

# Herbs and Alternative Therapies: Relevance to Hypertension and Cardiovascular Diseases

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Herbal remedies, supplements, and alternative therapeutic items are used by many patients with hypertension and cardiovascular diseases. Scientific knowledge about their efficacy and safety is lacking, and unfortunately, physicians are frequently not aware that patients are using these non-traditional forms of medical care. Patients may anticipate physicians' disapproval of their use, or not realize that it is important for the physician to know what they are taking. Therefore, it is imperative that patients are asked nonjudgmental questions about current and past use of herbals and alternative therapies. Even when physicians are aware of such use, they feel poorly trained to identify the constituents and effects. Although many such therapies are innocuous, several herbal or alternative therapeutic items can significantly elevate blood pressure or cause interactions with cardiovascular drugs. Practitioners in cardiovascular medicine should be competent and know current scientific evidence for the benefits and adverse effects of herbal supplements and provide patients reasonable advice. In this brief article, we review the epidemiology of alternative therapy use, and select several important herbal or other supplements that patients with hypertension and cardiovascular diseases may be taking. We discuss the therapies considered biological in nature as opposed to mind-body interventions or manipulative body or energy therapies.

## Introduction

Herbal remedies and alternative therapies are widely used by patients in the United States. Various studies have reported from 3% to 93% use of herbal products [1••]. Many of these therapies are considered biological in nature as opposed to mind-body interventions or manipulative body or energy therapies [2]. When questions about the use of complementary therapies were included in the

Behavioral Risk Factor Surveillance System in Michigan, it was found that 21% of adults reported using herbs in 2001 [3]. Other surveys in Minnesota and Mississippi found that 61% and 71%, respectively, of respondents had used an herbal of some sort in the preceding year [4,5]. Although estimates of adults using alternative therapies varies with differences in survey methodology and the population being studied, it is clear that herbs and alternative therapies are used by a growing segment of the population. Also, increasing amounts of consumer money is being spent on alternative therapies. In the White House Commission Report on Complementary and Alternative Medicine, it was estimated that \$17 billion was spent in 2000 on dietary supplements [6••]. Recognizing the importance of such care, a new National Institutes of Health Center on complementary medicine (National Center for Complimentary and Alternative Medicine) has been established to fund the study of safety and efficacy as well as interactions with conventional therapies. Therefore, complimentary medicine has come to center stage, and physicians in all specialties need to be aware of its strengths and limitations.

Demographic predictors of alternative medicine use are not reliably studied, with most reports suggesting that people with higher incomes used it more [7–9], whereas other reports suggest lower income was associated with more use [9]. The most frequently cited reasons for using these therapies included recommendations from friends or coworkers, a desire to avoid the side effects of conventional treatments, or failure of conventional treatments to cure a problem [10,11]. However, at least in one survey, dissatisfaction with conventional health care was not the reason for seeking out alternative therapies [9]. Therefore, current predictors of those likely to use alternative therapies is limited, and, in fact, all patients attending a medical care setting should be asked about supplements and herbs, regardless of socioeconomic status.

It is particularly important that herbal use be discovered in patients with hypertension and cardiovascular diseases. Hypertension is a very prevalent problem, with approximately 65 million American hypertensive adults in 1999 and 2000. The total hypertension prevalence rate is 31.3%, with most patients taking multiple antihyper-

tensive drugs [12]. Furthermore, there are now at least six classes of antihypertensive drugs with their unique mechanisms of action and potential for interactions with drugs and supplements or herbals.

In this brief review, we focus on benefits and adverse effects, and known and potential herb–drug interactions of commonly used herbs in hypertensive patients. Although the focus is on agents affecting the treatment of hypertension, reference is made to other cardiovascular drugs that are commonly taken by hypertensive patients.

## Regulation of Dietary and Herbal Supplements

In the United States, the Food and Drug Administration (FDA) classifies herbs, supplements, and natural products as dietary supplements. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), manufacturers are allowed to distribute dietary supplements from state to state, as long as no claims are made regarding a specific disease [13••]. There is no responsibility of the manufacturer to prove safety or efficacy before sales. This has led to a largely unregulated growth in the herbal therapy market. However, when evidence accumulates to suggest a danger to the population, items may be removed from marketing. A recent example of this is the FDA ban on the sale of ephedra-containing substances in 2004 after it was linked to 155 deaths and dozens of heart attacks, strokes, and arrhythmias. The FDA indicated that the ephedra-containing substances posed “an unreasonable risk or illness or injury” [14].

## History Taking

Because many patients do not consider supplements, herbs, or alternative treatments to be relevant to medical practice, they may either intentionally or unintentionally not tell the physician about their use. This makes it very important to ask patients specifically about alternative medicine use in a nonjudgmental way, after establishing patient confidence. Inquiry should not only include items bought over the counter but also items from another country or bought over the Internet or through mail order. An appreciation of the cultural background and beliefs of the patient regarding herbal dietary supplements may help in establishing trust with the patient. Such history taking is also important in the hypertension or cardiology clinic.

## Specific Herbs and Dietary Supplements

### Garlic

A member of the lily family, garlic is one of the world’s most ancient “medicines,” and is commonly used by hypertensive patients. Proponents of garlic use point to its anti-platelet, anti-atherosclerosis, possible cholesterol lowering, and profibrinolytic effects [15]. Garlic increases nitric oxide synthase activity intracellularly [16], and also

reduces angiotensin-converting enzyme [17], suggesting a possible role in lowering blood pressure. However, research into the potential benefit of garlic has been hampered by lack of standardization and detailed definition of the active ingredients.

The effect of garlic on lipids has been the subject of many studies and appears consistent in showing a small lowering in total cholesterol over a 3-month period [18]. If one includes all types of garlic preparations studied, data suggest that reductions in total cholesterol averaged 1 to 17 mg/dL at 1 month and 12 to 25 mg/dL at 3 months. There is a tendency for standardized preparations to give a larger reduction in total cholesterol [18]. Although these reductions are small, they may translate into important reductions in atherosclerotic vascular disease if applied in a large population.

High-quality, adequately powered studies examining the effect of garlic on blood pressure are lacking. Thus, the available studies have given varied results. The general consensus has been that garlic may have a small effect on blood pressure [19]. A recent randomized, controlled trial of the effect of garlic on blood pressure [20] in healthy adults could not demonstrate any effect. However, garlic may still have a small clinically important effect. All studies on the effect of garlic measured blood pressure using conventional office readings, a method that has much variability, and use of ambulatory blood pressure monitoring is preferred. Garlic and its products have generally been free of major side effects or drug interactions, although some care should be exercised in persons taking warfarin or other anticoagulants. In addition, a recent report suggests that a garlic preparation may interact with siquinavir and lower serum concentrations [21]. In general, the intake of garlic is likely to be safe, but its therapeutic benefits remain difficult to prove.

### St. John’s wort

St. John’s wort is the derivative of *Hypericum perforatum*, a long-living plant with yellow flowers. This plant has been taken for centuries to treat mental disorders as well as nerve pain. St. John’s wort is marketed as capsules, teas, or oils. The plant derivative contains several active ingredients with a variety of effects on neurochemical signals in the central nervous system. Its components can inhibit the uptake of serotonin, noradrenaline, and dopamine. It also weakly inhibits monoamine oxidase. Data from 35 double-blind, randomized trials showed that St. John’s wort is well tolerated and more effective than placebo, and it is at least as effective as standard antidepressants, with fewer side effects in the treatment of mild depression [22,23]. However, it was no more effective for treating major depression of moderate severity than was placebo [24], although this study may have been underpowered. Although it may have some therapeutic potential, clinicians must be aware of its large potential for adverse effects and drug interactions (Table 1).

**Table 1. Possible drug interactions of St. John's wort with cardiovascular drugs**

Drug	Effect	Clinical consequence
Warfarin	Decreased anticoagulant effect	Thromboembolism
Digoxin	Reduced concentration	Worsening of atrial fibrillation or congestive heart failure
Simvastatin	Decreased concentration	Increased cholesterol
Calcium channel blockers	Decreased bioavailability	Increased blood pressure and heart rate or worsening angina

Two case reports suggest that St. John's wort may induce hypertension [25,26]. The clinical features ranged from moderate to severe hypertension that resolved after discontinuing the drug. No definite temporal association has been established thus far.

Several cardiovascular and noncardiovascular drugs may have an interaction with St. John's wort [27•,28–37]. The available data indicate that more than short-term exposure to St John's wort induces CYP3A4 and P-glycoprotein. In a carefully done study in normal volunteers, 300 mg three times daily of St. John's wort reduced the area under the curve as well and increased clearance of alprazolam, apparently due to CYP3A4 induction [27•]. Data from human studies and case reports indicate that St John's wort decreased the blood concentrations of digoxin [28], simvastatin [29], warfarin [30], and possibly calcium channel blockers [31]. St. John's Wort reduces serum cyclosporine [32] and tacrolimus levels [33], and several cases of solid organ transplant rejection have been reported [34,35].

It is important for the practitioner to remember that the metabolism of other drugs can be affected by St. John's wort. These include protease inhibitors [36], reverse transcriptase inhibitors [37], and oral contraceptives [38]. Because of the neurochemical effects, concurrent use with selective serotonin re-uptake inhibitors should be avoided.

### Ginseng

*Panax ginseng* (Asian) and *Panax quinquefolius ginseng* (North American) are widely used for a variety of ailments and to promote health. The active ingredients may include ginsenoside and panaxoside, both steroid nucleus-based glycosides. Therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, improvement of cognitive and physical performance, and sexual function.

Despite its wide use, the effects of ginseng on blood pressure and heart rate are not well studied. In one study, the use of red ginseng for 8 weeks (4.5 g/d) in 26 subjects with essential hypertension was associated with a decrease in 24-hour mean systolic blood pressure ( $P = 0.03$ ) but not in diastolic blood pressure ( $P = 0.17$ ) [39]. In another study [40], in which blood pressure was measured using office methods, diastolic blood pressure fell from  $75 \pm 5$  mm Hg at baseline to  $70 \pm 6$  mm Hg at the same time point ( $P = 0.02$ ). In another randomized, double-blind clinical trial of 20 elderly hypertensive persons, no significant difference in blood pressure control was observed in

both treatment groups. [41]. Hypotensive effects have been attributed to enhanced synthesis of nitric oxide [42]. Despite this possible mechanism to lower blood pressure, current research shows no convincing evidence that ginseng lowers blood pressure.

In contrast, abuse of ginseng has been reported to cause hypertension and behavioral changes. In an observational study of 133 chronic ginseng users, 22 developed elevated blood pressure, especially with preparations containing Siberian ginseng [43].

Ginseng may also have important drug interactions. It has been reported that ginseng may reduce the effectiveness of warfarin and lead to subtherapeutic anticoagulation [44]. However, another study could not show a change in the pharmacokinetics of warfarin when ginseng was taken [30]. Despite these different conclusions, it would be wise to monitor the anticoagulant effect of warfarin closely in patients starting or stopping ginseng preparations.

### Licorice

True licorice candy contains an extract from the root of the licorice plant, *Glycyrrhiza glabra*. This licorice root has been used since ancient times to flavor and sweeten candies, teas, throat lozenges, pharmaceuticals, and other products. Today most "licorice" candies available in the United States do not contain licorice. It is also marketed for gastritis and upper respiratory tract infections.

The active constituents of licorice—glycyrrhizic acid, glycyrrhetic acid, and several related compounds—are associated with a form of pseudoaldosteronism manifesting as weight gain, hypertension, hypokalemia, and metabolic alkalosis [45]. Biochemically, the patient has low aldosterone and plasma renin activity, increased cortisol half-life, and reduced cortisone levels. It inhibits  $11\beta$ -hydroxysteroid dehydrogenase and, hence, increases levels of cortisol that combine with the mineralocorticoid receptor (an acquired apparent mineralocorticoid excess) [46]. There are several case reports in literature that link licorice to hypertensive encephalopathy [47], dilated cardiomyopathy [48], hypokalemic paralysis [49], and chronic refractory hypertension [50].

Susceptibility to licorice varies greatly. Subjects with underlying hypertension and women may be more sensitive [51]. Adverse effects usually reverse on stopping the herb and replenishing potassium, although it takes some time, owing to suppression of the renin-angiotensin-aldosterone axis and large volume of distribution.

**Table 2. Cardiovascular drugs that may be affected by the grapefruit interaction**

Drug	Adverse effect
Atorvastatin, lovastatin, simvastatin	Increased risk for rhabdomyolysis
Felodipine, nicardipine, nifedipine, nisoldipine, nitrendipine	Increased risk for hypotension
Losartan	Increased risk for hypotension*
Sildenafil, tadalafil, verdenafil	Vasodilation and hypotension
Oral amiodarone	Arrhythmias

\*Several parameters in pharmacokinetics are altered, making it difficult to translate into clinical effect.

### Yohimbine

Yohimbine is a prescription drug that has long been known to be present in the bark of the tree *Pausinystalia yohimbe*. Although it is not available as an over-the-counter product, it can be found in herbal supplements and is promoted as treatment for erectile dysfunction.

Yohimbine is a presynaptic alpha 2-adrenergic antagonist that increases central sympathetic outflow [52] and possibly inhibits monoamine oxidase. It has been fairly well documented that yohimbine, especially in higher doses, can increase blood pressure in humans and should be used with caution, if at all, in hypertensive patients [53]. The pressor effect of yohimbine is seen at low (10 mg) and higher doses (22 mg) [54]. One case report implicates yohimbine as the cause of a hypertensive emergency in a 63-year-old man taking yohimbine for erectile dysfunction [55]. Yohimbine has been evaluated as a treatment of orthostatic hypotension due to autonomic failure [56] and has been successfully used in some cases as adjuvant therapy. The drug should not be used in patients taking tricyclic antidepressants. Other adverse reactions include mania, bronchospasm, agranulocytosis, Raynaud's phenomenon, and a systemic lupus-like syndrome.

Although the studies of yohimbine have been small and of generally suboptimal quality, it appears to be better than placebo in treatment of erectile dysfunction [57]. However, it is very important to weigh risk versus benefit of the drug.

### Other Drug-Drug Interactions

Grapefruit juice, a food and not an herbal in the way used in this article, is also of concern to the hypertension physician because of its effects on the metabolism of many cardiovascular drugs [58•]. By inhibiting intestinal CYP3A, and affecting organic anion-transporting polypeptides, it can increase the bioavailability of many substrates of CYP3A, including immunosuppressive drugs, certain 3-hydroxy-3-methylglutaryl coenzyme A (HMG-

CoA) reductase inhibitors, and most dihydropyridine calcium channel blockers. The effect is much less pronounced in the highly bioavailable drugs, amlodipine and nifedipine [59]. This interaction is likely to be clinically significant when high doses of a drug are being given and grapefruit juice is co-administered. A list of potential interactions is shown in Table 2. Some cardiovascular drugs appear to have little or no interaction with grapefruit juice. These include carvedilol, digoxin, diltiazem, warfarin, fluvastatin, pravastatin, and rosuvastatin.

### Conclusions

It is essential for all physicians to obtain a history of any herbal, dietary, or supplement use from patients. Specific questioning is needed about grapefruit juice consumption. Written or electronic reference source for immediate consultation is imperative to give appropriate evidence-based information to the patient. Case reports and case series of hypertensive emergencies and serious cardiovascular complications illustrate the serious adverse effects that may occur. More vigilance is needed in monitoring the use of herbals, supplements, and other nontraditional medications in the hypertensive population.

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The medications involved in drug-grapefruit juice interactions are discussed, and the clinical implications of these interactions are addressed.