benefits on the cardiovascular system. In vitro studies with certain extracts have reported effects including inhibition of cholesterol synthesis, lowering of blood pressure by reducing sympathetic outflow from the central nervous system and antioxidant effects[8,9,10].

**MAIDENHAIR TREE (GINKGO BILOBA)**

The *Ginkgo* species of tree has existed on Earth for over 200 million years. The root and kernels of *G. biloba* are widely used in TCM[11]. A concentrated extract of *G. biloba* leaves was developed in the West in the 1960s. *G. biloba* extract (GBE) contains flavonoids that decrease capillary permeability and fragility and are free-radical scavengers, and terpenes (i.e., ginkgolides) that inhibit platelet-activating factors and decrease vascular resistance, thereby improving circulatory flow without appreciably affecting blood pressure. *G. biloba* has a clinically significant benefit for patients with peripheral arterial disease.

Adverse effects with GBE are rare but have included gastrointestinal disturbances, headache, and allergic skin rash.

**FOXGLOVE (DIGITALIS PURPUREA/LANATA)**

Potent cardioactive glycosides (digitalis, digitoxin, and digoxin) have been used in CHF for many years. Their treatment value is limited by a low therapeutic index, that is, the dose needing careful adjustment for each patient. Standardization of powdered digitalis, digitoxin, or digoxin is essential for safe and effective use[12]. There are many other plant sources of cardiac glycosides, including *Convallaria majalis* (lily of the valley, convallaria), *Helleborus*

*niger* (blackhellebore), *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Strophanthus hispidus* and *S. kombe* (strophanthus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill), to name but a few, and the venom of the cane toad (*Bufo marinus*) also contains cardiac glycosides. The skin and venom glands of the Chinese toads *Bufo gargarizans* and *B. melanostictus* is used in a TCM called *chansu* and a proprietary Chinese medicine called Lu Shen Wan. These contain bufotoxins, which have a digoxin-like effect and may cause toxicity when taken in excessive doses. Some other herbal remedies such as Siberian ginseng (*Eleutherococcus senticosus*) may cause apparent increases in digoxin levels. Reports of accidental poisonings and even suicide attempts with cardiac glycosides are frequent, and oleander species are often involved; The use of digoxin in heart failure has gradually declined since the Digitalis Investigation Group study showed that digoxin did not reduce overall mortality in heart failure patients[13,14]. However, it is still commonly used to control the heart rate in atrial fibrillation.

**GINSENG (PANAX SPECIES)**

Ginseng has been used medicinally in East Asian countries for thousands of years as an adaptogen and a tonic. The two species that have been the most extensively researched are *Panax ginseng* (Asian ginseng) and *P. quinquefolius* (American ginseng). The name *Panax* is derived from the Latin word "panacea," which illustrates the usage of this herb for a wide range of conditions. *P. ginseng* and *P. notoginseng* are used in TCM for hemostasis and the treatment of patients with angina and CAD.

The mode of action here may be as a calcium ion channel antagonist in vascular tissues, which may result in a lowering of blood pressure. In vitro studies of *P. notoginseng* show an enhancement of blood fibrinolytic parameters. Inhibition of atherogenesis by *P. notoginseng* saponins through decreased proliferation of smooth muscle cells and dilatation of coronary arteries in rabbit tissue in vivo suggest its possible use in angina[15].

**OTHER HERBAL MEDICINES**

Many other herbal materials have been used for treating cardiovascular conditions. For hyperlipidemia, the herbal

extract from the resin of the *Commiphora mukul* or mukul myrrh tree, known as guggul, is widely used in Asia based on Indian Ayurvedic medicine. The presumed bioactive compounds, guggulsterones, are suggested to antagonize the farnesoid X receptor (FXR) involved in controlling cholesterol metabolism. A short-term safety and efficacy study of a standardized guggul extract (guggulipid, containing 2.5% guggulsterones) in healthy adults with hyperlipidemia. Extracts of Chinese red yeast rice (*Monascus purpureus*) contain several active ingredients, including lovastatin, which can lower LDL cholesterol[16]. These preparations appear to be safe in moderate doses, but they may not be standardized well and are likely to have the same side effects and drug interactions as lovastatin when taken in large amounts[17,18].

Extracts of rosemary (*Rosmarinus officinalis*) do appear to have antiproliferative, antioxidant, and anti-inflammatory properties in various cell line studies. The component tetrandrine isolated from *Stephania tetrandra* has antihypertensive and antiarrhythmic effects that have been demonstrated in experimental hypertensive animals and in hypertensive patients. Rauwolfia preparations and veratrum alkaloids are mainly of historical interest in hypertension treatment. Extracts of horse chestnut (*Aesculus hippocastanum*) have been used in the treatment of chronic venous insufficiency, and they were found to be safe and well tolerated, with some beneficial effects in one study[19,20].

**SUMMARY**

Overall, many of the herbal medicines discussed here do appear to have pharmacological effects in vitro and in animal studies, which may influence CVD. However, the evidence from properly conducted clinical trials is generally insufficient to draw definitive conclusions. The problems with standardization of herbal preparations and performance of properly controlled clinical trials to acceptable international standards need to be addressed before the true clinical value of these herbs can be defined.

**HERBAL MEDICINE AND DRUG INTERACTIONS**

Herbal medicines are frequently used in combination with conventional drugs, and interactions are likely to be more common than those that manifest clinically. Herb-drug interactions have been extensively reviewed in the literature and some of the common ones are mentioned. Pharmacokinetic interactions mediated by drug-metabolizing enzymes or transporters are involved in many herb-drug interactions. Polymorphisms in the genes for these enzymes and transporters may influence the interactions mediated through these pathways.

Herb-drug interactions are likely to be more serious with drugs having a narrow therapeutic index, such as warfarin or digoxin. Herbs can interact with warfarin in several different ways). The interaction with danshen is mentioned

in and probably occurs by inhibition of warfarin metabolism through CYP2C19. St. John's wort (*Hypericum perforatum*); interacts with warfarin and a number of other drugs by inducing the expression of several CYP enzymes and the drug transporter P-glycoprotein (P-gp or ABCB1), resulting in decreased plasma concentrations of the drugs involved and lowered efficacy. Digoxin is a substrate for P-gp, and St. John's wort can lower digoxin levels by increasing the activity of this transporter.

The finding that grapefruit juice substantially increased the plasma concentrations of felodipine by decreasing presystemic metabolism through selective post-translational downregulation of CYP3A4 expression in the intestinal wall identified another potential mechanism for drug interactions with natural products. This is important with other dihydropyridine calcium-channel blockers and drugs that undergo substantial presystemic metabolism mediated by CYP3A4, including lovastatin and simvastatin in the cardiovascular field. This interaction seems to be most prominent with grapefruit juice and has not been described to date with herbal medicines. Grapefruit juice may also have a small effect on digoxin pharmacokinetics, possibly through inhibition of the organic anion transporting polypeptide (OATP) rather than P-gp.

#### RESEARCH NEEDS

The evidence from large clinical trials is generally not supportive of the cardiovascular benefits from supplements of antioxidant vitamins or other EMNs, and guidelines generally recommend increasing intake of foods that are rich in these materials rather than using specific supplements. Omega-3 PUFAs may be one exception, and niacin in pharmacological doses clearly has effects on plasma lipids. With the herbal medicines used in the prevention or treatment of CVD, the clinical trial evidence is mostly not sufficient to support any definitive recommendations. Many of the trials have been too small, and different trials have often used different herbal preparations with different standardizations, so the meta-analyses of herbal treatment effects may not always consider the same active compounds. Many herbal medicines do have ingredients with demonstrable pharmacological effects, but larger clinical trials with properly standardized materials are needed before any clear conclusions can be drawn. The potential antihyperglycemic effects of various ginseng preparations and possibly of lingzhi (*G. lucidum*) are areas for further investigation, and more clinical trials with garlic preparations for treating hyperlipidemia or hypertension are warranted. The role of danshen (*S. miltiorrhiza*) in treating CVDs can still be defined more clearly with appropriate clinical trials, and although some well-controlled studies with hawthorn extracts in heart failure have not shown significant benefits, there may still be a role for some hawthorn preparations in

hyperlipidemia or other areas of CVD prevention.

#### CONCLUSIONS

The cardinal importance of a well-balanced diet that includes adequate fruit and vegetables has been rediscovered after some years of oversight during the era of great pharmaceutical and therapeutic advances. In times of plenty, it is important to control calorie intake and lower the consumption of animal fats and alcohol in association with taking adequate regular physical exercise and mental recreation for the maintenance of good health. A worldwide chronic disease epidemic of obesity, diabetes, and consequent CVDs is replacing the diminished burden of infectious diseases. It is evident that there is a place for the use of EMNs where these are deficient, but their value in treating established CVDs is unproved in most instances. Herbal remedies, although they have a long history of use in traditional medicine and show promising biological actions, remain clinically unproved and are as yet often insufficiently standardized to be recommended as therapy. This situation is likely to change with further research. The evidence to support the use of these alternative therapies from clinical trials is not yet secure, but custom and practice make it likely that they will continue to be used for the prevention or treatment of CVDs, among other indications.

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