Dietary supplements and herbal remedies effective in the treatment of hypertension

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Hypertension is a growing problem that remains difficult to treat despite conventional medication. Alternative medicine, specifically dietary supplements, have shown antihypertensive potential, and may prove to be a part of the hypertension solution. Coenzyme Q_{10} is a powerful antioxidant with no known side effects and many studies supporting its hypotensive effect. Potassium works by counteracting the hypertensive effect of salt, and interacting with norepinephrine, but has many drug interactions and is contraindicated in patients with impaired kidney function. Magnesium interacts with angiotensin II and calcium to effectively lower blood pressure with few side effects and drug interactions in many robust human studies. In contrast, the antioxidants vitamins C and E have less evidence supporting their efficacy, and significant side effects and drug interactions that should preclude their use as antihypertensives until safety and efficacy are established. Garlic has the most extensive range of hypotensive mechanisms, including antioxidative, and calcium and angiotensin interactions, although patients should be cautioned against using asparin and other anti-thrombotics, which have harmful interactions with garlic. Hawthorn is a relatively recent therapy for hypertension, and more research is warranted before it gains status as an antihypertensive option. In addition to increasing physician knowledge and acceptance of alternative medicine, doctors should consider it as an adjunctive treatment to conventional medicine. **Considering the prevalence of hypertension and the efficacy of standard hypertension treatments, dietary supplements could prove to substantially impact and prolong the lives of many individuals.**

Key words: coenzyme Q_{10}, garlic, hawthorn, hypertension, magnesium, potassium, vitamin C, vitamin E

Introduction

Hypertension, or high blood pressure, affects 27% of North American adults, and approximately 50 million individuals in the USA alone [1]. The lifetime risk of developing hypertension approaches 90% among adults older than 50 [2]. Hypertension is most often defined as systolic blood pressure >140 mm Hg, and/or diastolic blood pressure >90 mm Hg [1]. Not only is hypertension an indicator of kidney disease, it is a major risk factor for heart disease and stroke, which are the first and third leading causes of death in the USA respectively [3]. Essential- or primary hypertension is a general term defined as high blood pressure with no readily identifiable cause, making it difficult to treat. Secondary hypertension is high blood pressure with an identifiable cause, which generally makes it more treatable or reversible [4]. Unfortunately, since 90% of all cases of hypertension are essential, treatment is very difficult [4]. Currently, only 27% of cases of hypertension among Americans are successfully controlled with medication. Because of this, people are now seeking alternate forms of treatment, such as alternative medicine, to control their hypertension [4].

An estimated one third of adults in the USA are currently using some form of alternative medicine for a variety of ailments [5]. Alternative medicine is especially attractive because it follows many people's values, beliefs, and philosophical orientations towards health and life [6]. Alternative health care comprises of those practices "neither taught widely in U.S. medical schools nor generally available in U.S. hospitals" [7]. Alternative medicine includes chiropractoric, acupuncture, massage, herbal and mind-body therapies, as well as over-the-counter nutritional and dietary supplements [8]. Recent public interest has led to many clinical trials examining the efficacy of alternative medicine [5]. However, doctors are largely unaware of alternative medicine and its prevalence since most patients do not volunteer use of alternate

medicine, largely because they feel their physicians would disapprove [9]. Furthermore, most doctors fail to enquire about alternate treatments utilized by patients [9].

Dietary supplementation was used by 25% of people in the USA in 2002, and includes vitamins, minerals, proteins, amino acids, botanicals, extracts, fibers, and compounds not generally recognized as food [8]. Nutrient supplements include compounds required by the body at all times such as vitamins, minerals, proteins, and amino acids, whereas herbal remedies are medicinal plant compounds that can be beneficial to, but not normally necessary for the body to function [8]. The nutrient supplements coenzyme Q_{10} (CoQ_{10}), potassium (K), magnesium (Mg), vitamin C, and vitamin E are currently used or being explored as antihypertensives [10-14]. Herbal remedies have been used for thousands of years across all cultures [7]. Although hypertension is a relatively modern problem, herbal treatments such as garlic and hawthorn have proven effective in lowering blood pressure [15,16].

With the abundance of available alternative ways to manage hypertension, this review attempts to identify and investigate some of the most beneficial and clinically proven alternative treatments.

Nutrient Supplements

COENZYME Q_{10} (CoQ_{10})

Coenzyme Q_{10}, also known as ubiquinone, is produced by the body and supplemented naturally with meat [17]. A mobile electron carrier, CoQ_{10} is an essential cofactor for adenosine triphospate (ATP) production in the mitochondrial oxidative phosphorylation pathway [18]. Additionally, the reduced form of the enzyme is the only endogenously synthesized lipophilic antioxidant in humans [19].

Coenzyme Q_{10} deficiency is a symptom of cardiovascular disorder, and correlates with increased blood pressure [18]. Coenzyme Q_{10}'s hypotensive action may be through its antioxidant properties, since oxidative stress is known to occur in and worsen hypertension [10]. Oxidative stress impairs the ability of the endothelium to induce nitric oxide mediated relaxation of underlying smooth muscle, causing vasoconstriction and an increase in blood pressure [10]. Coenzyme Q_{10} acts both directly and indirectly as an antioxidant by attacking oxidative molecules while also inhibiting the creation, or peroxidation, of new oxidants [17,20].

Efficacy of CoQ_{10} supplementation has been very encouraging in many large-scale animal and human experiments [17,18]]. A recent meta-analysis of 12 clinical trials including 362 patients concluded that CoQ_{10} has the potential to significantly lower both systolic and diastolic blood pressure in hypertensive patients [10]. Pooled mean estimates of systolic blood pressure (SBP) decreased by 14.5 mm Hg in the treatment group compared to the placebo. Pooled mean estimates of diastolic blood pressure (DBP) decreased by 6.3 mm Hg more in the treatment group than the placebo group. This effect was consistent between randomized controlled, crossover, and open-label studies. Formulation type may explain the variation in efficacy between trials, since there is significant variation in the bioavailability of CoQ_{10} supplements among the many existing formulations [21].

Bioavailability, the amount of a drug utilized by the body, depends on drug metabolism and absorption [21]. Coenzyme Q_{10} is a large lipophilic compound, and thus is insoluble in the blood and difficult to direct to and absorb at target tissues. Although oil-based and powder-capsule formulations exist, nanoparticle formulations have recently shown promise towards delivering therapeutic doses of CoQ_{10} in rat models [21]. Typical doses range from 100 to 225 mg/day [18].

Based on a large-scale randomized, double-blinded trial including over 300 patients, CoQ_{10} is safe and has no serious side effects [10]. Cholesterol-lowering medications known as statins may interact with endogenous CoQ_{10}, since cholesterol and CoQ_{10} are synthesized through pathway that statins inhibit [22]. Plasma CoQ_{10} concentrations decrease as much as 54% following statin therapy, warranting an increase in CoQ_{10} supplement dosage [22].

POTASSIUM

Humans evolved to function efficiently with the low-sodium, high-potassium diet we consumed for the first 99.8% of our time on Earth [23]. Potassium depletion is known to cause hypertension, based on several animal and human studies [24-26]. Essential hypertension correlates strongly with salt intake, and one of potassium's hypotensive mechanisms appears to be counteracting the negative effects of salt [24]. Potassium increases sodium excretion, which decreases extracellular fluid volume, alters the pressure-sodium excretion relationship, decreases intracellular sodium concentrations, and inhibits the release of a circulating Na+, K+-ATPase inhibitor [11]. Turnover rates of norepinephrine, a vasocontrictor, are accelerated in rats with high salt intake, and supplementation with potassium returns norepinephrine levels to normal [11]. Therefore, potassium's hypotensive mechanism is likely to influence sodium excretion and influencing renal sympathetic activity [25].

In humans, as potassium intake increases, blood pressure decreases [27-29]. Likewise, increasing potassium intake in rats with sodium-induced hypertension lowers blood pressure and improves survival [30]. A review of several studies showed that individuals with essential hypertension, or high blood pressure with no readily identifiable cause, had significantly lower SBP and DBP's after consuming high potassium diets with normal sodium intake [11].

Similarly, a meta-regression of 20 randomized, placebo-controlled trials revealed SBP and DBP decreases of 2.42 mm Hg and 1.57 mm Hg respectively after 4 weeks of treatment [28]. A more recent review of five randomized, parallel or crossover, placebo-controlled trials found clinically significant decreases of 11.2 mm Hg in SBP and 5.0 mm Hg in DBP compared to controls [31]. Although the reason is unknown, African Americans seem to have a particularly high sensitivity to the blood pressure lowering effects of potassium [32].

Supplement doses range from 1.3-3.3 g/d [29]. However, a recent study recommends an intake level of 4.7 g/d, which corresponds to the average potassium intake in clinical trails and the recommendations by the Institute of Medicine committee [33]. Adult men and women in America typically consume between 2.9 to 3.2 g and 2.1 to 3.2 mg of potassium per day respectively [33]. Because potassium is easily obtained through diet rather than medication, dietary intake through fruits and vegetables is the preferred strategy to increase potassium levels [34,35]. In a high fruit low salt trial, the groups that increased fruit and vegetable consumption had decreases in blood pressure [34,35]. Although excess potassium is readily excreted in the urine, and thus normally poses no risk, excess potassium may cause adverse cardiac effects like arrhythmias for those with impaired kidney function [36]. Diabetes, chronic renal insufficiency, end-stage kidney disease, severe heart failure, adrenal insufficiencies, and old age all increase the risk of decreased potassium excretion. Furthermore, ACE inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory agents, and potassium-sparing diuretics substantially impair potassium excretion and thus are contraindications to potassium supplementation [36].

MAGNESIUM

Magnesium is an essential cofactor in protein metabolism, and also plays a role in insulin-mediated glucose uptake, vascular tone, and blood pressure homeostasis [37]. Magnesium deficiency corresponds to hypertension, although very few randomized, placebo-controlled trials about the efficacy of magnesium supplementation exist [37,38].

The antihypertensive action of magnesium is through the relaxation of the smooth muscles in blood vessels, inhibition of platelet calcium uptake, inhibition of intracellular free calcium uptake, and decrease in intracellular free calcium concentrations [4,39]. In addition, magnesium may diminish the vasoconstrictive actions of angiotensin II [40].

Magnesium is effective in preventing blood pressure elevation in hypertensive rats compared to controls [4]. A randomized, placebo-controlled study including 82 diabetic individuals showed a significant inverse relationship between increase in serum magnesium and decrease in SBP and DBP at four months [12]. Difference in change of SBP and DBP were –16.1 and –7.9 more than the placebo. A meta-analysis of 20 randomized trials including 2200 patients found a net change of –0.6 mm Hg in systolic blood pressure and –0.8 mm Hg in diastolic blood pressure compared to controls, with doses ranging from 10 to 40 mM of magnesium per day [41]. For each 10 mM/day increase in dosage, a 4.3 mm Hg reduction of systolic blood pressure ($P<0.001$) and of 2.3 mm Hg reduction of diastolic blood pressure ($P = 0.09$) were observed, indicating the dose-dependence of magnesium's antihypertensive action [41].

Tolerance of magnesium was good in all trials, with no serious adverse effects, events, or participant withdrawals due to side effects [39,41-43]. No cases of treatment withdrawal due to side effects [12,39,41,43]. Drug interactions include Captopril, which increases magnesium levels, causing a synergistic effect and resulting in lower doses of magnesium needed to achieve therapeutic effects [44]

VITAMIN C

Vitamin C, ascorbic acid, impacts defective endothelium-dependent vasodilation [45]. Although the mechanism is not fully known, ascorbic acid may function as an antioxidant to either enhance the synthesis or prevent the breakdown of nitric oxide by free radicals generated by salt [45]. Vitamin C counteracts the norepinephrine-sensitivity of vascular smooth muscle cells that frequently accompanies hypertension and causes vasoconstriction [46].

Blood pressure of rats given salt and vitamin C was significantly lower than the salt only treatment group after six weeks ($P<0.05$) [47]. Therefore, long-term vitamin C supplementation may reduce the degree of hypertension induced by salt [47]. Another study employed a diet deficient in vitamin c, followed by a diet rich in vitamin C- each for 30 days- and found plasma vitamin C was inversely related to diastolic blood pressure, which remained after multivariate analysis to control for relevant factors [48]. In a randomized, double-blind, placebo-controlled study, vitamin C supplementation lowered blood pressure in hypertensive patients [13]. Mean systolic blood pressure decreased from 155 mm Hg to 142 mm Hg after 30 days in the ascorbate group [13]. Mean diastolic blood pressure decreased but was not significant [13]. No large-scale meta-analyses or reviews assessing the efficacy of vitamin C are currently available.

The recommended daily intake of vitamin C is 60 mg, although supplementation is tolerable up to 2000 mg/d [49]. Increased risk of kidney stones exists in patients with chronic kidney disease, but there is no association between high doses of vitamin C and risk of stone formation in individuals without kidney disease [50]. Dose-related adverse events include gastrointestinal discomfort, headaches, fatigue, and insomnia [51]. Drug interactions include iron,

acetaminophen, anticoagulants, vitamin B_{12}, copper, aluminum-containing antacids, and non-steroidal anti-inflammatories [8].

VITAMIN E

Vitamin E, discovered in vegetable oil by Evans and Bishop in 1922, was first called "factor X", and was found to cure sterility in rats [52]. Vitamin E is common in foods such as cereals and oils, and inadequate levels of the vitamin are rare [53]. The antioxidant effects of vitamin E have made it a candidate for the treatment of hypertension and cardiovascular disease [54]. Although findings from many clinical trials exist, the efficacy of vitamin E is largely inconsistent and concerns exist about uncertainties of possible side effects and interactions [55].

Although the certainty of vitamin E's hypotensive effect is disputable, several confirmed mechanisms suggest a therapeutic action [54]. Through its antioxidative properties, vitamin E increases endothelium-dependent vasodilation, inhibits smooth muscle proliferation and platelet aggregation, and improves arterial compliance [14]. Furthermore, vitamin E protects polyunsaturated acids from peroxidation, thus preventing the beginning of the oxidative cascade [14].

Alpha-tocopherol, an active component of vitamin E, significantly reduces blood pressure in rats when compared to a control group [56]. Hypertensive rats had lower plasma nitric oxide than normotensive rats, and treatment with alpha-tocopherol increased nitric oxide activity, resulting in a decrease in blood pressure. In a randomized, placebo-controlled study of hypertensive humans, blood pressure did not decrease after three months of supplementation [57]. Another study revealed that high plasma concentrations of alpha-tocopherol, induced by a well-balanced diet, were associated with significantly lower total and cause-specific mortality in

older male smokers [58]. Several studies have suggested that only individuals with oxidative stress, a poorly defined term, will benefit from vitamin E supplementation [54,55,59]. Evidence exists that CoQ_{10} is more effective than vitamin E due to structural differences allowing higher affinity of CoQ_{10} for free radicals (oxidants) [60].

Human trials have used 300 mg/day doses of vitamin E, however, the only study that found a significant reduction of SBP used 600 mg/day of vitamin E [57]. Dietary supplementation is easily achieved and the preferred method of delivery. However, diet eliminates the possibility of specific doses of the vitamin [58]. No clinical trials investigating the efficacy of vitamin E supplementation through diet were identified.

Vitamin E is metabolized by cytochrome p450, which also metabolizes 60% of all prescription drugs [61]. Although no firm conclusions are currently available, suspicion exists that vitamin E may interact with these prescription drugs, and more knowledge of the topic is evidently warranted [54]. High doses of vitamin E, found to increase blood pressure in rats, and might seriously compromise mandatory therapy of pre-existing diseases in humans [58,62]. In the largest systematic review of the topic, over 100,000 patients enrolled in 26 studies had an overall increase in all-cause mortality following vitamin E supplementation, although the mechanism is unknown [63].

Herbal Remedies

GARLIC

Allium sativum (garlic), has been used medicinally in Asia and the Middle East for many years, and today, is eaten by individuals in many cultures on a daily basis [4]. Decreasing total and LDL-cholesterol, increasing HDL-cholesterol, lowering triglycerides and fibrinogen, lowering

blood pressure, improving circulation, enhancing fibrinolysis, inhibiting platelet aggregation, and reducing plasma viscosity are garlic's current cardiovascular indications [4]. In addition, garlic has numerous anti-cancer, anti-thrombotic, anti-platelet aggregation, and antioxidant properties [64-66].

Garlic's antihypertensive properties may be linked to its allicin and hydrogen sulphide production [67]. Allicin inhibits angiotensin II, resulting in vasodilation and blood pressure reduction in humans and animals [68-70]. Allicin may also open calcium ion channels in the vascular smooth muscle membrane, affecting hyperpolarization and resulting in vasodilation [71].

It is difficult to conduct blinded studies due to detection of garlic odor: in one study, 20% of the garlic group reported odor compared to control; 2/3 of participants in each group correctly identified the intervention [72]. In a recent meta-analysis, garlic reduced SBP and DBP by 16 and 9 mm Hg respectively [67]. This is comparable to the effect of prescription antihypertensive drugs, but with fewer side effects [67]. Blood pressure reductions within this range also decrease risk of coronary events and stroke by 30 and 46% respectively [73,74]. Another meta-analysis with eleven high quality articles showed garlic supplementation to exert a 4.56 mm Hg greater effect than placebo in reducing SBP in normotensive patients, which increased to an 8.38 mm Hg greater decrease than placebo upon subgroup analysis of hypertensive patients [15]. The meta-analysis also found garlic to reduce mean DBP by 7.27 mm Hg more than the placebo in hypertensive individuals. Garlic did not cause hypotension in normotensive to bordeline hypertensive patients (SBP 129-139 mm Hg) [67].

Most studies examine garlic powder doses of 600-900 mg/day, although different preparations have variable effectiveness on blood pressure depending on allicin content [15].

Garlic preparations contain significantly more allicin content than fresh garlic cloves, have fewer side effects such as garlic breath and garlic odour, and are not subject to possible destruction of active compound during the cooking process [75].

Side effects of garlic supplementation are similar to those with the conventional use of garlic, such as gastrointestinal symptoms and garlic breath upon supplementation [76]. However, in clinical trials examining the effect of garlic on hypercholesterolemia, garlic was found to be relatively harmless, and no participants discontinued use due to side effects [76,77]. Specific gastrointestinal symptoms include increased bowel movement, flatulence and bloating, but were not different between treatment and placebo groups [77]. Garlic interacts with and other anti-thrombotics, and therefore should not be taken with these medications [67].

HAWTHORN

Hawthorn extract is derived from *Crataegus monogyna* or *Crataegus laevigat*a [16]. Used traditionally for cardiovascular disorders in many cultures, hawthorn contains flavonoids, catechins, triterpine saponins, amines, and oligomeric proanthocyanidins [4].

Hawthorn increases muscle contraction abilities while decreasing heart rate, which results in lowered blood pressure [16]. It is hypothesized that hawthorn dilates coronary blood vessels via nitric oxide mediated relaxation [78]. Epicatechin, chlorogenic acid, isoquercitin, and hyperoside are the suspected active constituents of hawthorn, and share similar properties to digoxin, a common cardiovascular medication [79]. Studies have shown hawthorn to potentially prevent arrhythmias, and to affect contractile function and calcium channel regulation [80].

A meta-analysis of 310 patients in randomized, double-blind, placebo-controlled trials found hawthorn extract more effective in lowering blood pressure than the control, although no

actual blood pressure values were provided (P<0.01) [16]. Considering the claimed benefits of hawthorn, more research is warranted to justify its use for the treatment of hypertension.

Formulations of different parts of the plant have different effects and potencies, with hawthorn berries exerting a lesser effect than the whole plant extract [81]. Side effects are infrequent, and include nausea, dizziness, and minor unspecified cardiovascular and gastrointestinal complaints [16]. No drug interactions were reported.

Conclusions

Although many dietary supplements to treat hypertension exist, appropriate treatment likely differs between individuals due to the differences in mechanism, side effects, and drug interactions for each supplement (Table 1). Furthermore, the efficacy for the treatment of hypertension varies between supplements, and substantial data is lacking for many treatments (Figure 1). Conclusions from data in Figure 1 should be made with caution because protocols, article quality, and assessment measures vary widely within and between the meta-analyses.

Of the available data, magnesium and CoQ_{10} appear to have the fewest side effects and interactions, while exerting the most dramatic decreases in SBP. Although vitamin C and garlic appear promising, the many side effects and drug interactions may decrease their appeal. Too little substantial information is available regarding the efficacy and side effects of vitamin E and hawthorn, and until more conclusions are available, their use should be cautioned.

The antioxidant properties of many dietary supplements are the suspected cause of their antihypertensive effects, since the endothelial vasodilator response- mediated by nitric oxide- appears to be impaired in essential hypertension [82]. Dietary supplements interact with nitric

oxide to reestablish the pathway, resulting in the enhancement of vasodilating action of nitric oxide and subsequently reducing blood pressure [82].

Increased salt intake, typical of the American diet, correlates with hypertension, and thus, decreased salt intake is recommended in addition to supplementation [83]. Salt mediates hypertension through altering osmolality of cells, and causing the kidneys to work harder in order to excrete the salt [84]. Kidneys regulate blood pressure, and when are impaired by salt-overload, blood pressure regulation diminishes and hypertension occurs [83]. For those that cannot manage to reduce salt, supplementation with potassium may be effective in counteractive the nephrotoxic effects of salt [28]. However, potassium is harmful to those with established renal impairment, so the window of opportunity for potassium utilization may be narrow [84].

Although current use of dietary supplements is high, most people self-prescribe [4]. This practice, without sufficient education of indications, dose, side effects, and drug interactions is very dangerous considering the contraindications of many therapies. Therefore, individuals should be encouraged to discuss treatment options with their physician or a licensed naturopathic doctor. Additionally, physicians should be educated of relevant supplements, and encourage patients to report their use of alternative medicine in a nonjudgmental manner. Furthermore, physicians may incorporate nutrient supplements into their practice in the treatment of hypertension. Considering the prevalence of hypertension and the efficacy of standard hypertension treatments, dietary supplements could prove to substantially impact and prolong the lives of many individuals.

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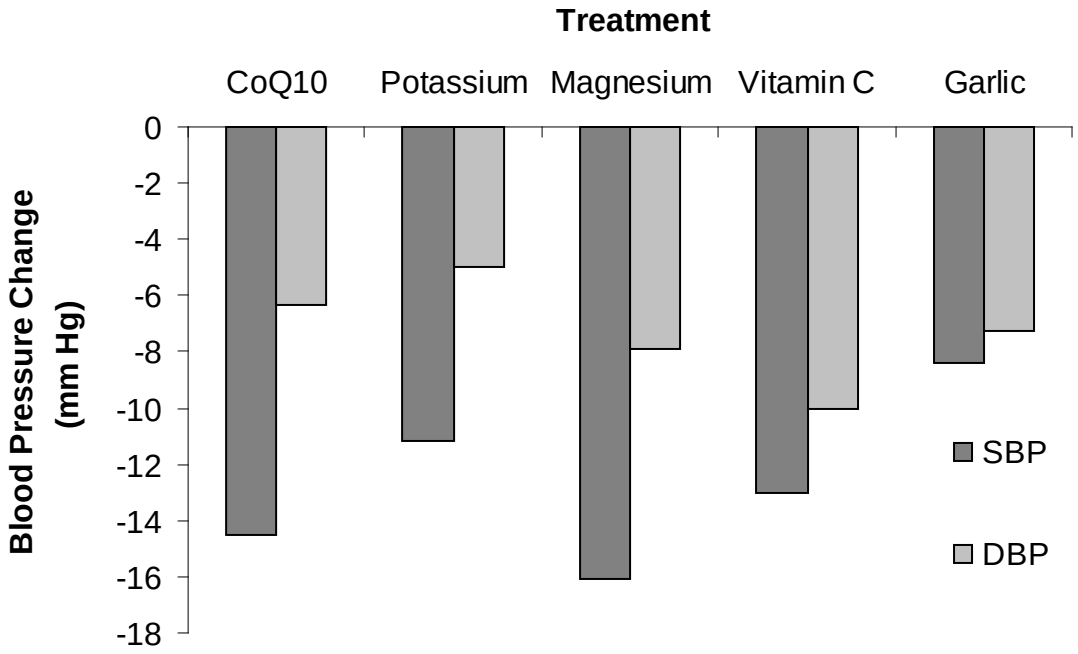
Figure 1. Blood pressure lowering effect of dietary supplements in comparison to placebo controls based on pooled results of individual meta-analyses. Coenzyme Q_{10} [10], potassium [28], magnesium [37], vitamin C [48**]**, and garlic [15] all show clinically-relevant effects on systolic and diastolic blood pressure.

Table 1. Summary of antihypertensive mechanism, dose, side effects, and drug interactions for dietary supplements.

		Anti-oxidant?	Other BP Lowering Interactions	Daily Dose	Known Side Effects	Interactions
Nutrient Supplements	**Coenzyme Q10**	Yes [10]	-	100-225 mg [18]	None [10]	- Statins [22]
	Potassium	No	- Sodium [24] - NE [11]	1.3-4.7 g [29,84]	- Cardiac events in patients with impaired kidney function [84]	- ACE inhibitors [84] - Angiotensin receptor blockers [84] - NSAIDs [84] - Some diuretics [84]
	Magnesium	No	- Calcium [39] - Angiotensin II [40]	10-40 mM [41]	None	- Captopril [44]
	Vitamin C	Yes [45]	- NE [46]	60-2000 mg [49]	- Kidney stones in patients with impaired kidney function [50] - Gastrointestinal discomfort [51] - Headaches [51] - Fatigue [51] - Insomnia [51]	- Iron [8] - Acetaminophen [8] - Anticoagulants [8] - Vitamin B_{12} [8] - Copper [8] - Some antacids [8] - NSAIDs [8]
	Vitamin E	Yes [14]	-	300-600 mg [57]	- Increased blood pressure [62] - Increased all-cause mortality [63]	- Drugs metabolized by cytochrome p450 [61]
Herbal Remedies	**Garlic**	Yes [66]	- Calcium [68] - Angiotensin II [85]	600-900 mg [15]	- Increased bowel movement [76] - Flatulence [76] - Bloating [76] - Garlic breath [76]	- Aspirin [67] - Anti-thrombotics [67]
	Hawthorn	No	- Calcium [80]	Not reported	- Nausea [16] - Dizziness [16] - Minor cardiovascular and gastrointestinal complaints [16]	- None reported

* NE = norepinephrine, NSAIDs= non-steroidal anti-inflammatories

Figure 1.


Treatment
CoQ10
Potassium
Magnesium
Vitamin C
Garlic
Blood Pressure Change (mm Hg)
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
SBP
DBP