An Integrative Approach to Hypertension: A Comprehensive Review of Antihypertensive Nutrients and Botanicals

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ABSTRACT

Objective: We conducted a comprehensive review of the most current data available on the antihypertensive effects of 29 different nutraceuticals.

Design: In this review, we collected evidence from clinical trials and meta-analyses of clinical trials with human subjects that are representative of the general adult population; studies of infants, children, and pregnant women were excluded. Observational studies were included in some cases as supplementary evidence, and *in vitro* or animal studies were included only for the purpose of explaining hypotensive mechanisms. PubMed served as the primary search engine.

Outcome measures: The efficacy of each nutrient and botanical was demonstrated by a treatment that resulted in a reduction of either systolic or diastolic blood pressure in humans.

Results: All of the reviewed botanical and nutrient supplements, with the exception of French maritime pine bark extract and maitake (*Grifola frondosa*), have been demonstrated to effectively lower blood pressure in humans with good tolerability.

Conclusions: Current data supporting the use of nutrients and botanicals in the treatment of blood pressure are encouraging.

Keywords: Hypertension; Vitamins; Minerals; Nutrients; Botanicals; Orthomolecular medicine; Blood pressure

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INTRODUCTION

Hypertension, or high blood pressure (HBP), can be simply defined as an abnormally high level of pressure within the blood vessels due to the constriction of the arterial walls.[1] Approximately one-third of adults in the United States have this condition.[1] This widespread prevalence of hypertension is a major public health concern because it is a contributing factor to heart attack, stroke, chronic heart failure, and other diseases that combined cause the deaths of approximately 1000 Americans every day.[2] HPB can go undetected for years and comes in two forms: primary (essential) and secondary hypertension. The former, also called *idiopathic hypertension*, is responsible for 95% of cases of hypertension.[3] The latter is the result of other health conditions, such as obstructive sleep apnea, endocrine disorders, drug and alcohol abuse, and renal vascular disease, and is usually reversed once the underlying cause is resolved.[4,5] Hypertension can also be divided into stage 1 (systolic blood pressure [SBP] 140–159 mmHg and/or diastolic blood pressure [DBP] 90–99 mmHg) and stage 2 (SBP 160+ mmHg and/or DBP 100+ mmHg), with stage 2 representing more severe cases.[5] Physical inactivity, obesity, alcohol abuse, tobacco use, and poor diet are known to increase essential hypertension risk.[5]

CURRENT TREATMENT METHODS FOR HYPERTENSION

There are a variety of medications that are currently used to treat mild to severe hypertension. Common classes include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, β-blockers, and α-blockers.[6] While these drugs are generally able to produce a modest reduction in blood pressure (BP), this outcome is often accompanied by undesirable side effects. Diuretics, which lower BP by causing the kidneys to excrete excess water and sodium, may cause the body to increase potassium excretion and cause muscle cramps and weakness.[6] ACE inhibitors decrease BP by blocking the angiotensin II hormone (Ang II); however, patients who use this drug may experience dry mouth, coughing, muscle pain, and other unwanted side effects. ARBs can produce side effects similar to those of ACE inhibitors, with the exception of cough. Calcium channel blockers reduce the amount of calcium that enters the muscles of the heart and blood vessel walls, diminish the ability of these muscles to contract, and thereby cause blood vessels to dilate and the heart to beat with less force. These drugs may provoke headache, nausea, peripheral edema, and gingival hyperplasia. β-Blockers prevent norepinephrine and epinephrine from binding to their respective receptors in the heart, blood vessels, kidneys, and other areas of the body. Side effects include aggravation of lung and peripheral vascular diseases, fatigue, reduced heart rate, and trouble exercising. α-Blockers promote vasodilation but may also cause constipation, headache, and rapid heartbeat.

The trade-off for these undesirable side effects is a reduction in cardiovascular disease (CVD) and stroke events. In a meta-analysis of 147 randomized trials that were conducted between 1966 and 2007 with a total 464,000 participants, it was found that calcium channel blockers, thiazides (a diuretic), β-blockers, ACE inhibitors, and ARBs all significantly reduced the risk of heart failure after approximately 3.5 years compared with a placebo.[7] Combined, these drugs had relative risks (RRs) of 0.85 (95% confidence interval [CI] 0.81–0.89) for coronary heart disease (CHD) events and 0.73 (95% CI 0.66–0.80) for stroke. Participants in this meta-analysis included people who had been diagnosed with CHD or stroke and those who had no prior history of either condition. This is important to note because treatment efficacy is affected by the patient's health status before the start of treatment. Among those in the primary prevention population, which includes those who have not been diagnosed with CVD, treatment for hypertension may have no effect at all. The authors of a Cochrane review of evidence derived from four randomized controlled trials (RCTs) wherein 8912 people diagnosed with mild hypertension were treated with antihypertensive drugs or a placebo for 4–5 years found that treatment did not significantly reduce CHD (RR 1.12, 95% CI 0.80–1.57), stroke (RR 0.51, 95% CI 0.24–1.08), total cardiovascular events (RR 0.97,

95% CI 0.72–1.32), or all-cause mortality (RR 0.85, 95% CI 0.63–1.15).[8]

This indicates that while traditional BP medications may be effective at preventing coronary events, those seeing the most benefit are likely to have severe or stage 2 hypertension. While treating those with severe hypertension is no less important that treating those with milder forms of this condition, the reality is that, among American adults with HBP, 86.4% have stage 1 hypertension.[9] This means that antihypertensive drugs may be practically useless for more than four of five patients with HBP. Perhaps even more disconcerting is the fact that although three-fourths of people with HBP are currently under conventional treatment for their condition, only about half of them have been able to get it under control.[10] According to the American Heart Association, $46.4 billion was spent in 2010 alone on efforts to reduce hypertension nationwide.[10]

Considering the debatable effect of traditional pharmaceutical treatments for a large portion of people with HBP and the exceptionally high costs associated with treatment, alternative solutions are worth exploring for both health professionals and patients alike. Throughout history, many botanical and nutritional supplements have been used to decrease BP with little to no harmful side effects. While in some cases only anecdotal evidence is available, several nutrients and botanicals have been subjected to rigorous scientific research with positive results. A comprehensive overview of the scientific literature evaluating the antihypertensive effects of 29 nutrients and botanicals is provided below. In all clinical trials that reported on tolerability, the results were positive.

ALTERNATIVE TREATMENTS FOR HYPERTENSION

ANTHOCYANINS

These are a class of flavonoids that give certain plants their red, blue, and purple hues. They help control BP by inhibiting ACE and increasing nitric oxide (NO) production.[11] In an RCT comparing the BP-lowering effects of 10 g/day of dried *Hibiscus sabdariffa* calyces with 50 mg/day of captopril (an ACE inhibitor) among adults diagnosed with hypertension, both treatments showed similar antihypertensive capacity ($P>0.560$ by χ^2 test).[12] Treatment with *H. sabdariffa* for 4 weeks, equivalent to 9.6 mg/day of anthocyanins, reduced SBP from 139.05 to 123.73 mmHg ($P<0.03$ by analysis of variance [ANOVA]) and DBP from 90.81 to 79.52 mmHg ($P<0.06$ by ANOVA). Other studies have confirmed the antihypertensive effects of *H. sabdariffa* both *in vitro*[13] and in patients with mild and severe hypertension.[14–17] In all cases, the supplement was well tolerated. The anthocynanins delphinidin and cyanin, which occur naturally in pomegranates, grapes, and a number of berries, have also shown ACE-inhibiting capacity *in vitro.*[18] Observational studies have also provided comparable results. A pooled, multivariate-adjusted analysis of food frequency data collected from 156,957 subjects during the Nurses' Health Study (NHS) and NHS II as well as the Health Professionals Follow-Up Study (HPFS) showed an 8% reduction in hypertension risk for those in the highest quintile of anthocyanin consumption.[19] For patients aged 60 years and above, the effect was more pronounced, with a 12% risk reduction. Further analysis of dietary intake data from NHS II showed an inverse association between anthocyanin consumption and incidence of myocardial infarction (hazard ratio 0.68, 95% CI 0.49–0.96).[20] In a separate study of approximately 2000 British women, researchers found that women who consumed the highest amounts of anthocyanins had lower central SBPs (quintile 5 versus quintile 1, mean±SE −3.0±1.4 mmHg, $P=0.02$).[21]

ARJUNA BARK (*Terminalia arjuna*)

This plant is a prominent feature of Ayurvedic medicine, and it has been proposed to reduce BP via cholinergic mechanisms.[22] Reductions in systolic BP have been observed in humans with CHD who ingested 500 mg of Arjuna bark powder, aspirin, and nitrates orally three times daily.[23] Oral doses as low as 90 mg/day have also been shown to be effective at reducing SBP.[24]

BLACK CUMIN SEEDS (*Nigella sativa*)

These tiny black seeds are found in the fruit of a flowering plant that is native to Southern Asia.

Oral administration of 100–200 mg of *Nigella sativa* extract twice a day for 8 weeks was shown to be effective at significantly lowering both SBP ($P<0.05$) and DBP ($P<0.01$) among persons with mild hypertension.[25] In another randomized trial, 5 mL/day of *N. sativa* oil was shown to decrease SBP by 8.17% and DBP by 12.46% among both normotensive and mildly hypertensive subjects.[26] Black cumin seeds contain various volatile oils, including thymol, thymoquinone, carvacrol, dithymoquinone, 4-terpineol, thymohydroquinone, and *trans*-anethole, which may contribute to its hypotensive activity.[27] Studies suggest that *N. sativa* decreases BP by reducing the activity of ACE and increasing the activity of heme oxygenase-1.[28] Other proposed mechanisms include reduction of myocardial contractility, activation of muscarinic receptors on blood vessels,[29] and blockage of calcium channels.[30,31]

CALCIUM

Calcium is essential for a plethora of bodily functions and can be found in great quantities in dairy foods; green, leafy vegetables; and some fortified foods. Data derived from observational studies indicate that people who consume more calcium tend to have lower BP and a lower risk of hypertension.[32–34] However, data derived from clinical trials are less convincing. Several meta-analyses of the hypotensive effect of dietary and supplementary calcium have been conducted, and in two cases there was only a modest reduction in SBP and no effect on DBP,[35,36] while another research team concluded that there was no effect on BP.[37] Griffith and colleagues conducted a meta-analysis of 42 randomized trials a few years later and found that the hypotensive effect of calcium supplements was modest at best (SBP mean reduction [MR] −1.44 mmHg, 95% CI −2.20 to −0.68; DBP MR −0.84 mmHg, 95% CI −1.44 to −0.24).[38] The authors of the most recent meta-analysis, published in 2015, analyzed the results of 16 clinical trials (n=3048) with exclusively normotensive subjects.[39] Once again, a modest yet significant effect was found (SBP mean difference [MD] −1.43 mmHg, 95% CI −2.15 to −0.72; DBP MD −0.98 mmHg, 95% CI −1.46 to −0.50). The mechanism by which calcium may reduce BP has not been confirmed; however, it has been suggested that when adequate amounts of calcium are consumed, the entry of calcium into cells is inhibited and as a consequence vasoconstriction is attenuated.[40]

CAROTENOIDS

Carotenoids comprise a vast array of organic pigments that give many plants, fruits, and vegetables their characteristic yellow and orange hues. Some carotenoids have been shown to have antioxidant properties, which may explain their role in decreasing BP.[41,42] Among young adults in the 20-year, prospective Coronary Artery Risk Development in Young Adults study, hypertension incidence was inversely correlated with total (lutein, zeaxanthin, α-carotene, β-carotene, and cryptoxanthin) serum carotenoid levels.[43] This result is consistent with the findings of other observational studies.[44,45] In a double-blind study including participants with moderate uncontrolled hypertension, lycopene-rich tomato extract significantly reduced BP after 6 weeks, and there was a significant correlation between serum lycopene and SBP (r=−0.49, $P<0.001$).[46] The hypotensive effect of tomato extract was also shown in a similar study that used Lyc-O-Mato® (Lycored, Orange, NJ), a proprietary blend of several carotenoids, to decrease BP in persons with mild hypertension (pretreatment 144±1.1 mmHg, posttreatment 134±2 mmHg, $P<0.001$).[47] Supplementation with 15 mg/day of lycopene for 8 weeks has also been shown to decrease SBP in healthy subjects (pretreatment126.0±2.16 mmHg, posttreatment 122.8±1.78 mmHg, P=0.037).[48] Interestingly, researchers in another study using the same dosage of lycopene for 12 weeks in healthy adults with prehypertension found no effect.[49] Nevertheless, Li and colleagues conducted a meta-analysis of six intervention trials, including the aforementioned trials, and found that overall this carotenoid did have a significant hypotensive effect in doses greater than or equal to 12 mg/day, but only for SBP (MR −4.953 mmHg, P=0.012).[42] The results of a four-study meta-analysis by Ried and colleagues are consistent with this finding, though their results suggest that a slightly higher dose of 25 mg/day or more is needed to produce any significant changes in BP (MR −5.60 mmHg, P=0.04).[50]

CHLOROGENIC ACIDS

This family of esters can be found in bamboo, several fruits, and coffee bean extract. The hypotensive effect of chlorogenic acids (CGAs) has been attributed to several mechanisms, among them inhibition of NAD(P)H oxidase, scavenging of free radicals, inhibition of ACE, and enhanced production of NO.[51] Several clinical trials support these findings. Kozuma and colleagues observed a dose–response relationship in a placebo-controlled RCT in which mildly hypertensive subjects who consumed the largest doses of green coffee bean extract (GCE) (93–185 mg/day GCE, 54% CGA by weight) experienced significant reductions in SBP and DBP.[52] The greatest effect was observed in the group consuming 185 mg/day of CGE, where there was a mean reduction of −5.6±4.2 mmHg (P<0.01) and −3.2±3.2 (P<0.01) in SBP and DBP, respectively. Larger doses of 140 mg/day of CGA have also been shown to be effective at significantly lowering BP without producing any harmful side effects.[53] The hypotensive effect of CGAs has been substantiated further by a meta-analysis of five RCTs (n=364 subjects).[54] In that study, researchers found that, on average, SBP was reduced by −4.31 mmHg (95% CI −5.60 to −3.01) and DBP was reduced by −3.68 mmHg (95% CI −3.91 to −3.45). These results should be interpreted and extrapolated with caution, given the fact that these study populations consisted exclusively of people of Asian descent. Further studies need to be conducted in ethnically diverse populations to determine if the hypotensive effects of CGAs persist across ethnic groups.

COENZYME Q_{10}

Human metabolic needs for coenzyme Q_{10} (CoQ_{10}) are fulfilled primarily via biosynthesis; however, it can also be obtained through diet from meats, fish, nuts, and certain plant foods. CoQ_{10} may help reduce BP by scavenging reactive oxygen species and augmenting the concentration of available NO.[55] Rosenfeldt and colleagues conducted a systematic review of four placebo-controlled RCTs, evaluating the BP-lowering effect of CoQ_{10} supplementation, and they found that doses of 100–200 mg/day produced a clinically significant effect (SBP reduction range −6 to −19 mmHg, DBP reduction range −2 to −16 mmHg).[55] In a later, larger meta-analysis, Rosenfeldt and colleagues found consistent positive and significant results for 60–120 mg/day of CoQ_{10} supplementation, derived from RCTs (n=120) (SBP MR −16.6 mmHg, P<0.001; DBP MR −8.2 mmHg, P<0.001), open-label studies (n=214) (SBP MR −13.5 mmHg, P<0.001; DBP MR −10.3 mmHg, P<0.001), and cross-over studies (n=18) (SBP MR −11 mmHg, P<0.001).[56] In contrast, a Cochrane systematic review of two randomized, double-blind, placebo-controlled trials concluded that CoQ_{10} had no clinically significant effect on BP.[57] That review, published in 2016, included a total of only 50 subjects, and its authors emphasized the need for more rigorous clinical trials before any definitive conclusion can be made.

EUROPEAN MISTLETOE (*Viscum album*)

Research on the antihypertensive effect of this plant is limited. Nevertheless, *in vitro* studies suggest that *Viscum album* may act as a natural calcium-channel blocker.[58] Among human subjects with essential hypertension, 30 drops/day for 12 weeks was shown to significantly reduce BP (P<0.0001).[59]

FISH OIL

The health benefits of fish oil are generally due to two omega-3 (n-3) fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Miller and colleagues conducted an extensive meta-analysis of 70 RCTs that measured the impact of EPA and DHA ingested through food or supplements on BP.[60] In this study, oral supplementation with at least 2 g/day of EPA+DHA produced a significant reduction in BP for normotensive and hypertensive subjects alike. The effect was most pronounced in those with untreated hypertension, in whom SBP was reduced, on average, by −4.51 mmHg (95% CI −6.12 to −2.83) and DBP by −3.05 mmHg (95% CI −4.35 to −1.74). Systematic reviews by other authors support this finding.[61–64] The Nordic Diet, of which polyunsaturated fatty acid (PUFA)-rich fish are an essential component, has also been shown to produce positive effects on BP.[65,66] Though the heart-healthy status of this diet is likely due to a combination of factors, these findings are consistent with what would be expected for a diet rich in n-3 fatty acids. PUFAs have been

shown to reduce BP by multiple mechanisms. Nyby and colleagues demonstrated that adding fish oil to the diet of fructose-fed rats led to upregulation of endothelial nitric oxide synthase (eNOS).[67] Among males with mild hypertension, supplementation with 3–15 g of n-3 fatty acids has been shown to increase metabolism of thromboxane A3 (a vasoconstrictor) and temporarily increase the production of vasodilatory prostacyclins after 1 month.[68] This same researcher later observed that a reduction in blood triacylglycerols and blood viscosity may also contribute to the hypotensive effect of n-3 fatty acids.[69] Yet another mechanism was proposed by Raimondi and colleagues, who reported that the formation of asymmetric dimethylarginine, an inhibitor of NO synthase, was suppressed by EPA and DHA supplementation in rats.[70] Last, n-3 fatty acids may suppress the synthesis of certain proinflammatory cytokines and promote acetylcholine release.[71]

FRENCH MARITIME PINE BARK EXTRACT

The standardized extract of this plant, marketed as Pycnogenol (Horphag Research, Geneva, Switzerland), has been demonstrated to scavenge free radicals, reduce inflammation, increase the activity of NO synthase, and moderately inhibit the activity of ACE.[72,73] No human trials supporting the use of French maritime pine bark extract for hypertension have been published to date.

GARLIC (*Allium sativum*)

Known for its pungent, spicy flavor, garlic is a used to season food almost ubiquitously. In their systematic review of nine placebo-controlled trials (*n*=482), Rohner and colleagues concluded that garlic has the potential to lower BP in hypertensive individuals (SBP weighted MD −9.1 mmHg, 95% CI −12.7 to −5.4).[74] A separate meta-analysis of 17 trials found that, among hypertensive patients, garlic significantly reduced SBP (MR −4.4 mmHg, 95% CI −7.37 to −1.42) and DBP (MR −2.68 mmHg, 95% CI −4.93 to −0.42).[75] Additional meta-analyses corroborate these findings,[76–78] and among those researchers who conducted subgroup analysis, no effect was observed for normotensive subjects.[75,76] Garlic is rich in bioactive compounds, several of which have been shown to have antioxidant and anti-inflammatory properties. It has been shown to inhibit the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells transcription factor, a component of the hypertension signaling process in endothelial cells. It can also inhibit ACE, increase bioavailability of NO, boost H_2S production, and reduce the proliferation of vascular smooth muscle cells.[79]

GRAPE SEED EXTRACT

Grape seed extract (GSE), as the name implies, is extracted from the ground-up seeds of grapes. It is rich in proanthocyanidins, a class of known antioxidants.[80] Pooled data derived from nine RCTs (*n*=298) showed that 150–2000 mg/day of GSE significantly decreased SBP (weighted MD −1.54 mmHg, 95% CI −2.85 to −0.22) but not DBP.[80] The most recent randomized, placebo-controlled trial evaluating the BP-lowering efficacy of GSE was conducted with 36 prehypertensive subjects, and the researchers found that 300 mg/day of GSE for 6 weeks produced significant reductions in both SBP (−5.6%, *P*=0.012) and DBP (−4.7%, *P*=0.049).[81] Yet, a previous 8-week intervention study comparing the same dosage of GSE with a placebo among subjects with prehypertension and mild hypertension found no significant results.[82] Given these conflicting results and the small sample sizes, further research is necessary to better assess the hypotensive potential of GSE.

HAWTHORN (*Crataegus*)

Few clinical trials evaluating the efficacy of hawthorn for lowering BP have been conducted, and there are conflicting results among these. Walker *et al.* found a modest BP-lowering effect among people with both type 2 diabetes and hypertension who ingested 1200 mg/day of hawthorn extract; however, these results are dubious, given that the majority (71%) reported use of hypotensive drugs during the study.[83] The trial with the longest duration to date required subjects to consume 60 drops of plant extract per day for 3 months, and the researchers found that this resulted in a significant reduction in both SBP (post-treatment; placebo group 142±5.73 mmHg, treatment group 133±5.97 mmHg, *P*=0.002) and DBP (post-treatment; placebo group 89±3.29 mmHg,

treatment group 84±3.51 mmHg, *P*=0.003).[84] Suggested mechanisms for lowering BP include the inhibition of low-density lipoprotein oxidation[85] and NO-mediated vasodilation.[86] Studies using hawthorn extract in combination with camphor have yielded contradictory results which suggest that this herbal drug may actually increase BP.[87–89] Inconsistencies in trial duration, dosage, and drug mixing may partially explain these inconsistent results, and further research is warranted.

L-ARGININE

Found in fish and meat, L-arginine is considered a conditionally essential amino acid, given that it is produced in sufficient amounts in healthy humans but may need to be supplemented in those with conditions affecting its biosynthesis. Human clinical trials assessing the efficacy of L-arginine as a hypotensive agent tend to lack statistical power due to small sample size and often yield conflicting results. Notwithstanding these considerations, the authors of a meta-analysis of 11 randomized, placebo-controlled, double-blind trials (*n*=387) with doses of L-arginine ranging from 4 to 24 g/day concluded that supplementation with this amino acid can produce significant reductions in both systolic (MR −5.39 mmHg, 95% CI −8.54 to −2.25) and diastolic BP (MR −2.66 mmHg, 95% CI −3.77 to −1.54).[90] Researchers have associated this effect with increased production of NO[91] and improved endothelium-dependent vasodilation.[92,93]

MAGNESIUM

Magnesium is found in small amounts in a variety of foods, including dairy products, legumes, fruits, vegetables, and meats. There is a copious amount of evidence derived from epidemiologic and observational studies that suggest an inverse association between dietary and/or serum magnesium and BP[33,94–103]; however, clinical trials have yielded incompatible results. In a meta-analysis of 20 RCTs in which test subjects ingested 10–40 mmol/day of magnesium, pooled data showed no significant association between magnesium supplementation and BP (SBP MR −0.6 mmHg, 95% CI −2.2 to +1.0, DBP MR −0.8 mmHg, 95% CI −1.9 to +0.4).[104] Possible antihypertensive mechanisms include increased production of prostaglandin E_1 and NO (vasodilators), competitive binding with sodium on smooth muscle cells, and cooperative binding with potassium.[105]

MAITAKE (*Grifola frondosa*)

This edible mushroom has been demonstrated to lower BP only in rats.[106] To date, there are no published human trials confirming or denying its hypotensive effects in humans.

MELATONIN

This naturally occurring hormone is commonly prescribed as a sleep aid. While only a few studies have tested its ability to reduce BP, overall the results have been promising. Scheer and colleagues found that, after 3 weeks of supplementing with 2.5 mg/day of melatonin, 16 men with hypertension had their mean nocturnal SBP and DBP reduced by 6±10 mmHg (*P*=0.046) and 4±6 mmHg (*P*=0.020), respectively.[107] Another study using a test dose of 5 mg/day for 3 months and a larger sample size (*n*=30) supports these findings.[108] Among elderly people, melatonin secretion has been shown to be inversely related to nocturnal BP.[109] Melatonin and its metabolites have been proven to be potent antioxidants, and their ability to scavenge free radicals may contribute to the hypotensive effect that was observed in these studies.[110,111]

OLIVE (*Olea europaea*) LEAF

As the name implies, olive leaf comes from the olive tree. Through animal studies, researchers have found that olive leaf extract may work as a natural calcium channel blocker[112] and a vasodilator.[113,114] Olive leaf extract may also enhance the effects of traditional antihypertensive drugs, such as ACE inhibitors, calcium channel blockers, and β-blockers.[115] Human trials have shown mostly positive results. Cherif and colleagues showed that 1600 ng/day of aqueous olive leaf extract for 3 months significantly (*P*<0.001) reduced BP in persons with hypertension.[116] Similarly, average SBP was reduced by −3.95 mmHg (*P*=0.027) and average DBP by −3.00 mmHg (*P*=0.025) after 6 weeks in a clinical trial testing the hypotensive effect of 136 mg/day of oleuropein combined with 6 mg/day of hydroxytyrosol on 60 hypertensive men.[117] These

results are supported by other clinical studies.[118–120] Conversely, Wong and colleagues found that 1000 mg/day of olive leaf extract for 6 weeks had no effect on BP.[121] Though most studies found a positive association, more research needs to be done.

POMEGRANATE (*Punica granatum*)

This fruit is characterized by its deep red color and abundance of edible seeds. In a small (n=13) study testing the acute effects of 150 mL of pomegranate juice (PJ) on the BP of hypertensive men, SBP decreased by 7% (P=0.013) and DBP by 6% (P <0.010) after 4–6 hours.[122] A subsequent study by the same research team with an extended trial period of 2 weeks supports the conclusion that regular consumption of PJ can aid in BP management.[123] Additional studies support these findings.[124,125] Inhibition of ACE activity as a consequence of PJ consumption has been observed in both animals[126] and humans[127] and is therefore a likely mechanism by which pomegranate can lower BP. Reduced expression of inflammatory markers such as cytokine transforming growth factor β1 and enhanced eNOS expression may also account for the hypotensive effect of PJ.[128]

POTASSIUM

This mineral can be found in many fruits and vegetables. High intake of potassium has been linked to lower BP in a variety of studies.[129] Furthermore, several observational studies indicate a dose-dependent BP-lowering effect for potassium.[33,94,130,131] In one study involving about 30,000 male health professionals, it was found that those who consumed less than 2.4 g/day of potassium had a 50% increased risk for developing hypertension relative to those who consumed 3.6 g/day or more.[33] Data derived from a meta-analysis of 19 clinical trials (n=586) strengthens the evidence for potassium as an effective supplement for decreasing BP.[132] Supplementation with 48–140 mmol/day of potassium lowered SBP and DBP by an average of −5.9 mmHg (95% CI −6.6 to −5.2) and −3.4 mmHg (95% CI −4.0 to −2.8), respectively. These findings are supported by other meta-analyses of clinical trials[133,134]; however, the authors of a more recent Cochrane systematic review of five RCTs (n=425) found no significant effect of potassium supplementation on BP.[135] While the mechanisms by which potassium contributes to vasodilation are not well established, sodium balance and related diuresis may play a role.[136] Increased synthesis of NO[137] and reduction in renin secretion[138] have also been suggested.

RESVERATROL

This polyphenol is found naturally in peanuts, cocoa, a variety of berries, and wine. It has been shown to have antioxidant properties and may aid in vasodilation by increasing NO synthesis and bioavailability according to rodent models.[139,140] The authors of a recent meta-analysis of six RCTs concluded that, overall, resveratrol supplementation in high doses (≥150 mg/day) was effective at producing a significant decrease in SBP (MR −11.90 mmHg, 95% CI −20.99 to −2.81).[141]

SESAME LIGNANS

Sesamin, a lignan found in the sesame plant, has been shown to lower BP in humans with mild hypertension, but only in a handful of studies. After just 1 month of consuming 60 mg/day of sesamin, test subjects experienced a mean decrease in SBP and DBP of −3.5 mmHg and −1.9 mmHg, respectively.[142] In another study, overweight men and women ingested 50 mg/day of sesamin for approximately 5 weeks, which led to a 28% reduction in plasma 20-hydroxyeicosatetraenoic acid, a vasoconstrictor.[143]

SOY ISOFLAVONES

Soy isoflavones are phytoestrogens that occur naturally in soybeans and their derivatives. According to a meta-regression by Liu and colleagues consisting of 11 RCTs (n=1173), among hypertensive subjects, soy isoflavone supplements significantly reduced SBP (MR −5.94 mmHg, 95% CI −10.55 to −1.34) and DBP (MR −3.35 mmHg, 95% CI −6.52 to −0.19) in doses ranging from 65 to 153 mg/day.[144] In a previous meta-analysis of 14 RCTs, Taku and colleagues found a significant reduction in SBP but not DBP.[145] Consuming isoflavones directly from soy products has also been shown to significantly lower BP in both hypertensive and normotensive subjects. Welty and colleagues found that adding

soy nuts to the Therapeutic Lifestyle Changes (TLC) diet produced a marked difference in mean SBP and DBP reductions.[146] Likewise, postmenopausal women who consumed soy biscuits every day (54 mg/day of isoflavones) for 8 weeks experienced slight reductions in BP.[147] Soy milk has also been tested as a hypotensive agent. When compared with regular cow's milk, drinking soy milk for 3 months led to much greater reductions in both SBP and DBP than cow's milk did.[148] Even pasta enriched with soy germ, which contains the isoflavone aglycons, was shown to reduce BP significantly in a trial where subjects with type 2 diabetes were instructed to consume one serving per day for 2 months.[149] The results of animal studies point to increased eNOS expression as a likely mechanism[150,151]; however, human trials suggest that this may not be the case.[152]

TAURINE

The sulfonic amino acid taurine is produced endogenously in healthy individuals and can also be obtained through meat and fish in the diet. Epidemiologic data suggest an inverse association between urinary taurine excretion and BP.[153] This same association was observed decades ago in a study comparing taurine clearance among people with normal BP, high BP receiving no treatment, and high BP receiving treatment.[154] Overall, the data showed a significant inverse correlation between daily urinary taurine excretion and SBP (r=–0.472, P<0.01) as well as DBP (r=–0.382, P<0.01), independent of BP status. The hypotensive effect of taurine has been shown in numerous rat studies[155,156]; however, robust evidence derived from human clinical trials is scarce and needs to be updated. In one placebo-controlled human trial, 10 borderline hypertensive subjects who were treated with 6 g/day of taurine for 1 week saw their SBP decrease by −9.0±2.9 mmHg (P<0.05) and their DBP decrease by −4.1±1.7 mmHg (P<0.05).[157] These results were replicated in a more recent trial by Militante and colleagues.[158] Taurine may lower BP via suppression of the sympathetic nervous system, partial inhibition of Ang II, and enhancement of NO production.[159]

VITAMIN C

This water-soluble vitamin is found in a variety of fruits and vegetables. Observational studies suggest that BP is inversely related to levels of vitamin C in plasma[160] and in the diet.[132] Given that this vitamin is also an antioxidant, it is not surprising that it has been shown to reduce oxidative stress[161] and improve NO production *in vitro*.[162] Ascorbic acid may also diminish the effects of Ang II.[163] In a meta-analysis, Juraschek and colleagues pooled the data of 29 clinical trials (n=1407) with a median vitamin C dose of 500 mg/day and median trial duration of 2 months. They concluded that, on average, supplementation with vitamin C lowered SBP by −3.84 mmHg (95% CI −5.29 to −2.38) and DBP by −1.48 mmHg (95% CI −2.86 to −0.10).[164] Nevertheless, the researchers cautioned that many of the trials had small sample sizes (mean sample size approximately 48) and that in some cases vitamin C was combined with other treatments; therefore, more robust clinical trials need to be conducted before ascorbic acid can be unequivocally recommended for treatment of hypertension. It is worth mentioning that an earlier RCT found that 50–500 mg/day of vitamin C had no effect on BP in the long term.[165] In this trial, 244 subjects supplemented with vitamin C for 5 years, and in both groups BP increased significantly. Furthermore, there was no difference in BP between the treatment groups and the control (dropout) group. Given this finding, it is crucial that further clinical trials have not only larger sample sizes but also longer durations.

VITAMIN D

Vitamin D is a fat-soluble vitamin that is produced endogenously in response to exposure to sunlight. It can also be obtained through the diet from meat, mushrooms, and fortified foods. Vitamin D has been shown to play a regulatory role in the renin–angiotensin system, and among normotensive individuals the circulating level of Ang II has been inversely correlated with that of 25-hydroxy vitamin D.[166] Additionally, the connection between hypovitaminosis D and increased hypertension risk has been reported in several observational studies.[167–171] Despite this, when Beveridge and colleagues pooled the data of 46 randomized clinical trials (n=4541) in which subjects took up to 1600 IU/day of vitamin D for at least 4 weeks, they found that vitamin D was not an effective hypotensive supplement (SBP effect size 0.0 mmHg, 95%

CI −0.8 to +0.8; DBP effect size −0.1 mmHg, 95% CI −0.6 to +0.5).[172] This is the most current meta-analysis available, and previous meta-analyses showed either no effect[173,174] or a modest hypotensive effect.[175,176]

VITAMIN K

This vitamin comes in several forms. Among these is phylloquinone, which is found primarily in green, leafy vegetables, and menaquinones, which can be obtained from animal products. The limited amount of data that suggests any beneficial effect of vitamin K on BP comes from either rat studies or a couple of small human studies. In one animal trial, a diet rich in vitamin K was shown to improve arterial distensibility by reversing arterial calcification.[177] A case study by Teperikidis suggests that a 100 μg/day menaquinone supplement could reduce BP,[178] but the very nature of the study makes it difficult to generalize the results. Moreover, evidence from a recent Cochrane review that included just one trial (n=60) suggested otherwise.[179]

WHEY PROTEIN PEPTIDES

Whey is a byproduct of cheese manufacturing, and the hydrolyzation of its constituent proteins creates whey protein peptides. The ability of these peptides to inhibit ACE has been documented in several animal[180–183] and *in vitro* studies,[184] but human trials have produced conflicting results. Subjects who consumed 150 mL/day of milk fermented with *Lactobacillus helveticus* LBK-16H and containing β-casein, a bioactive peptide, experienced a significant reduction in BP in a placebo-controlled trial of about 40 hypertensive subjects.[185] The average BP difference between test and control groups after 21 weeks was 6.7±3.0 mmHg (P=0.03) and 3.6±1.9 mmHg (P=0.059) for SBP and DBP, respectively. These results are supported by another clinical trial in which intake of fermented milk for 8 weeks significantly lowered BP.[186] Conversely, researchers in a placebo-controlled RCT using a slightly smaller dosage of milk supplemented with whey peptides for 12 weeks found no effect on BP.[187] Hydrolyzed whey protein isolate has also been shown to reduce SBP by 8.0±3.2 mmHg (P<0.05) and DBP by 5.5±2.1 mmHg (P<0.05) in subjects with mild hypertension.[188] These results have been replicated in overweight and obese individuals.[189]

YARROW (*Achillea millefolium and Achillea wilhelmsii*)

A common feature of traditional medicine in the Middle East,[190] yarrow has been shown to lower BP in both rats[191–193] and humans.[194] Extract of *Achillea wilhelmsii* taken as 15–20 hydroalcoholic drops twice daily for a period of 6 months produced a significant decrease in BP (P<0.05) among subjects with primary hypertension.[194] The dearth of human trials testing the hypotensive potential of yarrow precludes drawing any definitive conclusions.

CONCLUSIONS

Current data supporting the use of the aforementioned nutrients and botanicals in the treatment of BP are encouraging. Although it may appear insignificant, a 2.2-mmHg reduction in SBP has been estimated to reduce stroke mortality by 6% and CHD mortality by 4%, and a 5-mmHg reduction could possibly reduce stroke mortality by 14% and CHD mortality by 9%.[195] Almost all of the studies that were included in this review and had significant results showed a reduction in SBP that was greater than 2.2 mmHg, which shows that these supplements may have a clinically significant impact on people's lives. Further robust clinical trials studying the hypotensive effects of these 29 nutrients and botanicals are justified.

DISCLOSURE OF INTERESTS

The authors have nothing to disclose.

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