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REVIEW-THEMED ISSUE

Nutraceuticals with a clinically detectable blood pressure-lowering effect: a review of available randomized clinical trials and their meta-analyses

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AIMS

The aim of the present study was to review and comment on the available evidence on nutraceuticals with a clinically demonstrable blood pressure (BP)-lowering effect.

METHODS

We reviewed studies published in the English language from 1990 to 2015 on dietary supplements or nutraceuticals claiming to show an effect on human BP. An initial list of possibly effective agents and studies was obtained from the online reference, the Natural Medicine Comprehensive Database. Using PubMed, we searched agents identified from this list using the MeSH terms 'hypertension', 'blood pressure', 'dietary supplement' and 'nutraceuticals', alone and in combination. We then focused our attention on meta-analyses and randomized clinical trials.

RESULTS

Beyond the well-known effects on BP of the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet, a large number of studies have investigated the possible BP-lowering effect of different dietary supplements and nutraceuticals, most of which are antioxidant agents with a high tolerability and safety profile. In particular, a relatively large body of evidence supports the use of potassium, magnesium, L-arginine, vitamin C, cocoa flavonoids, beetroot juice, coenzyme Q10, controlled-release melatonin and aged garlic extract. The antihypertensive effect of all these nutraceuticals seems to be dose related and the overall tolerability is good.

CONCLUSION

Some nutraceuticals might have a positive impact on BP in humans. Further clinical research is needed, to identify from the available active nutraceuticals those with the best cost-effectiveness and risk–benefit ratio for widespread and long-term use in the general population with a low-added cardiovascular risk related to uncomplicated hypertension.

Introduction

High blood pressure (BP) is one of the most relevant independent risk factors for cardiovascular diseases and the most prevalent all over the world [1]. In particular, the lifetime risk of developing hypertension is a staggering 90% and it is estimated that the global burden of hypertension will increase to 1.56 billion afflicted individuals by 2025 [1]. From a global perspective, suboptimal BP accounts annually for 7.6 million premature deaths and a loss of 92 million disability-adjusted life-years (1 disability-adjusted life-year is equivalent to 1 lost year of healthy life) [2]. Recent studies have shown that the

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maintenance of normal BP levels reduces the incidence of cardiovascular complications, both in the hypertensive population and in subjects whose BP values are only slightly elevated above the optimal range [3]. This suggests the importance of improving BP control in the general population. However, as it is not reasonable actively to treat all subjects with suboptimal BP control with antihypertensive drugs, the main international guidelines [4, 5] stress the preventive impact of appropriate dietary and lifestyle interventions in order to reach and maintain optimal BP levels.

Established diet- and lifestyle-related risk factors for hypertension, such as high salt intake, high alcohol consumption and a sedentary lifestyle contribute significantly to the high prevalence of this condition. Additional dietary deficits have been implicated in the development of hypertension, however, including low fruit and vegetable intake, low consumption of dairy foods and low intake of oily fish. Deficiencies of single micronutrients such as folate, riboflavin, vitamin C and vitamin D have also been recently recognized as risk factors for hypertension . There is evidence that the intake of each of these factors in adults falls short of the ideal. These dietary and nutritional deficits, when superimposed on health-subversive behaviours and escalating rates of obesity, constitute a potent constellation of risk factors for hypertension. However, they also represent viable and potentially effective targets for health promotion initiatives [6].

Beyond the well-known effects on BP of the Dietary Approaches to Stop Hypertension (DASH) [7] and the Mediterranean diet [8], a large number of studies have investigated the possible BP-lowering effect of different dietary supplements and nutraceuticals, most of which are antioxidant agents with a high tolerability and safety profile [9] (Table 1). The aim of the present critical review was to resume the available evidence supporting the use of some dietary supplements with known BP-lowering effects in clinical practice.

Methods

We reviewed studies on dietary supplements or nutraceuticals claiming to have an effect on human BP, published in the English language from January 1990 to October 2015. An initial list of possibly effective agents and studies was obtained from the online reference, the Natural Medicine Comprehensive Database. Using PubMed, for confirmation, we rechecked agents identified from this list using the MeSH terms 'hypertension', 'blood pressure', 'dietary supplement' and 'nutraceuticals', alone and in combination. We then focused our attention on meta-analyses and randomized clinical trials (RCTs).

Foods

Olive oil in the context of the Mediterranean diet

Among other epidemiological studies, in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study (20 343 subjects), the intake of extra-virgin olive oil, rich in polyphenols, was inversely associated with both systolic (SBP) and diastolic (DBP) BP [10]. In the PREvention with MEDiterranean Diet (PREDIMED) trial, carried out on 7447 patients with a high risk for cardiovascular disease, participants allocated to the Mediterranean diet group supplemented with extra virgin olive oil (1 l $week^{-1}$ for participants and their families) had a significantly lower DBP than those in the control group {–1.5 mmHg [95% confidence interval (CI) –2.0, –1.0]}[11]. A dose–response reduction in BP was also observed in monozygotic hypertensive twins treated with an olive leaf extract, at 500–1000 mg day^{-1} for 8 weeks, compared with placebo; the low-dose group had a decrease in BP of 3/1 mmHg and the high-dose group of 11/4 mmHg [12].

Beetroot juice

NO_3^- has received considerable attention in recent years as a health-enhancing nutritional supplement for adverse cardiovascular outcomes. Once ingested, inorganic NO_3^- is metabolized *in vivo* to bioactive nitrite (NO_2^-) and is subsequently salvaged and circulated in the bloodstream. NO_2^- exerts its effects on the body via its conversion to functional nitrogen oxides, including nitric oxide (NO) [13, 14].

The consumption of beetroot juice, as a concentrated sources of inorganic nitrates, at a dose of 250 ml daily, reduces BP acutely in normotensive/pre-hypertensive/mild hypertensive volunteers, via bioconversion to the vasodilator NO [15, 16]. Meta-analytical data from placebo-controlled, double-blind RCTs show that beetroot juice consumption [trial duration 2 h to 15 days; daily doses ranging from 5.1 mmol to 45 mmol (321–2790 mg)] is associated with dose-dependent changes in SBP [mean reduction −4.4 (95% CI −5.9, −2.8) mmHg; $P < 0.001$] [17].

Cocoa

A large number of dietary flavonoids exert vascular protective effects, being antioxidant, anti-inflammatory, improving NO metabolism and endothelial function; moreover, their intake is associated with a reduced risk of cardiovascular disease [18]. Cocoa flavonoids are the most studied in the clinical setting; flavanols from chocolate appear to increase NO bioavailability, protect the vascular endothelium and decrease cardiovascular disease risk factors. Studies have shown that endothelial function is impaired during hyperglycaemia, and that dark chocolate increases flow-mediated vasodilation in healthy and hypertensive subjects with and without glucose intolerance [19, 20].

A recent meta-analysis of 20 double-blind, placebo-controlled RCTs involving 856 mainly healthy participants revealed a statistically significant BP-reducing effect of flavanol-rich cocoa products, compared with control, in short-term trials of 2–18 weeks' duration [mean difference in SBP –2.8 (95% CI –4.7, –0.8) mmHg; $P = 0.005$; mean difference in DBP – 2.2 (95% CI –3.5, –0.9) mmHg, $P = 0.006$]. Trials provided participants with 30–1080 mg of flavanols (mean 545.5 mg) in 3.6–105.0 g of cocoa products per day in the active intervention group [21].

The final evidence on the benefit of cocoa polyphenols in improving cardiovascular health and preventing cardiovascular disease will be provided by the ongoing prevention study, coordinated by the Department of Epidemiology of

Table 1

Dietary supplements and nutraceuticals with a clinically relevant blood pressure-lowering effect in humans

Dietary supplement/ nutraceutical	Level of evidence	Potential mechanisms involved in blood pressure regulation
Aged garlic extract	Meta-analysis of randomized controlled trials	↑ NO production; ↑ H_2S; ↑ bradykinin; ↓ catecholamine sensitivity; ACE inhibition; calcium channel blocking
Beetroot juice	Meta-analysis of randomized controlled trials	↑ NO availability
Calcium (in pregnancy)	Meta-analysis of randomized controlled trials	Unknown
Chelated magnesium	Meta-analysis of randomized controlled trials	Calcium channel blocking; ↑ PGE; ↑ NO synthesis
Cocoa flavonoids	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging; ↑ NO production and endothelial function; ↓ inflammation; ↓ ROS production (NADPH oxidase inhibition)
Coenzyme Q10 (high dosage in hypertensive patients)	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging; ↑ vitamin and antioxidant regeneration; acts as a cofactor and coenzyme in mitochondrial oxidative phosphorylation; ↑ LDL and lipid oxidation
Controlled-release melatonin (night hypertension)	Meta-analysis of randomized controlled trials	↑ NO production; protection of vessels from oxidation; regulation of circadian rhythms
Fish peptides	Various small randomized controlled trials	ACE inhibition
Isoflavones	Meta-analysis of randomized controlled trials	ACE inhibition?
L-arginine (high dosages)	Meta-analysis of randomized controlled trials	↑ NO availability
Lactotripeptides	Meta-analysis of randomized controlled trials	ACE inhibition?
Lycopene	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging
Polyunsaturated fatty acids (high dosages)	Meta-analysis of randomized controlled trials	↓ TXA2 and inflammation; ↑ vasodilator PGs; ↑ NO synthase; ↓ insulin resistance; ↓ RAAS
Potassium	Different randomized controlled trials	↑ Natriuresis; ↑ baroflex sensitivity modulation; ↑ Na^+–K^+-ATPase; ↑ insulin sensitivity; ↓ ATII; ↓ catecholamine sensitivity; ↓ ADMA; ↓ oxidative stress; ↓ TGF- β production
Probiotics	Meta-analysis of randomized controlled trials	ACE inhibition?
Pycnogenol	Meta-analysis of randomized controlled trials	↑ NO production; ↓ ACE; ↑ endothelial function; ↓ myeloperoxidase activity; ↓ urinary albumin excretion
Resveratrol	Meta-analysis of randomized controlled trials	↑ NO production; protection of vessels from oxidation; ↓ vascular inflammation; ↓ platelet aggregation
Vitamin C	Meta-analysis of randomized controlled trials	↓ adrenal steroid production and serum aldehydes; ↓ binding affinity of the AT1R for ATII; ↑ Na^+–K^+-ATPase; ↑ natriuresis; ↑ superoxide dismutase; ↑ cyclic GMP; ↑ NO and PGI_2

ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; AT1R, angiotensin II type 1 receptor; ATII,, angiotensin II; H_2S, hydrogen sulfide, LDL, low-density lipoprotein; NO, nitric oxide; PG, prostaglandin, RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TX, thromboxane.

the Brigham and Women University, Boston, MA, USA and supported by Mars Symbioscience. This study will investigate 18 000 women aged >65 years and men aged >60 years, randomized to either placebo capsules or the isolated cocoa extract, with a 4-year follow-up; it will evaluate the effect of cocoa flavanols in reducing the risk of major cardiovascular events [22].

Teas

Regular consumption of either green or black tea for 4–24 weeks (2–6 cups per day) is associated with a significant reduction in BP; compared with baseline values, green tea significantly reduced SBP by 2.1 (95% CI –2.9, –1.2) mmHg and DBP by 1.7 (95% CI –2.9, –0.5) mmHg, while black tea reduced SBP by 1.4 (95% CI – 2.4, –0.4) mmHg and DBP by

1.1 (95% CI –1.9, –0.2) mmHg [23]. The effect was found to be greater for consumption for longer than 12 consecutive weeks [23].

The reason for the greater (even if mild) effect of green tea, compared with black tea, on BP is probably related to the higher content of phytochemicals (including phenols and catechins) in its leaves, suppressing NADPH oxidase activity and reducing the number of reactive oxygen species in the vascular system [24].

A meta-analysis of four RCTs, with a total of 390 patients, showed that *Hibiscus sabdariffa* tea (sour tea, 2–4 cups per day for 4–8 weeks) is also associated with a significant reduction in BP, even in subjects who are already receiving pharmacological treatment [25].

Nutrients

Omega-3 polyunsaturated fatty acids (PUFAs)

There are many suggested mechanisms by which PUFAs improve BP control: enhancement of the generation and bioavailability of endothelium-derived relaxing factor (NO) through upregulation and activation of endothelial NO synthase (eNOS); a shift in the prostaglandin balance towards greater production of vasodilator prostanoids; a decrease in insulin resistance; regulation of vascular tone by parasympathetic nervous system stimulation; and suppression of the renin–angiotensin–aldosterone system [26].

A large amount of data are available on the BP-lowering effect of omega-3 PUFAs. A meta-analysis of 70 RCTs showed that, compared with placebo, the consumption of omega-3 PUFAs (0.3–15 g day^{-1}) for 4–26 weeks reduced SBP [−1.5 (95% CI −2.2, −0.8) mmHg] and DBP [−1.0 (95% CI −1.5, −0.4) mmHg] [27]. The largest effects were observed among untreated hypertensive subjects [SBP = −4.5 (95% CI −6.1, −2.8) mmHg; DBP = −3.0 (95% CI −4.3, −1.7) mmHg] [27].

Another meta-analysis of RCTs also showed that PUFA supplementation for 6–105 weeks (900–3000 mg day^{-1}) was associated with an improvement in both pulse wave velocity (0.33 m s^{-1}; 95% CI 0.12, 0.56; $P < 0.01$) and arterial compliance (0.48; 95% CI 0.24, 0.72; $P < 0.001$) [28]. No safety concerns were raised beyond mild gastrointestinal discomfort at high doses [28].

Proteins, peptides and amino-acids

A meta-analysis of 40 RCTs including 3277 participants showed that, compared with carbohydrate, dietary protein intake was associated with significant changes in mean SBP and DBP, of –1.8 (95% CI –2.3, –1.2) mmHg and –1.2 (95% CI –1.6, –0.7) mmHg, respectively [29]. Both vegetable protein and animal protein were associated with significant BP changes of –2.3 (95% CI –3.4, –1.2) mmHg and –2.5 (95% CI –3.5, –1.5) mmHg, respectively, for SBP and –1.3 (95% CI –2.3, –0.3) mmHg and –0.9 (95% CI –1.7, –0.2) mmHg, respectively, for DBP [29].Part of the BP-lowering effect might have been caused by a component of the vegetable protein source other than protein. In particular, soy isoflavones (60–110 mg day^{-1}) are associated with a significant decrease in SBP [–5.9 (95% CI –10.5, –1.3) mmHg; $P = 0.01$] and DBP [–3.3 (95% CI –6.5, –0.2) mmHg; $P = 0.04$] in hypertensive subjects [30].

A rich natural source of peptides and amino acids is whey. Studies in animals and humans have shown that α-lactalbumin and β-lactoglobulin obtained from enzymatically hydrolysed whey inhibit angiotensin-converting enzyme (ACE), while lactorphins lower BP by normalizing endothelial function or by an opioid receptor-dependent mechanism [31].

Milk peptides (particularly the tripeptides Val-Pro-Pro and Ile-Pro–Pro, which are reported to have ACE inhibitory activity [32], given at 5–60 mg day^{-1} for 4–12 weeks) have variable BP-lowering effects, which are more evident in Asian subjects [33, 34].These peptides may also improve pulse wave velocity in mildly hypertensive subjects [35]. No safety concerns were raised [35].

Some fish have also been found to contain peptides with powerful ACE inhibitory activity, inducing a significant reduction in BP of around –9 ± 3/4 ± 1 mmHg in single clinical trials carried out in bonito, sardines, tuna and mackerel [36].

Among single amino acids, L-arginine, a semi-essential amino acid, is the natural substrate for NO synthase and is responsible for the production of the endothelium-derived relaxing factor NO, which is involved in a wide variety of regulatory mechanisms in the cardiovascular system [37].

A meta-analysis of 11 double-blind, placebo-controlled RCTs, involving 387 participants undergoing oral L-arginine supplementation at a dose ranging from 4 g day^{-1} to 24 g day^{-1}, over 2–12 weeks, concluded that, compared with placebo, L-arginine supplementation significantly lowered SBP by 5.4 (95% CI −8.5, −2.2) mmHg; $P = 0.001$) and DBP by 2.7 (95% CI −3.8, −1.5) mmHg; $P < 0.001$), suggesting that a 4-week treatment period is sufficient to produce the maximal effect [38].

Potassium, magnesium and other minerals

The effectiveness of restricted sodium (Na^+) or increased potassium (K^+) intake on mitigating the risk of hypertension has been demonstrated in observational research. A systematic review of RCTs and observational research related to this issue [39] suggested that the $Na^+ : K^+$ ratio is more strongly associated with BP outcomes than either Na^+ or K^+ alone in hypertensive adult populations [39].

A balanced diet should contain 4700 mg day^{-1} (120 mmol day^{-1}) K^+, with a $K^+ : Na^+$ ratio of about 4–5 : 1. Doubling the intake of K^+ is associated with a reduction of about 4–8 mmHg in SBP and 2.5–4 mmHg in DBP in hypertensive subjects. The response seems to be higher in black subjects and in patients with higher dietary Na^+ intake [40]. Higher K^+ is also associated with a lower incidence of cardiovascular and cerebrovascular incidents, type 2 diabetes, left ventricular hypertrophy, heart failure and cardiac arrhythmias, independently of BP reduction [41].

A meta-analysis of prospective studies concluded that a 1.64 g (42 mmol) per day higher K^+ intake was associated with a 21% lower risk of stroke [relative risk (RR) 0.79; 95% CI 0.68, 0.90; $P = 0.0007$], with a trend towards a lower risk of coronary and total cardiovascular disease that attained statistical significance after the exclusion of a single cohort (RR 0.93; 95% CI 0.87, 0.99; $P = 0.03$ and RR 0.74; 95% CI 0.60, 0.91;

$P = 0.0037$, respectively) [42]. It has also been estimated that each 1000 mg increase in K^+ intake and each 1000 mg decrease in Na^+ intake per day will respectively reduce all-cause mortality by 20% [43].

Numerous mechanisms have been proposed to explain the K^+-induced BP reduction: increased natriuresis; baroreflex sensitivity modulation; decreased sensitivity to catecholamines and angiotensin II; increased Na^+–K^+-ATPase activity in vascular smooth muscle cells; improved sympathetic nervous system function; and decreased NADPH oxidase activity, which lowers oxidative stress and inflammation, improves insulin sensitivity, decreases asymmetric dimethylarginine, reduces intracellular Na^+ and lowers the production of transforming growth factor-β [44].

K^+ in food or from supplementation should be used with caution in patients with renal impairment and those on medications that increase renal K^+ retention [45].

An inverse relationship between dietary magnesium (Mg^{++}) intake and BP has also been found. A meta-analysis of RCTs with 3–24 weeks of follow-up concluded that Mg^{++} supplementation is associated with a decrease in SBP of 3–4 ± 2 mmHg and in DBP of 2.5 ± 1 mmHg, which increased further with crossover designed trials and intake >370 mg day^{-1} [46]. The BP-lowering effect of Mg^{++} seems to be additive to the effect of high K^+ and low Na^+, both in treated and untreated hypertensive subjects [47].

Numerous mechanisms have been proposed to explain the Mg^{++}-induced BP reduction: a calcium (Ca^{++})-channel blocking action, an increase in prostaglandin (PG) E and an increase in NO synthesis [48].

The optimal supplemented dose seems to be between 500 mg and 1000 mg day^{-1}, and this can be improved by chelating it with an amino acid to improve absorption and to decrease the incidence of diarrhoea. Adding taurine at 1000–2000 mg day^{-1} seems to enhance the antihypertensive effects of Mg^{++} [49].

Magnesium supplements should be avoided in patients with severe renal insufficiency.

While Ca^{++} supplementation seems not to be efficacious in hypertensive subjects, it appears to be particularly useful in pregnant women. A meta-analysis of the Cochrane Collaboration, involving 13 RCTs and more than 15 000 women, supports its use during pregnancy as it appears approximately to halve the risk of pre-eclampsia, to reduce the risk of preterm birth and to reduce the rare occurrence of the composite outcome of death or serious morbidity, without evidence of any relevant side effects [50].

Vitamins

Deficiencies in vitamin C and vitamin D have been recognized as risk factors for hypertension [51].

The vitamin C or plasma ascorbate concentration in humans is inversely correlated with BP [52], and with the risk of cardiovascular disease [53, 54]. In particular, hypertensive subjects were found to have significantly lower plasma ascorbate levels compared with normotensive subjects (40 μmol l^{-1} *vs.* 57 μmol l^{-1}, respectively) [55]. A depletion–repletion study of vitamin C also confirmed an inverse correlation of plasma ascorbate levels with SBP and DBP [56]. Thus, in order to achieve a positive effect on BP, it is recommended that a serum ascorbate level of at least 100 μmol l^{-1} is maintained [57].

In a meta-analysis of clinical trials with a median vitamin C dose of 500 mg day^{-1} over a median 8-week period in hypertensive patients, SBP was reduced by 4.8 ± 1.2 mmHg ($P < 0.01$) but DBP was not reduced [58].

Vitamin C also seems to improve the efficacy of antihypertensive drugs such as amlodipine [59]. In elderly patients with refractory hypertension who are already on maximal pharmacological therapy, 600 mg vitamin C daily lowered the BP by 20 ± 8/16 ± 5 mmHg [60].

Numerous mechanisms have been proposed to explain the vitamin C-induced BP reduction: an increase in NO and PgI_2, leading to an improvement in endothelial function and arterial compliance [61]; the induction of Na^+ and water diuresis; a decrease in adrenal steroid production; an improvement in sympathovagal balance; an increase in Na^+–K^+-ATPase; an increase in superoxide dismutase; an increase in cyclic GMP; activation of potassium channels; a reduction in cytosolic Ca^{++} [62] and a decrease in serum aldehydes [63]. Moreover, vitamin C seems to decrease the binding affinity of the angiotensin II type 1 (AT1) receptor for angiotensin II by disrupting the AT1 receptor disulfide bridges [64].

The doses of vitamin C supplements that are proposed to improve BP (500–1000 mg day^{-1}) are usually well tolerated and do not require any specific attention.

Soluble fibre

While dietary fibre is associated with a small decrease in BP, especially when incorporated into a Mediterranean diet, the supplementation of soluble fibre has been associated with a significant BP reduction in a couple of recent RCTs, with a parallel positive effect on glucose and lipid metabolism [65, 66].

Soluble fibre, guar gum, guava, psyllium and oat bran may reduce BP, and also the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive diabetic subjects. The average reduction in BP is about 7.5/5.5 mmHg with a dose of 40–50 g day^{-1} of a mixed fibre [67].

Flaxseed is a rich dietary source of α-linolenic acid, lignans and fibre, with a number of positive health benefits on BP. A recent meta-analysis of 14 RCTs indicated that flaxseed supplementation slightly but significantly reduces SBP [–1.8 (95% CI–3.4, –0.1) mmHg; $P = 0.04$] and DBP [–1.6 (95% CI –2.6, –0.5) mmHg; $P = 0.003$], independently from the baseline BP values [68]. DBP seems to be particularly reduced for consumption of whole flaxseed [–1.9 (95% CI –3.6, –0.2) mmHg; $P < 0.05$] and for duration of consumption ≥12 weeks (–2.2 (95% CI –3.4, –0.9) mmHg; $P < 0.05$] [68].

Non-nutrient nutraceuticals

Resveratrol and grape seed extracts

Resveratrol (trans-3,5,4′-trihydroxystilbene) is a polyphenol that is particularly concentrated in grape. Many studies have shown the antihypertensive effects of resveratrol in different preclinical models of hypertension, through a multitude of mechanisms that include its antioxidant properties, the stimulation of endothelial NO production, the inhibition of vascular inflammation and the prevention of platelet aggregation [69].

In a meta-analysis of six RCTs, comprising a total of 247 subjects, only higher doses (≥150 mg day^{-1}) of resveratrol significantly reduced SBP, by –11.9 (95% CI –21.0, –2.8) mmHg; $P = 0.01$ [70].

A meta-analysis of nine double-blind, placebo-controlled RCTs, including 390 subjects, showed that grape seed extract (containing various amounts of resveratrol but also other polyphenols) slightly but significantly reduced SBP [weighted mean difference –1.5 (95% CI –2.8, –0.2) mmHg; $P = 0.02$]) but not DBP [71].

Coenzyme Q10 (CoQ10)

CoQ10 (ubiquinone) is a potent lipid phase antioxidant, particularly concentrated in raw red meat and fish. It is a free radical scavenger; reduces oxidative stress; regenerates other vitamins and antioxidants; reduces the oxidation of low-density lipoprotein; is a cofactor and coenzyme in mitochondrial oxidative phosphorylation, which lowers BP; and is often reduced in hypertensive patients [72].

A meta-analysis of placebo-controlled RCTs concluded that oral treatment with ≥100 mg CoQ10 in subjects with an SBP >140 mmHg or a DBP >90 mmHg resulted in a mean decrease in SBP of 11 (95% CI 8, 14) mmHg and in DBP of 7 (95% CI 5, 8) mmHg, usually after 4 weeks of treatment [73]. The main problem associated with the use of CoQ10 as an antihypertensive agent is its low bioavailability in humans; however, this might be improved by the use of CoQ10 nanoemulsion [74].

Lycopene

A recent meta-analysis of RCTs investigating the effect of the carotenoid lycopene (10–50 mg day^{-1} for 4–12 weeks) on SBP suggested a significant BP-reducing effect (mean SBP change ± standard error: –5.6 ± 5.3 mmHg; $P = 0.04$) [75]. The effect of lycopene on BP appears to be additive to that of antihypertensive drugs [76].

One major question is whether delivering lycopene through a supplement source is as effective as, or more effective than, consuming lycopene through whole-food sources – specifically, tomatoes, which are the richest source of lycopene in the Western diet. With the exception of BP management, for which lycopene supplementation was favoured, tomato intake provided more favourable results than lycopene supplementation on cardiovascular risk endpoints [77].

Pycnogenol

Bark extract of *Pinus pinaster* (French maritime pine), usually marketed as pycnogenol, acts as a natural ACE inhibitor; protects cell membranes from oxidative stress; increases NO and improves endothelial function; decreases myeloperoxidase activity; improves renal cortical blood flow; reduces urinary albumin excretion and decreases high-sensitivity C-reactive protein – all properties that support its potential positive effect on human BP [78].

Clinical evidence has shown that supplementation with 100 mg pycnogenol for 12 weeks in subjects treated with various antihypertensive drugs led to a reduction in the dose of the antihypertensive drug in nearly half of the patients [79, 80].

Melatonin

Melatonin is a hormone that is normally secreted from the pineal gland at night. It serves as the signal for darkness in the organism, and, as such, plays a pivotal role in the physiological regulation of circadian rhythms, including sleep. Melatonin seems to improve BP control both by central and peripheral mechanisms, protecting vessels from oxidation and improving NO metabolism, and consequently endothelial function [81]. In a recent meta-analysis of double-blind, placebo-controlled RCTs, comprising 221 participants treated with melatonin 2–5 mg day^{-1} for 7–90 days, controlled-release melatonin caused a significant decrease in both night SBP [–6.1 (95% CI –10.7, –1.5) mmHg; $P = 0.009$] and night DBP [–3.5 (95% CI –6.1, –0.9) mmHg; $P = 0.009$] , while fast release melatonin seemed not to improve night BP [82]. In addition, as β-blockers inhibit melatonin secretion, melatonin supplementation improves sleep in hypertensive patients treated with β-blockers [83]. Melatonin has also been tested as an adjuvant in the treatment of refractory hypertension, with some positive results [84].

Aged garlic extract

Garlic-derived polysulfides (in particular, S-allylcysteine) stimulate the production of the vascular gasotransmitter hydrogen sulfide (H_2S) and enhance the regulation of endothelial NO, which induces smooth muscle cell relaxation, vasodilation and BP reduction. Several dietary and genetic factors influence the efficiency of the H_2S and NO signalling pathways and may contribute to the development of hypertension. A sulfur deficiency might play a part in the aetiology of hypertension, and could be alleviated with supplementation of organosulfur compounds derived from garlic [85]. Dry aged garlic extract also has ACE inhibitory and Ca^{++}-channel blocking activity, both of which reduce catecholamine sensitivity, increase bradykinin and NO, and improve arterial compliance [86].

A recent meta-analysis of nine RCTs, including 482 individuals treated with aged garlic extract for 8–26 weeks, showed that SBP and DBP were reduced more effectively by treatment with garlic preparations than with placebo, with a weighted mean difference for SBP of –9.1 (95% CI –12.7, –5.4) mmHg and for DBP of –3.8 (95% CI –6.7, –1.0) mmHg [87]. This effect seems to be additive to that of standard antihypertensive therapy [88]. Despite the apparent high efficacy of garlic extract, its use is partially limited because gastrointestinal side effects are not uncommon.

Probiotics

A meta-analysis of RCTs suggested that consuming probiotics may improve BP to a modest degree, with a potentially greater effect when baseline BP is elevated, multiple species of probiotics are consumed, the duration of the intervention is ≥8 weeks or if the daily dose is $\geq 10^{11}$ colony-forming units [89].

Another meta-analysis of 14 RCTs, involving 702 participants, showed that, compared with placebo, probiotic fermented milk produced a slight but significant reduction of 3.1 mmHg in SBP and 1.1 mmHg in DBP. Subgroup analyses suggested a slightly greater effect on SBP in hypertensive than in normotensive participants [90].

Other nutraceuticals

Preclinical data and some preliminary clinical data suggest a slight but significant BP-reducing effect for black sesame, pomegranate juice, unroasted green coffee, hawthorn, vitamins B6 and D, α-lipoic acid, carnitines and taurine but the evidence for these is still inconsistent and needs to be confirmed in larger clinical trials [91].

Conclusion

On the basis of the available evidence, the use of nutraceuticals with well-established antihypertensive activity in humans, in association with a coherent improvement in diet and lifestyle, could represent a good compromise for treating prehypertensive patients and an excellent adjuvant, together with the pharmacological treatment, for hypertensive patients. In particular, increased intake of K^+, Ca^{++}, Mg^{++}, fish oil, fibre, NO donors, natural antioxidants, and milk- and vegetable-derived protein could improve BP control in a large number of subjects.

However, there is a need for data on the long-term safety of many of the above-discussed products, particularly when supplemented at a high dose and/or combined, in order also to make possible a pharmacoeconomic evaluation of this approach. In particular, further clinical research is advisable to identify from the available active nutraceuticals those with the best cost-effectiveness and risk–benefit ratio for widespread use in the general population with low-added cardiovascular risk related to uncomplicated hypertension.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work.

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