

REVIEW

The clinical significance and costs of herbs and food supplements used by complementary and alternative medicine for the treatment of cardiovascular diseases and hypertension

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Complementary and alternative medicine (CAM) is widely used by people in the United States and other countries for the treatment of health conditions that include hypertension (HTN), cardiovascular disease (CVD), heart failure, hyperlipidemia and other conditions. The visits to CAM practitioners result in significant out-of-pocket expenses, as CAM is not covered by health insurance in the majority of cases. The reasons for this are that the products used are not closely regulated by governmental regulatory agencies and lack scientific evidence about their effectiveness and safety. The people regard these products as being 'natural' and, consequently, safe. However, there is evidence that these products can be contaminated and adulterated with other substances and could cause harm to the persons who take them. The responsibility falls on the health professionals, who should become familiar with the various CAM products, inquire their patients whether they taking any of these products and advise them accordingly. This review is based on a recent statement issued by the American Medical for the use of CAM for the treatment of HTN. For its preparation, a Medline search of the English language literature was performed between 2010 and 2014 restricted in the use of CAM for CVD and HTN, and from the 88 abstracts reviewed, 23 pertinent papers were selected. These papers together with collateral literature will be discussed in this review regarding CAM and CAM products on their effectiveness and safety for the treatment of CVD and HTN.

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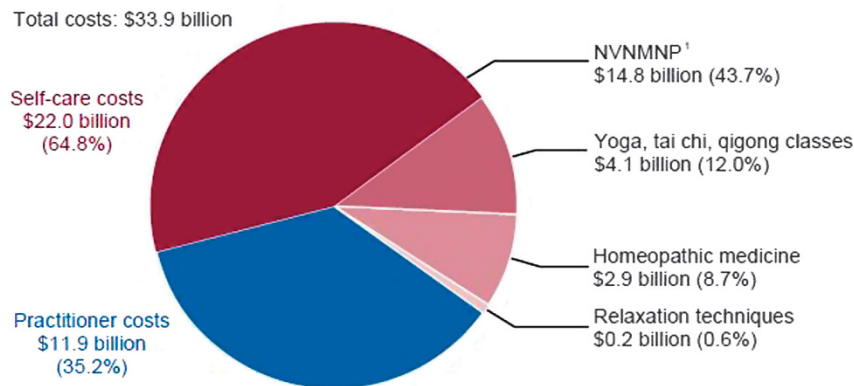
INTRODUCTION

Complementary and alternative medicine (CAM) is a diverse set of healing philosophies, therapies and products often used by patients for the treatment of various health conditions that include cardiovascular diseases (CVDs), heart failure (HF) and hypertension (HTN) among others. Over the last decade, the National Health Statistics Reports (NHSR) have shown a steady and substantial increase in the use of CAM¹ and according to NHSR 4 out of 10 (40%) of US adults interviewed used CAM. This increase is associated with significant out-of-pocket expenses, which according to 2007 National Health Interview Survey (NHIS) resulted in \$33.9 billion out-of-pocket expenses by US adults for visits to CAM practitioners (chiropractors, acupuncturists, massage therapists and others) and for the purchasing of CAM products.² This increase in CAM is possibly the result of mass media and marketing advertisements of a great variety of dietary supplements and herbal products as being effective and safe without any scientific evidence to back their claims.² The NHIS has also estimated that 38.1 million adults made 354.2 million visits to CAM practitioners for an estimated \$11.9 billion out-of-pocket expenses.² Therefore, it is imperative that physicians become aware of the wide variety of dietary supplements and herbal medicines available, as well as becoming familiar with their benefits and risks. Part of the problem is the paucity of scientific data on herbal medicines used in the United States, because they are sold as food supplements and do not require strict

regulations.^{3,4} In a recent epidemiological survey, 36% of participants with CVD stated that they used CAM in the previous 12 months with herbal products being the most common therapy.⁵ Many patients combine CAM with conventional medicine for the treatment of CVD and HTN. Recently, the American Heart Association issued a scientific statement for professionals regarding the use of CAM either alone or in combination with conventional medicine for the treatment of HTN, but did not include the use of herbs and food supplements.⁶ Therefore, this review of selected herbs and food supplements for the treatment of CVD and HTN is intended to serve as a compliment to this statement. For the preparation of this review, a Medline search of the English language literature was performed between 2010 and 2014 restricted to the use of CAM for the treatment of CVD and HTN, and of the 88 abstracts reviewed, 23 pertinent papers were selected and will be discussed in this review together with collateral literature.

REASONS FOR PATIENTS USING CAM

The reasons for patients using CAM either alone or in combination with conventional medicine is their belief in the 'holistic concept' of medicine and a desire for the experience of 'natural therapies' that are believed to have few if any adverse effects compared with conventional therapies and are dissatisfied with conventional treatment due to its ineffectiveness and adverse effects, or to its



¹ Nonvitamin, nonmineral, natural products.

NOTES: Percentage refer to the total out-of-pocket costs in 2007. Totalling individual self-care cost percentages is affected by rounding. Estimates are based on household interviews of a sample of the civilian, noninstitutionalized population.

DATA SOURCE: CDC/NCHS, National Health Interview Survey, 2007.

Figure 1. This figure depicts the percentage of out-of-pocket expenses in billions of dollars for CAM among United States adults ages ≥ 18 years in 2007. Estimates were based on household interviews. National Health Statistics report #18, 2009.²

high costs.⁷⁻⁹ There is also a desire by the patient to have control of his (her) care and the perception that CAM is less authoritative and less complicated than conventional therapy, or their philosophical congruence that alternative therapies are more compatible with their own religious beliefs and philosophies.⁹ In addition, users of alternative medicine have higher education, are older than nonusers and are a part of cultural group with love for the environment and the foreign and exotic. Another probable reason is the fact that alternative medicine is not well regulated by the health authorities and the CAM products are being advertised through the internet as being effective and safe without any scientific data to back up their claims.³ This has led to a significant increase in the purchase of CAM products by the patients with high out-of-pocket expenses as illustrated in Figure 1. The physician's role is to educate such patients about the effectiveness of these remedies and their side effects.^{3,4}

COMMONLY USED CAM PRODUCTS FOR THE TREATMENT OF CVDS AND HTN

There is a growing interest in the United States and worldwide in the use of CAM products for the treatment of CVD and HTN. The most commonly used herbs for the treatment of these diseases are the following and their effects and side effects are summarized in Table 1.

American ginseng (*Panax quinquefolius*)

Several studies have reported the use of this herb for the treatment of atherosclerosis, CVD and HTN. In a recent study by Mucalo *et al.*¹⁰ American ginseng (AG) used in 500 mg capsules thrice daily, reduced the blood pressure (BP) and augmentation index in patients with DM and HTN compared with placebo. Also, a recent study of the Korean ginseng (*Panax ginseng*) by Javanovski *et al.*¹¹ in normal volunteers given in dosages of 400 mg per day showed a significant decrease in central and brachial BP and augmentation index compared with placebo. Also, AG has been shown to be effective in patients with atherosclerosis and vascular stiffness, its effect has been attributed to its direct vasodilatory effect and could be due to the release of nitric oxide from vascular endothelial cells. However, these health benefits are not unique, as previous studies have demonstrated a neutral effect of AG on BP and renal function in patients with DM and HTN.^{12,13} These differences in results between the various studies are difficult to reconcile and they could be due to methodological problems.

St John's wort (*Hypericum perforatum*)

This herb is the best selling herb in the United States and is commonly used for the treatment of depression, anxiety and sleep disorders.^{14,15} It has also been shown to improve glucose tolerance in diabetic patients taking metformin.¹⁶ However, its unsupervised use could result in serious side effects, because it induces the cytochrome CYP3A4 enzyme involved in oxidative metabolism. Therefore, its coadministration with drugs that are metabolized by the CYP3A4 enzyme such as ethinyl estradiol, cyclosporine A and warfarin could significantly decrease their blood levels and their effectiveness,¹⁴ and in patients taking warfarin, it could decrease the prothrombin time and increase the risk of thromboembolism.¹⁴

Mother wort (*Leorunus heterophyllus* sweet)

Mother wort has a long history of use by both the European and Asian traditional medicine for its purported sedative, hypotensive, diuretic and against 'cardiac debility' properties.¹⁴ Also, its administration could lead to decreased platelet aggregation and increase the risk of bleeding.¹⁷

Ginkgo (*Ginkgo biloba*)

This herb is one of the oldest used for its purported beneficial effects in patients with CVD, cerebrovascular disease, peripheral vascular disease, HTN and especially for the treatment of dementia. However, a randomized, placebo-controlled trial did not show any difference in memory improvement between ginkgo- and placebo-treated patients,¹⁸ and treatment with ginkgo has resulted in decreased effectiveness of nifedipine, a drug used in patients with memory loss, possibly through interaction with the cytochrome P450.¹⁴ With respect to *Ginkgo biloba*'s effect on HTN, two systematic reviews showed that it decreased the BP in both hypertensive men and women,^{19,20} but it increased the systolic BP in the normotensive individuals and had no effect in the pre-hypertensive subjects.²⁰

Garlic (*Allium sativum*)

Garlic is purportedly indicated for its cholesterol lowering, antiatherosclerotic and BP lowering properties. Regarding the BP lowering effect of garlic, two systematic reviews and meta-analyses showed that garlic was better than placebo in reducing the BP,^{21,22} whereas its cholesterol-lowering properties were no better than placebo.²³ In their review of the subject, Rasmussen *et al.*²⁴ state that based on the inconsistencies of the effect of

Table 1. Herbs and food supplements used for the treatment of CVD and HTN

Herb/FS	Indication	Effect	Drug interaction	Side effect
Ginseng	CVD, HTN	Equivocal	Antidiabetic, digoxin, warfarin	Hypogly, Dig, tox thrombosis
St John's wort	Depression, DM	Poss. effective	Drugs affecting CYP3A4	Bleeding
Mother wort	Sedative, tachycardia	Poss. effective	Drugs affecting CYP3A4	Bleeding
Ginkgo	Demen., CVD, HTN	Equivocal	Drugs affecting CYP3A4	Bleeding
Garlic	Cholest. HTN, CVD	Poss. effective	Anticoagulants	Bleeding
Hawthorn	CVD, HF, HTN	Poss. effective	Glycosides	Dig. toxicity
Saw palmetto	BPH,	Poss. effective	Warfarin	Bleeding
Danshen	CAD, HTN	Poss. effective	Warfarin	Bleeding
Licorice	Peptic ulcer/Chinese	Poss. effective	Spironolactone	HTN, hypokal
	Food sweetener	No longer used		Cardiac arrhythmias
CoQ10	Cholest. HTN, CVD	Poss. effective	NA	NA
Vitamin E	Cholest. CVD	Poss. effective	NA	NA
Vitamin C	HTN	Poss. effective	NA	NA
Vitamin B	CVD, HF	Poss. effective	NA	NA
Fish oil	CVD, HTN	Poss. effective	NA	NA
L-Arginine, L-Creatinine, Taurine	CVD, HF	Poss. effective	NA	NA

Abbreviations: BPH, benign prostatic hypertrophy; CAD, coronary artery disease; CVD, cardiovascular disease; cholest., cholesterol; demen, dementia; HF, heart failure; HTN, hypertension; poss., possibly; hypokal, hypokalemia; NA, not applicant.

garlic on BP, it is difficult at this time to recommend its use for the treatment of HTN. With respect to drug interactions, the administration of garlic in patients with CVD receiving anticoagulants should be avoided for the danger of bleeding, because of its platelet antiaggregatory effects.²⁵ Regarding the mechanism for the hypotensive action of garlic, this has been attributed to its antioxidant properties, the production of hydrogen sulfide (H₂S), a vasodilator, and the increased production of nitric oxide, also a potent vasodilator.²⁴

Hawthorn (*Crataegus oxyantha*)

Hawthorn extract is commonly used by herbalists for the treatment of angina, HF, bradyarrhythmia and cerebral insufficiency. It purportedly has positive inotropic and vasodilatory effects and reduces the cardiac afterload. In two studies, its addition to conventional treatment of HF has resulted in improvement of the patient's symptoms,^{26,27} whereas another study showed that the addition of hawthorn extracts to conventional treatment of patients with HF did not improve their symptoms and did not stop the progression of HF.²⁸ Other studies have shown that the addition of hawthorn to patients receiving digitalis could increase its toxicity and it should be closely monitored.

Saw palmetto (*Serenoa repens*)

Saw palmetto is a shrub-like palm native to southwestern USA and West Indies and is frequently used for the treatment of benign prostatic hypertrophy, because it inhibits the enzyme 5- α -reductase, a prostatic growth factor,²⁹ but the results are not consistent. The coadministration of saw palmetto with warfarin could increase the risk of bleeding through its inhibitory effects of the enzyme cyclooxygenase.³⁰ Other side effects reported include cholestatic hepatitis and acute pancreatitis.

Danshen (*Salvia miltiorrhiza*)

Danshen is widely used by traditional Chinese medicine as well as by American alternative medicine for the treatment of angina in patients with coronary artery disease for its purported, vasodilatory and platelet antiaggregatory properties through suppression of thromboxane generation.³¹ In addition, danshen is used for the treatment of HTN for its angiotensin converting enzyme (ACE) inhibitory effect, hyperlipidemia for its inhibition of LDL-C

oxidation and for peripheral arterial disease through its vasodilatory action by opening the potassium channels.³² In a review and meta-analysis, danshen was better than isosorbide dinitrate in the treatment of angina.³³ Administration of danshen decreases the elimination of warfarin and could increase the risk of bleeding.

Licorice (glycyrrhizic acid)

Licorice is a US Food and Drug Administration approved food supplement used in many candy like products without strict regulations to prevent toxicity from overconsumption. It is, therefore, necessary that the public become aware of some of the serious side effects associated with increased licorice consumption.³⁴ Increased consumption of licorice in the form of licorice lollies could lead to a syndrome of pseudoaldosteronism with increased BP, hypokalemia, metabolic alkalosis and serious cardiac arrhythmias.^{35,36} Licorice inhibits the cortisol-converting enzyme 11- β -dehydrogenase and could lead to mineralocorticoid excess with increased potassium loss from the distal renal tubule resulting in severe hypokalemia and serious cardiac arrhythmias.³⁷

DIETARY SUPPLEMENTS

Several dietary supplements are used by people in the United States and elsewhere for their purported several health benefits.

Coenzyme Q10 (ubiquinone)

Coenzyme Q10 (CoQ10) is a naturally occurring fat-soluble quinone and it is found in high concentrations in the mitochondria of living organisms. It is an electron carrier for the respiratory transport chain and has an important function in cell membrane stabilization and in its reduced form serves as an antioxidant. Its name, CoQ10, is derived from the 10 isoprenoid units that it has in the side chain in humans. A number of clinical trials indicate that it may have cardioprotective effects. A placebo-controlled trial of 144 subjects with coronary artery disease showed that CoQ10 at 120 mg per day was better than placebo in reducing the angina attacks and the incidence of arrhythmias (9.5 vs 28.1% and 9.5 vs 25.3%, $P < 0.001$), respectively.³⁸ CoQ10 has also been used for the treatment of HF, but the data are not consistent. In one study of 641 patients, mean age 67 years with chronic HF (NYHA classes III–IV) treated with either placebo or CoQ10 2 mg kg⁻¹ per day for 2 years, the number of hospitalizations and the episodes of

pulmonary edema was lower in the CoQ10-treated group than the placebo-treated group.³⁹ However, two subsequent studies of patients with HF treated with CoQ10 100 mg per day and 33 mg three times daily showed either equivocal or neutral results.^{40,41} The beneficial effects of CoQ10 have been attributed to its antioxidant properties, as patients with HF exhibit high oxidative stress, which is detrimental to organ function. CoQ10 is also being promoted for the treatment of myalgias in patients taking statins due to false impression that they lower the muscular CoQ10 levels.⁴² However, a recent randomized study demonstrated that in such cases, administration of CoQ10 60 mg twice daily for 3 months, was ineffective and not better than placebo.⁴³ Considering the safety of CoQ10, it appears to be quite safe even in daily doses of 2400 mg, with the exception of mild gastrointestinal upset.⁴⁴

Multivitamins

Multivitamins are the most widely used food supplements throughout the world, and there has been a growing interest in the potential role of multivitamins in reducing the risk of chronic diseases including CVD, HTN, cancer and brain dysfunction.

Vitamin E (tocopherol)

Vitamin E is a fat-soluble vitamin found in vegetable oils, nuts, seeds, whole grains and egg yolks and its use prevents the oxidation of low-density lipoprotein cholesterol, smooth muscle cell proliferation and platelet aggregation and adhesion. For this reason, it is used for the primary and secondary prevention of CVD. Regarding primary prevention, several observational studies including the Health Professionals Follow-Up Study of 39 910 male subjects ages 40–75 years and the Nurses' Health Study of 87 245 women showed that daily use of vitamin E was associated with a 37% and 41% decreased risk of CVD in men and women, respectively.^{45,46} However, with respect to the secondary CVD prevention, several randomized trials have yielded mixed results. In the Cambridge Heart AntiOxidant Study (CHAOS), vitamin E supplementation (400–800 IU per day) decreased the non-fatal myocardial infarction by 77%, but not the cardiovascular and all-cause mortality.⁴⁷ Also, the Alpha-Tocopherol Beta-Carotene (ABCT) Cancer Prevention Study of 29 133 male Finnish smokers did not show any difference in the major coronary events among 1862 men with a previous myocardial infarction treated with vitamin E, beta-carotene or both compared with placebo-treated subjects.⁴⁸

Vitamin C (ascorbic acid)

Vitamin C is an antioxidant and among its other functions has been shown to decrease BP. In a randomized, double-blind, placebo-controlled, crossover study, 39 hypertensive patients were randomized to receive either vitamin C 500 mg per day or placebo, which were added to their background antihypertensive treatment and were followed for 1 year.⁴⁹ Vitamin C supplementation resulted in greater BP reduction than placebo ($P < 0.02$). The mechanism by which Vitamin C reduces BP is not clear, but it has been attributed to its antioxidant properties and the regeneration of vascular endothelial cell nitric oxide leading to arterial vasodilation.⁵⁰

B complex vitamins (B1 (thiamine), B2 (riboflavin) and B6 (pyridoxin))

These substances perform many functions in the body and could benefit patients with CVD and HF. Patients with chronic HF have been found to have decreased levels of these vitamins ranging 33%, 27% and 38% for B1, B2 and B6, respectively,⁵¹ which is due to oxidative stress, but not to the use of diuretics. On the basis of these findings, it has been hypothesized that their

supplementation could help improve the HF of these patients and this has been demonstrated in clinical studies.^{51,52}

Fish oil

Fish oil contains the highly unsaturated n-3 fatty acids, eicosapentaenoic and docosahexanoic acids, which appear to have antithrombotic, antiarrhythmic and antihypertensive effects. Fish oil consumption has also been shown to have cardioprotective and antihyperlipidemic effects. In the Physicians Health Study of 20 551 US male physicians, fish oil consumption was associated with reduced cardiovascular mortality.⁵³ Regarding its lipid-lowering effects, a review of 36 crossover and 20 parallel design studies showed that fish oil consumption resulted in mixed results with a decrease of very-low-density lipoprotein cholesterol, a slight increase in low-density lipoprotein cholesterol and no change in high-density lipoprotein cholesterol.⁵⁴ With respect to BP reduction, 31 placebo-controlled trials in 1356 subjects showed that fish oil consumption was associated with a 3.0/1.5 mm Hg decrease in BP.⁵⁵ Regarding its coronary artery restenosis protective effects after an angioplasty, the results are mixed.⁵⁶ Fish oil consumption is free of side effects with the exception of mild gastrointestinal upset.

L-arginine, L-creatinine, creatine and taurine

These substances are involved in many biological functions of the body and their deficiency could have adverse cardiovascular effects. Patients with chronic HF have been found to have depleted stores of these substances and their repletion has the potential to improve their condition. A systematic review and meta-analysis of 13 controlled trials (3629 patients) showed that L-carnitine supplementation was associated with significant secondary prevention of CVD.⁵⁷ These substances are all practically devoid of side effects.

DISCUSSION

From the data presented, it becomes clear that CAM therapy is used by a lot of people in the United States and other countries for the treatment of various health conditions with large out-of-pocket expenses and without any sure evidence about its effectiveness. This is due to the lack of scientific information regarding the effectiveness and safety of CAM and CAM products. The best way to document the effectiveness and safety of CAM products is by randomized, placebo-controlled trials. However, such trials are either lacking or have small number of subjects, have flaws in their design and have not been published in reputable medical journals. The CAM products are, usually, promoted through the internet or television as being safe and effective, because there is no regulatory oversight. Because of this lack of oversight, there are about 30 000 dietary supplements sold in the United States with additional 1000 new supplements being introduced per year.¹⁴ A new dietary supplement or new formulation can be introduced and marketed overnight without restriction by the US Food and Drug Administration, despite the fact that they contain new and experimental herbal ingredients. The Dietary Supplement Health and Education Act 1994 provides some oversight, but still allows untested herbal products to be sold on the market without safety testing.⁵⁸ This lack of quality control could lead to serious health problems through contamination with heavy metals and adulteration with pharmaceuticals and prohibited animal and plant ingredients.⁵⁹ In addition, unethical marketing techniques could add to this problem. The general public regards the herbal products as 'natural' and has the false impression that they are safe. The biggest consumers of CAM products are usually white elderly female subjects, educated and well off. Health care professionals should question their patients about taking any herb products, be familiar with these products

and closely evaluate any publication biases about these products and advise their patients accordingly. There are certain CAM products like garlic, CoQ10, fish oil and multivitamins, which may not be very effective in lowering the BP, serum cholesterol or not preventing CVD and HF, but they are safe and can be taken together with conventional medicines, although the evidence for benefit is neither strong nor consistent.⁶⁰ However, there are others such as ginseng, St John's wort, *Ginkgo biloba*, hawthorn, saw palmetto, danshen and licorice that can cause serious adverse effects through drug interactions or by themselves. Therefore, it is imperative that the health providers become familiar with these products and research diligently their benefits and harms and advise their patients accordingly. In addition, there is a need for definitive research studies on the potential benefits and risks of the various herbs, and, specifically, their adverse events and interactions with drugs of conventional medicine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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