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REVIEW ARTICLE

Nutraceuticals and Blood Pressure Control: Results from Clinical Trials and Meta-Analyses

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Abstract Beyond the well-known effects on blood pressure (BP) of the dietary approaches to stop hypertension (DASH) and the Mediterranean diets, a large number of studies has investigated the possible BP lowering effect of different dietary supplements and nutraceuticals, the most part of them being antioxidant agents with a high tolerability and safety profile. In particular relatively large body of evidence support the use of potassium, L-arginine, vitamin C, cocoa flavonoids, beetroot juice, coenzyme Q10, controlled-release melatonin, and aged garlic extract. However there is a need for data about the long-term safety of a large part of the above discussed products. Moreover further clinical research is advisable to identify between the available active nutraceuticals those with the best cost-effectiveness and risk–benefit ratio for a large use in general population with low-added cardiovascular risk related to uncomplicated hypertension.

Keywords Hypertension · Blood pressure (BP) · Dietary supplements · Nutraceuticals · Clinical evidence · Review

1 Introduction

From an epidemiological point of view, recent data indicate that 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 [2]. In this context, 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) [1]. On the other side, recent studies have shown that the maintenance of a normal blood pressure (BP) levels reduces the incidence of cardiovascular complications both in the hypertensive population and in subjects whose blood pressure values are only slightly elevated above the optimal range [2]. This would imply the importance of improving blood pressure control in the overall population. However, since it is not reasonable to actively treat all subjects with suboptimal BP control with antihypertensive drugs, the main international guidelines [3, 4] stress the preventive impact of an adequate dietary and lifestyle intervention 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 physical inactivity are believed to contribute significantly to BP increase. Additional dietary deficits have been also implicated in the development of hypertension, including low fruit and vegetable intake, low dairy food consumption and low intake of oily fish. Deficiencies of single micro-nutrients such as folate, riboflavin, vitamin C and vitamin D have also been recently recognised as risk factors for hypertension. 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 [5].

Beyond the well-known effects on BP of the DASH [6] and the Mediterranean diets [7], a large number of studies has investigated the possible BP lowering effect of

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different dietary supplements and nutraceuticals, the most part of them being antioxidant agents with a high tolerability and safety profile (Table 1). In fact nutrient–gene interactions and epigenetics are predominant factors in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Macronutrients and micronutrients can prevent, control and treat hypertension through numerous mechanisms related to vascular biology [8].

In this context, the aim of this review is to resume the available evidence supporting the use of some dietary supplements with known BP in clinical practice.

2 Methods

We reviewed studies published in English language from 1990 to 2014 on dietary supplements or nutraceuticals claiming to show an effect on human blood pressure. An initial list of possibly effective agents and studies was obtained from the online reference Natural Medicine Comprehensive Database. Using PubMed, we searched agents identified from this list and the MeSH terms "hypertension", "blood pressure", "dietary supplement", and "nutraceuticals" alone and in combination. Then we focused our attention on meta-analyses and randomized clinical trials.

Table 1 Dietary supplements and nutraceuticals with clinically relevant blood pressure lowering effect in humans

Dietary supplement/ nutraceutical	Level of evidence	Putative mechanism of action
Polyunsaturated fatty acids (high dosages)	Meta-analysis of RCTs	↓ TXA2 and inflammation, ↑ vasodilator PGs, ↑ NO synthase, ↓ insulin resistance, ↓ RAAS
Isoflavones	Meta-analysis of RCTs	ACE-inhibition, direct endothelial effect
Lactotripeptides	Meta-analysis of RCTs	ACE-inhibition
Fish peptides	Different small RCTs	ACE-inhibition
L-Arginine (high dosages)	Meta-analysis of RCTs	↑ NO availability
Potassium	Different RCTs	↑ Natriuresis, ↑ baroflex sensitivity modulation, ↑ Na-K ATPase, ↑ insulin sensibility, ↓ Ang. II, ↓ catecholamines sensitivity, ↓ ADMA, ↓ oxidative stress, ↓ TGF-beta
Chelated magnesium	Meta-analysis of RCTs	Ca channel blockers, ↑ PGE, ↑NO synthesis
Calcium (in pregnancy)	Meta-analysis of RCTs	Unclear
Vitamin C	Meta-analysis of RCTs	↓ Adrenal steroid production and serum aldehydes, ↓ the binding affinity of the AT1-r by Ang. II,↑ Na-K ATPase, ↑ natriuresis, ↑ superoxide dismutase, ↑ cGMP, ↑ NO and PGI2
Cocoa flavonoids	Meta-analysis of RCTs	Antioxidant, free radical scavenger, ↑ NO production and endothelial function, ↓ inflammation, ↓ ROS (NADPH oxidase inhibitor)
Coenzyme Q10 (high dosage in hypertensives)	Meta-analysis of RCTs	Antioxidant, free radical scavenger, ↑ vitamins and antioxidants regeneration, co-factor and co-enzyme in mitochondrial oxidative phosphorylation, ↑ LDL and lipid oxidation
Lycopene	Meta-analysis of RCTs	Antioxidant, free radical scavenger
Controlled release melatonin (night hypertension)	Meta-analysis of RCTs	↑ NO production, protecting vessels from oxidation, regulation of circadian rhythms
Aged garlic extract	Meta-analysis of RCTs	↑ NO production, ↑ H2S, ↑ Bradikinin, ↓ catecholamine sensitivity, ACE inhibition, Ca channel blocking
Beetroot juice	Meta-analysis of RCTs	↑ NO availability
Probiotics	Meta-analysis of RCTs	Unclear/Multiple
Pycnogenol	Meta-analysis of RCTs	↑ NO production, ↑ endothelial function, ↓ myeloperoxidase activity
Resveratrol	Meta-analysis of RCTs	↑ NO production, ↓ oxidation, ↓ vascular inflammation

RCTs randomized clinical trials

3 Nutrients

3.1 Fats

Different epidemiological data and some trials suggest that the consumption of monounsaturated fatty acids, in particular when provided by olive oil in the context of a Mediterranean diet, could be associated to lower level of BP [9, 10]. In a recent study on 7447 patients at high risk for cardiovascular disease, participants allocated to the Mediterranean diet group supplemented with extra virgin olive oil had significantly lower diastolic BP than the participants in the control group (−1.53 mmHg, 95 % confidence interval (CI) −2.01 to −1.04) [11]. However, scarce data are available for monounsaturated fatty acids assumed as a dietary supplement: in a study of 40 hypertensive monozygotic twins, olive leaf extract demonstrated a dose response reduction in BP at doses of 500–1000 mg/days in 8 week compared to placebo. The low dose groups decreased BP 3/1 mmHg and the high dose 11/4 mmHg [12].

On the contrary a larger amount of data is available as it regards the effect on omega 3 polyunsaturated fatty acids (PUFAs): in a number of clinical trials different dosages of supplemented PUFAs (in the most part of cases included between 2000 and 4000 mg/day) have been associated to a variable improvement of both systolic (SBP) and diastolic BP (DBP) of around 4/2 mmHg [13].

A recent meta-analysis also showed that PUFA supplementation is associated to improvement in both pulse wave velocity ($g = 0.33$; 95 % CI 0.12, 0.56; $P < 0.01$) and arterial compliance ($g = 0.48$; 95 % CI 0.24, 0.72; $P < 0.001$). No safety concerns were raised beyond mild gastrointestinal discomfort for high dosages [14].

The suggested mechanisms by which PUFAs improve BP control are numerous: enhancement of the generation and bioavailability of endothelium-derived relaxing factor (nitric oxide—NO) through up-regulation and activation of endothelial NO synthase (eNOS), prostaglandins synthesis balance toward vasodilating ones, insulin-resistance reduction, vascular tone regulation by parasympathetic nervous system stimulation, and suppression of the renin–angiotensin–aldosterone system [15].

3.2 Proteins, peptides and amino-acids

A recent meta-analysis of 40 randomized controlled trials (including 3277 participants in total) evaluated the association of dietary protein intake with blood pressure. Compared with carbohydrate, dietary protein intake was associated with significant changes in mean systolic and diastolic blood pressure of −1.76 mmHg (95 % CI: −2.33, −1.20) and −1.15 mmHg (95 % CI: −1.59, −0.71), respectively (both P's < 0.001). Both vegetable proteins and animal proteins were associated with significant BP changes of −2.27 mmHg (95 % CI: −3.36, −1.18) and −2.54 mmHg (95 % CI: −3.55, −1.53), respectively, for SBP (both P's < 0.001) and −1.26 mmHg (95 % CI: −2.26, −0.26) and −0.95 mmHg (95 % CI: −1.72, −0.19), respectively, for DBP (both P's $= 0.014$). Blood pressure reduction was not significantly different when vegetable protein was compared directly with animal proteins. These findings indicate that partially replacing dietary carbohydrate with protein may be important for the prevention and treatment of hypertension [16].

The intake of plant proteins should be preferable because they could have a less negative impact on renal function [17]. However it is not easy to discriminate between the effect of plant proteins and of other dietary associated components on BP level. In particular, isoflavones assumed with soy could be the real responsible of the soy-related decrease in BP: a recent meta-analysis show that in hypertensive patients soy isoflavones intake is associated to a SBP decrease by −5.94 (95 % CI −10.55, −1.34 mmHg, $P = 0.01$) and of DBP by −3.35 (95 % CI −6.52, −0.19 mmHg, $P = 0.04$) [18].

A rich natural source of peptides and amino acids is whey. It has been reported in numerous studies that biological active peptides isolated from cow's milk whey may affect BP regulation. Studies on animals and humans have shown that α-lactalbumin and β-lactoglobulin obtained from enzymatically hydrolysed whey inhibit angiotensin converting enzyme (ACE), while lactorphins lower blood pressure by normalizing endothelial function or by opioid receptors dependent mechanism [19].

Milk peptides (particularly the tripeptides Val–Pro–Pro and Ile–Pro–Pro), supposed to have ACE inhibitory activity [20], given at 5–60 mg per day have variable reductions in BP, more evident in Asian subjects: in a meta-analysis by our group considering 18 randomized clinical trials the pooled effect of peptides was a reduction of −3.73 mmHg (95 % CI −6.70, −1.76) for SBP and 1.97 mmHg (95 % CI: −3.85, −0.64) for DBP [21]. More recent data show that these peptides could also positively modulate pulse wave velocity in mildly hypertensive subjects. No safety concerns were raised [22].

Also some fish meat seems to contain peptides with powerful ACE inhibitory activity, that induced significant reduction of BP around $-9 \pm 3/4 \pm 1$ mmHg in single clinical trials carried out with bonito, sardine, tuna and mackerel meat [23], but these evidence have to be confirmed by repeated and larger clinical trials.

Among single amino acids, L-Arginine, a semi-essential amino acid, is the natural substrate for nitric oxide (NO) synthase and responsible for the production of the endothelium-derived relaxing factor NO, which is involved in

a wide variety of regulatory mechanisms of the cardiovascular system [24]. A recent meta-analysis of 11 randomized, double-blind, placebo-controlled trials involving 387 participants with oral L-arginine intervention ranging from 4 to 24 g/day concludes that, compared with placebo, L-arginine intervention significantly lowered SBP by 5.39 mmHg (95 % CI −8.54, −2.25, P = 0.001) and DBP by 2.66 mmHg (95 % CI −3.77, −1.54, P < 0.001), suggesting that a 4 weeks treatment is already sufficient to determine the maximal effect [25].

In a randomized clinical trial carried out in type 2 diabetic patients, the combination of arginine (1200 mg per day) and *N*-acetyl cysteine (600 mg bid) over 6 months lowered BP, increased HDL-C, decreased LDL-C and oxLDL, reduced systemic inflammation biomarkers and vascular adhesion molecule level and intima-media thickness, suggesting a sort of synergistic effect of these two amino acids [26].

3.3 Potassium, magnesium and other minerals

The effectiveness of restricted sodium or increased potassium intake on mitigating hypertension risk has been demonstrated in clinical and observational research, influencing the renin–angiotensin system, arterial stiffness, and endothelial dysfunction. In particular recent findings suggest that the sodium-to-potassium ratio appears to be more strongly associated with hypertension incidence and related outcomes than either sodium or potassium alone in hypertensive adult populations [27].

A balanced diet should contain potassium (K^+) 4700 mg/day (120 mmol/day) with a K^+/Na^+ ratio of about 4–5 to 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 sodium intake [28]. Higher K^+ is also associated to a lower incidence of cardiovascular and cerebrovascular accidents, type 2 diabetes, left ventricular hypertrophy, heart failure, and cardiac arrhythmias, independently of BP reduction [29].

A recent meta-analysis concluded that a 1.64 g (42 mmol) per day higher potassium intake is associated with a 21 % lower risk of stroke (RR: 0.79; 95 % CI: 0.68, 0.90; p = 0.0007), with a trend toward lower risk of coronary and total cardiovascular disease that attained statistical significance after the exclusion of a single cohort, based on sensitivity analysis (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) [30]. It has also been estimated that each 1000 mg increase in K^+ intake per day will reduce all-cause mortality by 20 % and each 1000 mg decrease in sodium intake per day will decrease all-cause mortality by 20 % [31].

Numerous mechanisms have been supposed for the K^+ induced BP reduction: increased natriuresis, baroreflex sensitivity modulation, decreased sensitivity to catecholamines and angiotensin II, increased sodium-potassium ATPase in the vascular smooth muscle cells, improved function of the sympathetic nervous system, decreases in NADPH oxidase, which lowers oxidative stress and inflammation, improves insulin sensitivity, decreases asymmetric dimethylarginine, reduces intracellular sodium and lowers production of Tumor Growth Factor-beta [32].

Besides, K^+ in food or from supplementation should be used with caution in those patients with renal impairment or those on medications that increase renal potassium retention [33].

There is also an inverse relationship between dietary magnesium (Mg^{2+}) intake and BP. The maximum BP reduction observed in clinical trials has been 5.6 ± 2.2/2.8 ± 1.9 mmHg, but there is a large variability in answer in different studies. However a recent meta-analysis of randomized clinical trials concluded that Mg^{2+} supplementation is associated to a decrease in SBP of 3.4 ± 2 mmHg and DBP of 2.5 ± 1 mmHg, which further increased with crossover designed trials and intake >370 mg/day [34]. The optimal supplemented dose seems to be between 500 and 1000 mg per day, better if chelated to an amino acid to improve absorption and to decrease the incidence of diarrhea. Adding taurine at 1000–2000 mg per day seems to enhance the Mg^{2+} anti-hypertensive effects [35].

The combination of high potassium and low sodium intake with increased magnesium intake had additive antihypertensive effects in both antihypertensive treated and untreated subjects [36].

Numerous mechanisms have been supposed for the Mg^{2+} induced BP reduction: calcium-channel blocking action, PGE increase, and nitric oxide synthesis improvement [37].

Magnesium supplements should be avoided or used with caution in patients with known renal insufficiency or in those taking medications that induce magnesium retention.

While in hypertensive subjects calcium supplementation seems not to be efficacious in term of BP reduction, it appears to be particularly useful in pregnant women: a recent meta-analysis of the Cochrane Collaboration involving 13 studies of good quality and more than 15,000 women supports its use during pregnancy, as it appears to approximately halve the risk of pre-eclampsia, to reduce the risk of preterm birth and to reduce the rare occurrence of the composite outcome ‘death or serious morbidity’ without evidence of any relevant side effect [38].

3.4 Vitamins

Deficiencies of vitamin C and vitamin D have been recognized as risk factors for hypertension, while Vitamin C or plasma ascorbate concentration in humans is inversely correlated to BP [39] and to a reduced risk of cardiovascular disease [40, 41]. In particular, hypertensive subjects were found to have significantly lower plasma ascorbate levels compared to normotensive subjects (40 vs. 57 μmol/l, respectively) [42]. A depletion–repletion study of vitamin C also confirmed an inverse correlation of plasma ascorbate levels, SBP and DBP [43]. Thus, in order to achieve a positive effect on BP, it is recommended to maintain an ascorbate serum level of at least 100 μmol/l [44].

In a recent meta-analysis of clinical trials with a median vitamin C dose of 500 mg per day over a median 8 week period reduced SBP by 4.85 ± 1.21 mmHg ($P < 0.01$) and DBP by 1.67 ± 0.72 mmHg ($P = 0.17$) in hypertensive patients. No safety concerns were raised [45].

Vitamin C also seems to improve the efficacy of effective antihypertensive drugs such as amlodipine [46]. In elderly patients with refractory hypertension already on maximum pharmacologic therapy, 600 mg of vitamin C daily lowered the BP by 20 ± 8/16 ± 5 mmHg [47].

Numerous mechanisms have been supposed to be the cause of Vitamin C induced BP reduction: nitric oxide and PgI_2 increase that lead to, endothelial function and arterial compliance improvement [48], sodium water diuresis induction, adrenal steroid production decrease, sympathovagal balance improvement, Na/K ATPase increase, superoxide dismutase increase, cyclic GMP increase, potassium channels activation, cytosolic calcium reduction [49] and serum aldehydes decrease [50]. Moreover, it seems to decrease the binding affinity of the AT1 receptor by angiotensin II by disrupting the ATR1 disulfide bridges [51].

The supplemented doses of vitamin C suggested to improve BP (500–1000 mg/day) is usually well-tolerated and does not require specific attention.

Patients with hypertension are also more likely than controls to have diminished levels of vitamin B6 [52]. A couple of clinical trials supported a BP reducing effect of vitamin B6 supplementation [53, 54], but no further data confirmed this effect.

Patients with hypertension are also more likely than controls to have diminished levels of vitamin D [55]. However, beyond some suggestive experimental and observational studies, a relative large number of recent meta-analyses of the available clinical data gives conflicting data about the Vitamin D effect on BP [56].

3.5 Flavonoids

Epidemiological studies have suggested that the daily intake of flavonoids is associated with a decreased risk of developing cardiovascular disease [57].

A large number of dietary flavonoids exert vascular protective effects, being antioxidant, antinflammatory, improving NO metabolism and endothelial function, moreover its intake is associated to a reduced risk of cardiovascular disease [58]. Cocoa flavonoids are the most studied ones in clinical setting; flavanols from chocolate appear to increase nitric oxide bioavailability, protect vascular endothelium, and decrease cardiovascular disease (CVD) risk factors. Nitric oxide plays a pivotal role in regulating vascular tone. Different studies show endothelial function is impaired during hyperglycemia Dark chocolate increases flow-mediated dilation in healthy and hypertensive subjects with and without glucose intolerance [59, 60].

A recent meta-analysis of 20 randomized, double-blind, placebo-controlled, clinical trials involving 856 mainly healthy participants revealed a statistically significant blood pressure reducing effect of flavanol-rich cocoa products compared with control in short-term trials of 2–18 weeks duration: mean difference SBP −2.77 (95 % CI: −4.72, −0.82) mmHg, $p = 0.005$; mean difference DBP −2.20 (95 % CI: −3.46, −0.93) mmHg, $p = 0.006$. Trials provided participants with 30–1080 mg of flavanols (mean = 545.5 mg) in 3.6–105 g of cocoa products per day in the active intervention group. In half of the trials ($n = 10$) the active group consumed 500–750 mg of flavanols per day. The control group received either a flavanol-free product ($n = 12$) or a low-flavanol containing cocoa powder (6.4 and 41 mg flavanols, $n = 8$). The large eterogenity of the trial characteristics and the enrollment of mostly healthy subjects has probably reduce the potential impact of cocoa flavonols on BP, however it remains statistically significant [61]. Data on coffee are more conflicting [62].

Some clinical trials demonstrated that chlorogenic acid from non-roasted green coffee is associated to a significant reduction in BP [63]. The roasting of ordinary coffee induce the synthesis of hydroxyhydroquinone (HHQ) that inhibits the effect of chlorogenic acid, so that coffee seems to be also able to reduce BP inversely to the HHQ content [64].

Recent data show that regular consumption of both green [65] and black [66] tea are associated to significantly lower BP level, as well. In particular, findings from several animal studies suggest that green tea lowers BP by suppressing the NADPH oxidase activity and reducing the numbers of reactive oxygen species in the vascular system [67].

A systematic review including 20 randomised clinical trials comprising 1536 participants were included revealed a significant reduction in SBP favouring green tea (MD: −1.94 mmHg; 95 % CI −2.95 to −0.93; $P = 0.0002$) vs. placebo. Adverse events included rash and abdominal discomfort [68].

A meta-analysis of four randomized, placebo-controlled clinical trials, with a total of 390 patients show that *Hibiscus sabdariffa* tea (sour tea) is also associated to a significant reduction of BP, even in already pharmacologically treated subjects; however the considered studies were relatively small and short-term [69].

3.6 Resveratrol

Resveratrol (*trans*-3,5,4′-Trihydroxystilbene) is a rich source of polyphenols which have anti-oxidant effects in vivo [70]. Many studies have shown anti-hypertensive effects of resveratrol in different pre-clinical models of hypertension, through a multitude of mechanisms that include its anti-oxidant properties, the stimulation of endothelial production of NO, the inhibition of vascular inflammation and the prevention of platelet aggregation [71].

Six studies comprising a total of 247 subjects were included in a meta-analysis. The overall outcome of the meta-analysis indicates that resveratrol consumption cannot significantly reduce SBP and DBP. Subgroup analyses indicated that higher-dose of resveratrol consumption (≥150 mg/day) significantly reduces SBP of −11.90 mmHg (95 % CI −20.99, −2.81 mmHg, P = 0.01), whereas lower dose of resveratrol did not show a significant lowering effect on SBP [72].

3.7 Other dietary components

While dietary fibers are associated to a very mild decrease in BP, especially when incorporated in a Mediterranean diet, the supplementation of soluble fibers has been associated to a significant BP reduction in a couple of recent randomized clinical trials, with parallel positive effect on glucose and lipid metabolism [73, 74].

Soluble fiber, guar gum, guava, psyllium, and oat bran may reduce BP and reduce 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 on 40 to 50 g/day of a mixed fiber [75, 76].

Black sesame consumption has also been associated in a number of clinical trials, especially in Asian subjects [77], but not in the context of a Western diet [78].

Pomegranate juice has also potent antioxidant, antiatheromasic and ACE inhibitory activity determining significant BP reduction in humans [79], but long-term studies are required [80].

3.8 Coenzyme Q10 (CoQ10)

Co-Enzyme Q10 (Ubiquinone) is a potent lipid phase antioxidant, free radical scavenger, reduces oxidative stress, regenerates other vitamins and antioxidants, reduces oxidation of LDL, is a co-factor and co-enzyme in mitochondrial oxidative phosphorylation that lowers BP, often reduced in hypertensive patients [81].

A relatively large number of clinical trials support the antihypertensive effect of high dosages of CoQ10. A meta-analysis of randomized, placebo-controlled, clinical trials conclude that oral treatment with 100 mg or more CoQ10 in subjects with systolic BP >140 mmHg or diastolic BP >90 mmHg resulted in mean decreases in SBP of 11 mmHg (95 % CI 8, 14) and DBP of 7 mmHg (95 % CI 5, 8), usually after 4 weeks of treatment [82, 83].

The main problem of CoQ10 as antihypertensive agent is the high cost of the high doses needed to obtain a significant BP reduction, because of the low bioavailability of CoQ10 in humans, that could be improved by the use of partly CoQ10 emulsification and nanoparticles improve intestinal absorption and serum levels [84].

3.9 Lycopene

A recent meta-analysis of randomized clinical trials investigating the effect of the carotenoid lycopene (10–20 mg/day) on systolic BP suggested a significant BP reducing effect (mean systolic BP change ±SE: −5.60 ± 5.26 mmHg, p = 0.04) [85]. The effect of lycopene on BP appears to be additive to the one of antihypertensive drugs [86].

A 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 the tomato, which is the richest source of lycopene in the Western diet. In fact, with the exception of BP management where lycopene supplementation was favored, tomato intake provided more favorable results on cardiovascular risk endpoints than did lycopene supplementation [87].

3.10 Pycnogenol

Bark extract of *Pinus pinaster* (French maritime pine), usually marketed as pycnogenol, acts as a natural angiotensin-converting enzyme 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 hs-CRP, all properties that support its potential positive effect on human BP [88].

Clinical evidence clearly shows that supplementation with 100 mg pycnogenol in subjects treated with different antihypertensive drugs led to the reduction of the drug doses in nearly the half of patients [89, 90]. However no clear evidence of an antihypertensive effect in non-pharmacologically treated patients is available, beyond some small positive trials [91].

3.11 Melatonin

Melatonin is a hormone normally secreted from the pineal gland at night. It serves as the signal of darkness in the organism, and as such plays a pivotal role in the physiological regulation of circadian rhythms, including sleep [92]. Melatonin seems to improve BP control both by central mechanisms and peripheral, protecting vessels from oxidation, improving NO metabolism and consequently endothelial function [93]. A meta-analysis of randomized, double-blind, placebo-controlled, clinical trials (three of controlled-release and four of fast-release melatonin) with 221 participants, night SBP decreased significantly with controlled-release melatonin (−6.1 mmHg; 95 % CI: −10.7, −1.5; P = 0.009) but not fast-release melatonin (−0.3 mmHg; 95 % CI −5.9, 5.30; P = 0.92). Night diastolic BP also decreased significantly with controlled-release melatonin (−3.5 mmHg; 95 % CI −6.1, −0.9; P = 0.009) but not fast-release melatonin (−0.2 mmHg; 95 % CI −3.8, 3.3; P = 0.89). No safety concerns were raised [94]. Besides, because beta-blockers inhibit melatonin secretion, melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers [95]. No side effect have been till now reported after melatonin use.

3.12 Aged garlic extract

Garlic supplements have shown promise in the treatment of uncontrolled hypertension, lowering BP by about 10 mmHg systolic and 8 mmHg diastolic, similar to standard BP medication. Aged garlic extract, which contains S-allylcysteine as the bioactive sulfur compound, in particular is standardizable and highly tolerable, with little or no known harmful interaction when taken with other BP-reducing or blood-thinning medication. Garlic-derived polysulfides stimulate the production of the vascular gaseotransmitter hydrogen sulfide (H_2S) and enhance the regulation of endothelial NO, which induce smooth muscle cell relaxation, vasodilation, and BP reduction. Several dietary and genetic factors influence the efficiency of the H_2S and NO signaling pathways and may contribute to the development of hypertension. Sulfur deficiency might play a part in the etiology of hypertension, and could be alleviated with supplementation of organosulfur compounds derived from garlic [96].

Aged dry garlic extract also have ACE inhibitory and calcium channel blocking activity, that reduce catecholamine sensitivity, increase bradykinin and NO, and improve arterial compliance [97].

A recent meta-analysis of randomized, placebo-controlled, clinical trials shows a mean decrease of 4.6 ± 2.8 mmHg for SBP in the garlic group compared to placebo (p = 0.001), while the mean decrease in the hypertensive subgroup was 8.4 ± 2.8 mmHg for SBP (p < 0.001), and 7.3 ± 1.5 mmHg for DBP (p < 0.001). Regression analysis revealed a significant association between BP at the start of the intervention and the level of BP reduction (SBP: R = 0.057; p = 0.03; DBP: R = −0.315; p = 0.02) [98]. The effect seems to be addictive also to antihypertensive drugs [99].

Garlic extract has also a mild positive effect on cholesterolemia, but is often associated to mild gastrointestinal side effects.

3.13 Beetroot juice

The consumption of beetroot juice on a low nitrate diet as a source of inorganic nitrate (NO_3) may lower BP [100].

NO_3^- has received considerable attention in recent years and is quickly gaining traction as a health and performance enhancing nutritional supplement for adverse cardiovascular outcomes including stroke, myocardial infarction, systemic and hypertension. Once ingested, inorganic NO_3^- metabolizes in vivo to bioactive nitrite (NO_2^-) and is subsequently salvaged and circulated in human blood flow. NO_2^- exerts these effects in the body via its conversion to functional nitrogen oxides, including NO [101, 102].

Single dose administration of dietary NO_3 (250 ml daily, as beetroot juice) acutely reduces BP in normotensive/pre-hypertensive/mild hypertensive volunteers, via bioconversion to the vasodilator nitric oxide [101, 103]. In a meta-regression of the available clinical data, inorganic nitrate and beetroot juice consumption were associated with greater changes in systolic BP (−4.4 mmHg, 95 % CI −5.9, −2.8; P < 0.001) than diastolic BP (−1.1 mmHg, 95 % CI −2.2, 0.1; P = 0.06) [104].

3.14 Probiotics

Probiotic consumption may improve BP control. Jayasinghe et al. [105] concluded in a meta-analysis of randomized, controlled trials, that consuming probiotics may improve BP by a modest degree, with a potentially greater effect when baseline BP is elevated, multiple species of probiotics are consumed, the duration of intervention is

≥8 weeks, or daily consumption dose is $\geq 10^{11}$ colony-forming units.

This effect could be improved when probiotics are assumed as fermented milk. In fact a meta-analysis of fourteen randomised placebo-controlled trials involving 702 participants showed that probiotic fermented milk, compared with placebo, produced a significant reduction of 3·10 mmHg (95 % CI 24·64, 21·56) in systolic BP and 1·09 mmHg (95 % CI 22·11, 20·06) in DBP. Subgroup analyses suggested a slightly greater effect on systolic BP in hypertensive participants than in normotensive ones (23·98 vs. 22·09 mmHg). Analysis of trials conducted in Japan showed a greater reduction than those conducted in European countries for both SBP (26·12 vs. 22·08 mmHg) and DBP (23·45 vs. 20·52 mmHg) [19].

4 Conclusion

Dietary modifications such as salt restriction, moderation of alcohol drinking, and a diet rich in fruits, vegetables, and legumes and low in snacks, sweets, meat, and saturated fat are helpful in the treatment of hypertension. Consumption of dark chocolate is also associated with a drop in systolic blood pressure. Individual dietary factors that may reduce blood pressure include increased intakes of potassium, calcium, fish oil, fiber, and milk-based and vegetable-based protein.

The use of nutraceuticals with antihypertensive activity, in association to a coherent improvement of diet and lifestyle, in addition to constituting a cornerstone in the prevention of cardiovascular disease, represents a good compromise for pre-hypertensive patients and excellent adjuvant together with the pharmacological treatment in hypertensive patients.

However there is a need for data about the long-term safety of a large part of the above discussed products. Moreover further clinical research is advisable to identify between the available active nutraceuticals those with the best cost-effectiveness and risk–benefit ratio for a large use in general population with low-added cardiovascular risk related to uncomplicated hypertension.

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