EXPERT REVIEWS

Nutrition and nutraceutical supplements in the treatment of hypertension

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Macronutrient and micronutrient deficiencies are very common in the general population and may be even more common in patients with hypertension and cardiovascular disease due to genetic, environmental causes and prescription drug use.. Vascular biology assumes a pivotal role in the initiation and perpetuation of hypertension and target organ damage sequelae. Endothelial activation, oxidative stress and vascular smooth muscle dysfunction (hypertrophy, hyperplasia, remodeling) are initial events that start hypertension. Nutrient-gene interactions determine a broad array of phenotypic consequences such as vascular problems and hypertension. Optimal nutrition, nutraceuticals, vitamins, antioxidants, minerals, weight loss, exercise, smoking cessation and moderate restriction of alcohol and caffeine in addition to other lifestyle modifications can prevent, delay the onset, reduce the severity, treat and control hypertension in many patients. An integrative approach combining these lifestyle suggestions with the correct pharmacologic treatment will best achieve new goal blood pressure levels, reduce cardiovascular risk factors, improve vascular biology, vascular health, reduce target organ damage including coronary heart disease, stroke, congestive heart failure and renal disease and reduce health care expenditure. The expanded scientific roles for nutraceutical supplements will be discussed in relation to the prevention and treatment of essential hypertension and cardiovascular diseases.

KEYWORDS: antioxidants • hypertension • natural treatment • nutrition • vascular biology

Hypertension is a consequence of the interaction between genetics and the environment. Macronutrients and micronutrients are crucial in the regulation of blood pressure (BP) and subsequent target organ damage (TOD). Nutrient–gene interactions, subsequent gene expression, oxidative stress and inflammation have positive or negative influences on vascular biology in humans. Endothelial dysfunction (ED) and vascular smooth muscle dysfunction (VSMD) initiate and perpetuate essential hypertension. The optimal combination of macronutrients and micronutrients significantly impacts hypertension prevention, treatment and the potential vascular complications [1].

The transition from the Paleolithic diet to our modern diet has produced an epidemic of nutritionally related diseases [1,2]. Hypertension, atherosclerosis, coronary heart disease (CHD), myocardial infarction (MI), congestive heart failure (CHF), cerebrovascular accidents (CVAs), renal insufficiency (RI), renal failure (RF), Type 2 diabetes mellitus, metabolic syndrome and obesity are some of these diseases [1,2]. A short-term reduction in BP utilizing nutrition results in intermediate and long-term improvements in morbidity and mortality, including CVAs, CHD and MI [1,2].

Nutrition & disease prevention

An integrative approach that uses nutrition, vitamins, antioxidants, minerals, functional foods, nutraceuticals, weight loss, exercise, judicious use of alcohol and caffeine with tobacco cessation combined with optimal pharmacologic therapy is the best means to reduce BP and TOD in most hypertensive patients. To achieve lower BP goals will require a combination of lifestyle modifications and drug therapy [1–3].

Such lifestyle changes may prevent or delay the onset of hypertension and reduce BP levels and the progression of CVD, allowing for fewer drugs and/or lower doses. Finally, there may be additive or synergistic improvements in cardiovascular risk factors, and vascular function, structure and health [1,4].

Approximately 50–60% of essential hypertensive patients are excellent and appropriate candidates for preliminary and prolonged lifestyle

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modifications, as long as the BP is frequently evaluated, and clinical TOD, clinical cardiovascular disease, diabetes mellitus or significant risk factors are not present at that time and do not develop later [3,4].

This article will review the basic science and clinical studies of nutraceutical supplements, vitamins, antioxidants, minerals, macronutrients and micronutrients, and their impact on the prevention and treatment of hypertension. It is important to integrate nutrition and nutraceutical science with traditional drug therapy to reduce BP and TOD, and improve the dismal statistics of BP control worldwide [5].

Hypertension & oxidative stress in humans

Oxidative stress with an imbalance between reactive oxygen species (ROS) and the anti-oxidant defense mechanisms may contribute to the etiology of hypertension in animals [6] and humans [6,7].

Hypertensive patients have an impaired endogenous and exogenous antioxidant defense mechanism [8]. In addition, hypertensive patients have more oxidative stress with more ROS produced and a greater than normal response to oxidative stress [8,9].

The proposed mechanisms of ROS-induced hypertension in humans are shown in Box 1.

Antioxidant deficiency and excess free radical production have been implicated in human hypertension in numerous epidemiologic, observational and interventional studies [8–10].

A summary of the present research and conclusions of the role of oxidative stress in animal and human hypertension is shown in Box 2. The inter-relations of neurohormonal systems, oxidative stress and cardiovascular disease is shown in Figure 1 [8,9]. The increased oxidative stress and inflammation in human hypertension is thus a combination of the increased generation of ROS, an exacerbated response to ROS and a decreased antioxidant reserve [8–12].

Evolutionary nutrition

Humans have evolved from a pre-agricultural, hunter-gatherer society to commercial agriculture with highly processed, refrigerated and fast foods that have imposed an unnatural and unhealthy nutrition. The human genetic makeup is 99.9% that of our Paleolithic ancestors, yet our nutritional, vitamin and mineral intakes are vastly different [13]. The macronutrient and micronutrient variations contribute to the higher incidence of hypertension and other cardiovascular diseases through a complex nutrient–gene interaction (Figure 2) [14,15]. Poor nutrition, coupled with obesity and a sedentary lifestyle, have resulted in an exponential increase in nutritionally related diseases. In particular, the high Na^+/K^+ ratio of modern diets has contributed to hypertension, stroke, CHD, CHF and renal disease [13]. In addition, the relatively low intake of omega-3 polyunsaturated fatty acids (PUFAs) and increase in omega-6 PUFA saturated fat and *trans* fatty acids has contributed to the increased incidence of CHD, hypertension, diabetes mellitus and hyperlipidemia [16].

Box 1. Hypertension and oxidative stress: reactive oxygen species in hypertension.

Mechanisms of ROS in high BP

- Direct action on endothelial cell with structural and functional damage
- Degradation of NO by ROS
- Effects on eicosanoid metabolism in endothelial cell
- Oxidative modification of LDL-C
- Hyperglycemia
- Hyperinsulinemia
- Fatty acid mobilization
- Catecholamines
- Angiotensin II increases O_2^- via NADPH oxidase

BP: Blood pressure; C: Cholesterol; NO: Nitric oxide; ROS: Reactive oxygen species.

Sodium

The average sodium (Na^+) intake in the USA is 5000 mg per day, with some areas of the country consuming 15,000–20,000 mg per day [14]. However, the minimal requirement for Na^+ is probably approximately 500 mg per day [17]. Epidemiologic, observational and controlled clinical trials demonstrate that an increased Na^+ intake is associated with higher blood pressure [17]. A reduction in Na^+ intake in hypertensive patients, especially salt-sensitive patients, will significantly lower blood pressure by 4–6/2–3 mmHg, respectively, which is proportional to the severity of Na^+ restriction [18,19]. Na^+ has a major impact on cardiovascular, cerebrovascular and renal disease [20,21]. Studies have documented a direct relationship between Na^+ intake and increased platelet reactivity, stroke (independent of BP), left ventricular hypertrophy, MI, CHF, sudden death and left ventricular filling [20,21]. The renal plasma flow falls and the glomerular filtration rate increases, leading to an increase in intraglomerular capillary pressure, microalbuminuria, proteinuria, glomerular injury and renal insufficiency [20,21]. Na^+ also reduces arterial compliance independent of BP changes [20,21].

Salt sensitivity (≥10% increase in mean arterial pressure with salt loading) is a key factor in determining the cardiovascular, cerebrovascular, renal and blood pressure response to dietary salt intake [22]. Cardiovascular events are more common in salt-sensitive patients than in salt-resistant ones, independent of BP [23].

The evidence is very suggestive that a reduction of dietary salt intake reduces target organ damage (brain, heart, kidney and vasculature) that is both dependent on the small BP reduction, but also independent of the decreased BP [20,21]. A balance of Na^+ with other nutrients is important, not only in reducing and controlling BP, but also in decreasing cardiovascular and cerebrovascular events.

Potassium

The average US dietary intake of potassium (K^+) is 45 mEq per day with a K^+:Na^+ ratio of less than 1:2 [24]. The recommended intake of K^+ is 650 mEq per day with a K^+/Na^+ ratio of over 5:1 [24]. Numerous epidemiologic, observational and clinical trials have demonstrated a significant reduction in BP with increased dietary K^+ intake [24,25]. The magnitude of BP reduction with a

K^+ supplementation of 60–120 mEq per day is 4.4/2.5 mmHg in hypertensive patients [24,25]. Alteration of the K^+/Na^+ ratio to a higher level is important for both antihypertensive, as well as cardiovascular and cerebrovascular effects [26]. High K^+ intake reduces the incidence of cardiovascular and CVAs independent of BP reduction [24–26]. Gu *et al.* recently demonstrated for the first time that K^+ supplementation at 60 mmol of KCl per day for 12 weeks significantly reduced systolic BP (SBP) by 5.0 mmHg (range: -2.13 to -7.88 mmHg; $p < 0.001$) in 150 Chinese men and women aged 35–64 years [26].

Box 2. The role of oxidative stress in hypertension from animal models and human clinical studies.

- Impaired antioxidant status (endogenous and exogenous)
- More oxidative stress, more ROS production
- Greater than normal response to oxidative stress
- ROS contribute to ED in aorta and resistance arteries with imbalance of vasoconstrictors and vasodilators
- ROS is both a cause and consequence of hypertension
- Antioxidants as single or combined agents reduce BP
- Inverse relationship between BP and antioxidant intake in observational and interventional studies.
- ED leads to VSM contraction, increased SVR and BP

BP: Blood pressure; ED: Endothelial dysfunction; ROS: Reactive oxygen species; SVR: Systemic vascular resistance; VSM: Vascular smooth muscle.

Magnesium

A high dietary intake of magnesium of at least 500–1000 mg per day reduces BP in most of the reported epidemiologic, observational and clinical trials, but the results are less consistent than those seen with Na^+ and K^+ [24,27]. In most epidemiologic studies, there is an inverse relationship between dietary magnesium intake and BP [24,27]. A study of 60 essential hypertensive subjects given magnesium supplements showed a significant reduction in BP over an 8-week period documented by 24-h ambulatory BP, home and office blood BP [24,27,28].

Magnesium competes with Na^+ for binding sites on vascular smooth muscle and acts like a calcium channel blocker, it increases PGE, and binds in a necessary cooperative manner with K^+, inducing endothelial vasodilation and BP reduction [24,27,28].

Magnesium is an essential cofactor for the δ-6-desaturase enzyme that is the rate-limiting step for the conversion of linoleic acid (LA) to γ-linolenic acid (GLA) [24,27,28]. GLA elongates to form dihomo-γ-linoleic acid (DGLA), the precursor of prostaglandin E_1 (PGE_1), a vasodilator and platelet inhibitor [24,27,28].

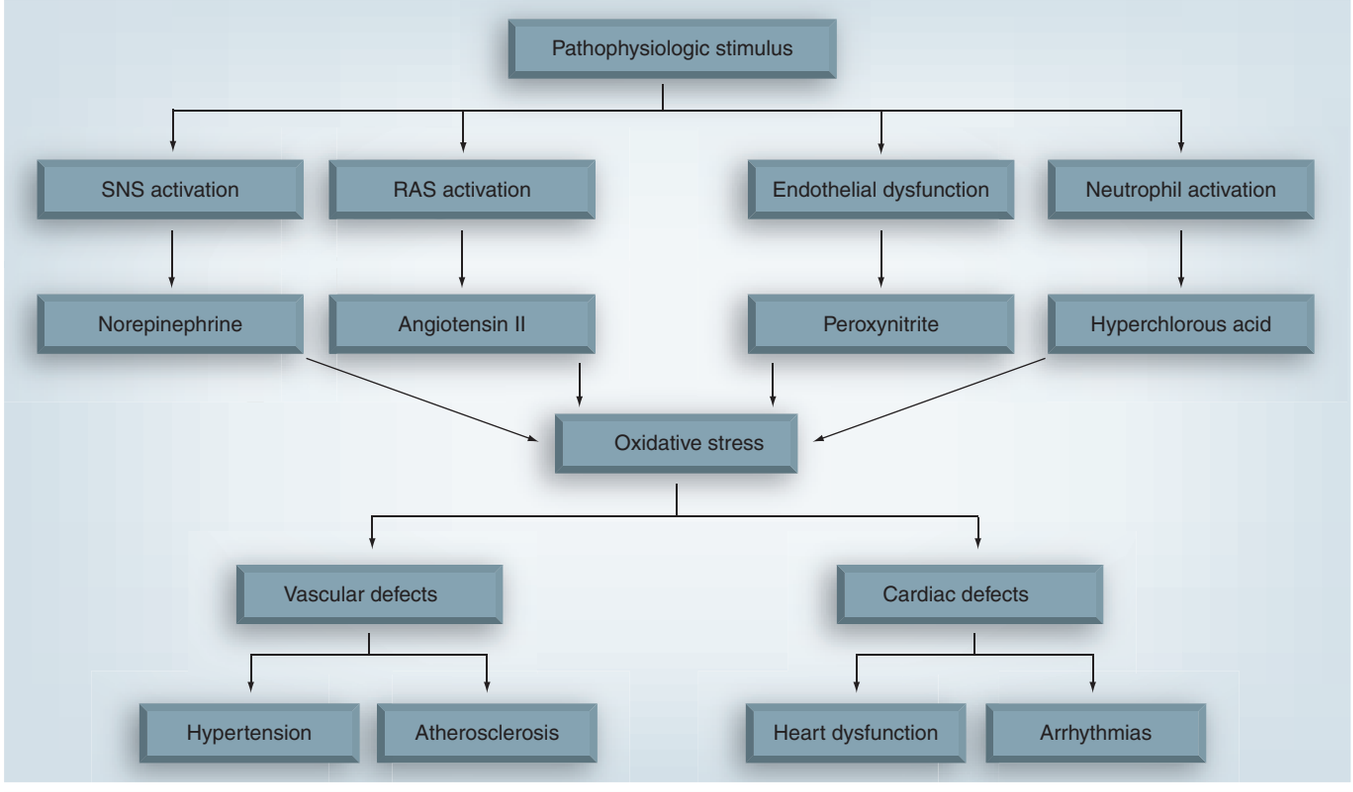

Figure 1. Role of different extracardiac and extravascular systems in the genesis of oxidative stress and development of cardiovascular abnormalities.
RAS: Renin–angiotensin system; SNS: Sympathetic nervous system.

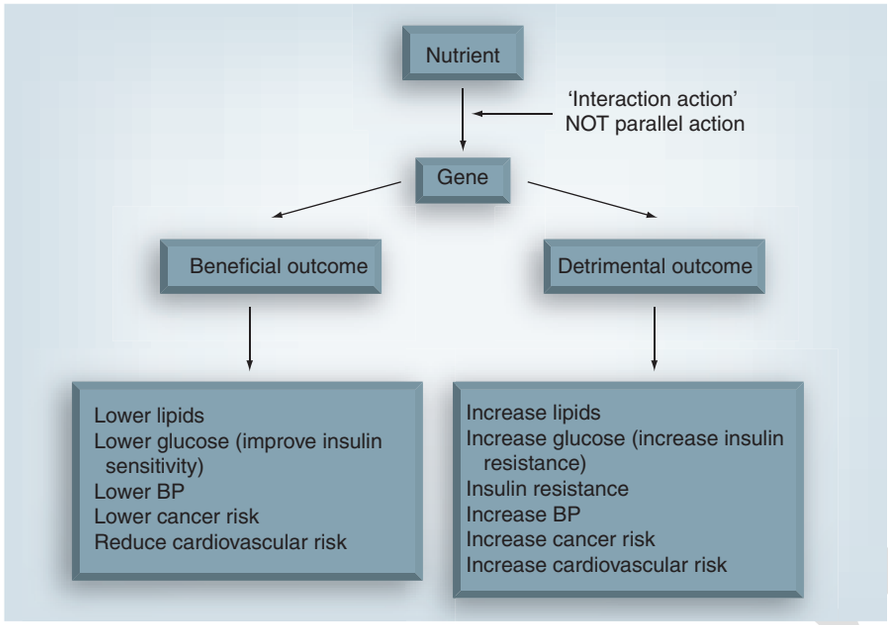

Figure 2. Nutrient regulation of gene expression.
BP: Blood pressure.

Magnesium regulates both SBP, diastolic BP (DBP), intracellular Ca^{2+}, Na^{+}, K^{+} and pH, as well as left ventricular mass, insulin sensitivity and arterial compliance [24,27,28].

Calcium

Population studies show a link between hypertension and calcium [29], but clinical trials that administer calcium supplements to patients have shown inconsistent effects on BP [24,29]. The heterogeneous responses to calcium supplementation have been explained by Resnick [30]. This is the 'ionic hypothesis' of hypertension, cardiovascular disease, and associated metabolic, functional and structural disorders [30].

Zinc

Low serum zinc levels in observational studies correlate with hypertension as well as CHD, Type 2 diabetes, hyperlipidemia), elevated lipoprotein a (Lp[a]), 2-h postprandial plasma insulin levels and insulin resistance [31].

Bergomi *et al.* evaluated Zn^{2+} status in 60 hypertensive compared with 60 normotensive control subjects [32]. An inverse correlation between BP and serum Zn^{2+} was observed. BP was also inversely correlated with Zn^{2+}-dependent enzyme-lysyl oxidase activity. Zn^{2+} inhibits gene expression and transcription through NF-κB and activated protein-1 (AP-1) [31,32]. These effects, plus those on insulin resistance, membrane ion exchange, the renin–angiotensin–aldosterone system and sympathetic nervous system effects, may account for Zn^{2+} antihypertensive effects [31,32]. Zinc intake should be between 15 and 30 mg per day [1].

Protein

Observational and epidemiologic studies demonstrate a consistent association between a high protein intake and a reduction in BP [33]. The protein source is an important factor in the BP effect; animal protein being less effective than non-animal protein [33,34]. However, lean or wild animal protein with less saturated fat and more essential omega-3 and -6 fatty acids may reduce BP, lipids and CHD risk [33].

Fermented milk supplemented with whey protein concentrate significantly reduced BP in human studies [35–37]. An administration of 20 g per day of hydrolyzed whey protein supplement rich in bioactive peptides significantly reduced BP over 6 weeks by 8.0 ± 3.2 mmHg in SBP and 5.5 ± 2.1 mmHg in DBP [36]. Powdered fermented milk with *Lactobacillus helveticus*, which contains two inhibitory peptides for ACE, significantly lowered BP by 11.2/6.5 mmHg in 4 weeks [37]. Pins and Keenan administered 20 g of hydrolyzed whey protein to 30 hypertensive subjects and noted a BP reduction of 11/7 mmHg compared with controls at 1 week that was sustained throughout the study [38]. These data indicate that the whey protein must be hydrolyzed in order to exhibit an antihypertensive effect, and the maximum BP response is dose dependent.

Bovine casein-derived peptides and whey protein-derived peptides exhibit ACE-I activity [35–38]. These components include B-caseins, B-lg fractions, B2-microglobulin and serum albumin [35–38]. The enzymatic hydrolysis of whey protein isolates releases ACE-I peptides.

Sardine muscle protein, which contains Valyl-Tyrosine (VAL-TYR), significantly lowers BP in hypertensive subjects [39]. Kawasaki *et al.* treated 29 hypertensive subjects with 3 mg of VAL-TYR sardine muscle concentrated extract for 4 weeks and lowered BP 9.7/5.3 mmHg ($p < 0.05$) [39]. Levels of A-I increased as serum A-II and aldosterone decreased, indicating that VAL-TYR is a natural ACE inhibitor (ACE-I). A similar study with a vegetable drink with sardine protein hydrolysates significantly lowered BP by 8/5 mmHg in 13 weeks [40].

In addition to ACE-I effects, protein intake may also alter catecholamine responses and induce natriuresis [39,40]. Low protein intake coupled with low omega-3 fatty acid intake may contribute to hypertension in animal models [41]. The optimal protein intake, depending on the level of activity, renal function, stress and other factors, is approximately 1.0–1.5 g/kg/day.

Fats

Observational, epidemiologic, biochemical, cross-sectional studies and clinical trials of the effect of fats on BP have been disappointing and inconsistent [42].

Omega-3 PUFA

α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) comprise the primary members of the omega-3 PUFA family. Omega-3 fatty acids are found in

cold-water fish (herring, haddock, Atlantic salmon, trout, tuna, cod and mackerel), fish oils, flax, flax seed, flax oil and nuts [43,44]. Omega-3 PUFAs significantly lowered BP in observational, epidemiologic and in some small prospective clinical trials [43–47]. Studies on the effects of fish oil on BP have shown a dose-related response in hypertension, as well as a relationship to the specific concomitant diseases associated with hypertension [43–47].

Studies indicate that DHA is very effective at reducing BP and heart rate (HR) [43]. However, the formation of EPA and ultimately DHA from ALA is decreased in the presence of increased linoleic acid in the diet (omega-6 FAs), increased dietary saturated fats and *trans* fatty acids, alcohol, and aging through inhibitory effects or reduced activity of δ-6-, δ-5- or δ-4-desaturases [43]. Eating cold-water fish three times per week is as effective as high-dose fish oil in reducing BP in hypertensive patients, and the protein in the fish may also have antihypertensive effects [1,43].

The omega-6 FA family, which includes linoleic acid (LA), GLA, DGLA and arachidonic acid (AA), do not usually lower BP significantly, but may prevent increases in BP induced by saturated fats [42]. The ideal ratio of omega-3 to omega-6 FAs is between 1:1 and 1:2, with a polyunsaturated to saturated (P/S) fat ratio greater than 1.5–2:0 [48].

The omega-3 FAs have a multitude of other cardiovascular consequences whose interplay modulates BP [49].

Omega-9 FAs

Olive oil is rich in monounsaturated fatty acids (MUFAs), omega-9 FAs and oleic acid, which have been associated with BP and lipid reduction in Mediterranean and other diets [50,51]. In one study, the SBP fell 8 mmHg ($p \leq 0.05$) and DBP fell by 6 mmHg ($p \leq 0.01$) in the MUFA-treated subjects compared with the PUFA-treated subjects [50]. In addition, the need for antihypertensive medications was reduced by 48% in the MUFA group versus 4% in the PUFA (omega-6 FA) group ($p < 0.005$).

Olive oil is rich in oleic acid (omega-9 FA). Extra-virgin oil has 5 mg of phenols in 10 g of olive oil, a rich polyphenol antioxidant [50,51]. Other fats such as palmitoleic acid may deacrease BP and reduce CVAs from intracranial hemorrhage [1].

Fiber

Clinical trials with various types of fiber to reduce BP have shown inconsistent results [52]. Soluble fiber, guar gum, guava, psyllium and oat bran reduce BP and reduce the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive-diabetic subjects [52].

Garlic

Good clinical trials utilizing the correct type, long-acting preparations and dose of garlic have shown consistent reductions in BP in hypertensive patients, with an average reduction in BP of 8.4/7.3 mmHg [53,54]. Not all garlic preparations are processed similarly and are not comparable in antihypertensive potency [1]. In addition, cultivated garlic (allium sativum) [1], wild uncultivated garlic or bear garlic (allium urisinum), and aged or fresh garlic and long-acting garlic preparations will have variable effects [53,54].

Approximately 10,000 µg of allicin (one of the active ingredients in garlic) per day, the amount contained in four cloves of garlic (4 g) is required to achieve a significant BP-lowering effect [1]. In humans, the average reduction in SBP is 5–8 mmHg [1,53,54].

Tea: green & black

The effects of chronic green or black tea ingestion on blood pressure in humans has not been studied extensively and results are inconsistent [55]. However, green tea, black tea and extracts of active components in both have demonstrated reductions in BP [55].

Seaweed

Wakame (*Undaria pinnatifida*) is the most popular edible seaweed in Japan [56]. In humans, 3.3 g of dried Wakame consumed for 4 weeks significantly reduced both the SBP (14 ± 3 mmHg) and DBP (5 ± 2 mmHg; $p < 0.01$) [57]. A study of 62 middle-aged male subjects with mild hypertension given a K^+-loaded, ion-exchanging, Na^+-adsorbing, K^+-releasing seaweed preparation showed significant BP reductions at 4 weeks on 12 and 24 g/day of the seaweed ($p < 0.01$) [58]. The mean arterial pressure fell by 11.2 mmHg ($p < 0.001$) in the Na^+-sensitive subjects and 5.7 mmHg ($p < 0.05$) in the Na^+-insensitive subjects, which correlated with plasma renin activity.

Seaweed and sea vegetables contain most of seawater's 771 minerals and rare earth elements, fiber and alginate in a colloidal form [56]. The primary effect of Wakame appears to be through its ACE-I activity from at least four parent tetrapeptides, and possibly their dipeptide and tripeptide metabolites, especially those containing the amino acid sequence TYR–LYS in some combination [56]. Its long-term use in Japan has demonstrated its safety. Other varieties of seaweed may reduce BP by reducing intestinal Na^+ absorption and increasing intestinal K^+ absorption [58].

Box 3. Foods and nutraceuticals with angiotensin-converting enzyme inhibitor activity.

- Sour milk will decrease BP in humans
- Casein
- Zein
- Geletin
- Sake
- Sour milk
- Sardine muscle
- Tuna muscle
- Dried salted fish
- Dried bonito
- Fish sauce
- Porhyda yezoensis
- Hijikia fusiformis and seaweed (wakame)
- Garlic
- Hawthone
- Pycnogenol
- Egg yolk (chicken)
- Hydrolyzed whey protein
- Omega-3 fatty acids

Box 4. Antihypertensive mechanisms of vitamin C.

- Reduces ED and improves EDV and lowers BP and SVR in high BP, HLP, CHD, smokers
- Diuretic effect
- Increases NO and PGI_2 levels
- Decreases adrenal steroid production
- Improves sympathovagal balance
- Decrease cystosolic Ca^{2+}
- Antioxidant
- Recycles vitamin E, glutathione and uric acid
- Reduces neuroendocrine peptides
- Reduces thrombosis and decreases TxA_2
- Reduces lipids (decreases TCs, LDLs, TGs and HDLs)
- Reduces leukotrienes
- Improves aortic collagen, elasticity and aortic compliance
- Increases cGMP and activates VSM K^+ channels

BP: Blood pressure; Ca^{2+}: Calcium; CHD: Coronary heart disease; ED: Endothelial dysfunction; EDV: Endothelial vasodilation; HLP: Hyperlipidemia; K^+: Potassium; SVR: Systemic vascular resistance; TC: Total cholesterol; TG: Triglyceride; TxA_2: Thromboxane A_2; VSM: Vascular smooth muscle.

Natural ACE-Is

Many other foods have demonstrated ACE-I activity *in vitro*, but whether they are active after oral ingestion *in vivo* remains to be proven in human studies (**Box 3**) [1].

Vitamin C

Vitamin C is a potent water-soluble antioxidant that recycles vitamin E, improves endothelial dysfunction and produces a diuresis [59]. Numerous epidemiologic, observational and clinical studies have demonstrated that the dietary intake of vitamin C or plasma ascorbate concentration in humans is inversely correlated to SBP, DBP and HR [59–61]. Long-term epidemiologic and observational follow-up studies in humans also show a reduced risk of CVD, CHD and CVAs with increased vitamin C intake [62].

Published clinical trials indicate that 250 mg twice daily will lower BP by approximately 7/4 mmHg, improve arterial compliance, improve endothelial function, reduce serum aldehydes, enhance the efficacy of amlodipine, decrease the binding affinity of the AT 1 receptor for angiotensin II, and enhance antihypertensive effects of medications in the elderly with refractory hypertension [63–68]. The lower the initital ascorbate serum level, the better is the BP response. SBP and 24-h ambulatory blood pressure monitor show the most significant reductions with vitamin C administration orally over time [63–68]. In an elegant depletion–repletion study of vitamin C, Block *et al.* demonstrated an inverse correlation of plasma ascorbate levels, SBP and DBP [69].

Mechanisms of action & conclusions regarding the effect of vitamin C on blood pressure

The multitude of proposed mechanisms for the effect of vitamin C on hypertension and other cardiovascular diseases is outlined in **Box 4**. Conclusions on the effects of vitamin C are summarized in **Box 5** [1].

Vitamin C: a perspective

Combined nutrients, vitamins, minerals and antioxidants have clearly been shown to lower BP [1]. Although these varied diets confer more antihypertensive and cardiovascular benefits than any single nutrient, it is also quite probable that vitamin C as a single nutrient plays a significant role in the regulation of BP in both normotensive and hypertensive patients. Almost all studies and reviews reported have shown an inverse relationship between vitamin C intake and plasma ascorbate levels that is reasonably consistent among different

Box 5. Vitamin C: conclusions.

- BP is inversely correlated with vitamin C intake and plasma ascorbate levels in humans and animals in epidemiologic, observational, cross-sectional and controlled prospective clinical trials
- A dose response relationship between lower BP and higher plasma ascorbate levels is suggested
- DBP fell by approximately 2.4 mmHg per plasma ascorbate quartile in a depletion/repletion study
- SBP fell by 3.6–17.8 mmHg for each 50 mmol/l increase in plasma ascorbate level
- BP may be inversely correlated to tissue levels of ascorbate
- Doses of 100–1000 mg per day are needed
- SBP is reduced proportionately more than DBP, but both are decreased; 24-h ABM indicates a predominate daytime SBP reduction and lower heart rate; office BP also shows a reduction in SBP and DBP
- The greater the initial BP, the greater the BP reduction
- BP is reduced in hypertensives, normotensives, hyperlipidemics, diabetics and in patients with a combination of these diseases.
- Vitamin C improves ED in high BP, HLP, PAD, DM, CHD, CHF, smokers and in conduit arteries, epicardial coronary arteries and forearm-resistance arteries
- Long-term epidemiological studies indicate an inverse correlation of Vitamin C intake and ascorbate levels with RVR of CVD, CHD, and CVAs
- The lipid profile seems to be beneficial with small reductions in TC, TG, and LDL and oxLDL, and with increases in HDL (women)
- Combinations of Vitamin C with other antioxidants such as vitamin E, β-carotene or selenium provide synergistic antihypertensive effects

ABM: Ambulatory blood pressure monitor; BP: Blood pressure; CHD: Coronary heart disease; CHF: Congestive heart failure; CVA: Cerebrovascular accident; DBP: Diastolic blood pressure; DM: Diabetes mellitus; D: ; ED: Endothelial dysfunction Endothelial dysfunction; oxLDL: Oxidized low-density lipoprotein; PAD: ; RVR: Renal vascular resistance; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride; TOD: Target organ damage.

study groups, populations and variable study designs [59–69]. Hypertensive subjects were found to have significantly lower plasma ascorbate levels compared with normotensive subjects (40 vs 57 µmol/l, respectively) [70]. Evidence supports that plasma ascorbate is inversely correlated with BP even in healthy, normotensive individuals [69]. The second National Health and Nutrition Examination Survey (NHANES-II) found 20% of US males have plasma ascorbate levels below 27 µmol/l and 30% of US black males had levels below 27 µmol/l [70]. This increased prevalence of lower plasma ascorbate levels in black males could partially account for the higher prevalence of hypertension in black Americans.

Table 1. Evolutionary diet changes.

Nutrient or mineral	Paleolithic intakes	Modern intakes
K^+	>10,000 meq/day (256 g)	150 meq/day (6 g)
Na^+	<50 mmol/day (1.2 g)	175 mmol/day (4 g)
Na^+/K^+ ratio	<0.13/day	>0.67/day
Fiber	>100 g/day	9 g/day
Protein	37%	20%
Carbohydrate	41%	40–50%
Fat	22%	30–40%
P/S ratio	1.4	0.4

P/S ratio: Polyunsaturated to saturated fat ratio.

Vitamin E

The relationship between vitamin E and BP has been studied in humans [71]. Patients with Type 2 diabetes mellitus and hypertension on prescription medications with an average BP of 136/76 mmHg were administered mixed tocopherols. BP actually increased by 7/5.3 mmHg in the study patients. This may be a reflection of drug interactions with tocopherols via cytochrome P450 and reduction in the serum levels of the pharmacologic treatments that were simultaneously being administered [71]. If vitamin E has an antihypertensive effect, it is probably small and may be limited to untreated hypertensive patients, or those with known vascular disease or other concomitant problems such as diabetes or hyperlipidemia.

Vitamin D

Epidemiological, clinical and experimental investigations all demonstrate a relationship between the plasma levels of 1,25-dihydroxycholecalciferol ($1_1 25\ [OH]_2\ D_3$), the active form of vitamin D and BP [72–75], including a vitamin D-mediated reduction in BP in hypertensive patients. Vitamin D may have an independent and direct role in the regulation of BP and insulin metabolism [72–75]. Vitamin D3 influences BP by its effects on calcium–phosphate metabolism, the renin–angiotensin–aldosterone system, the immune system, the control of endocrine glands and endothelial dysfunction [73]. Vitamin D3 markedly suppresses renin transcription by a VDR-mediated mechanism in cell cultures [74]. Its role in electrolytes, volume and blood pressure homeostasis indicates that vitamin D3 is important in the amelioration of hypertension [74].

The hypotensive effect of vitamin D was inversely related to the pretreatment serum levels of $1_1 25\ (OH)_2\ D_3$ and additive to antihypertensive medications [75]. Pfeifer *et al.* showed that short-term supplementation with vitamin D3 and calcium is more effective in reducing SBP than calcium alone [75]. In a group of 148 women with low $25\ (OH)_2\ D_3$ levels, administration of 1200 mg calcium plus 800 IU of vitamin D_3 reduced SBP 9.3% more ($p < 0.02$) compared with 1200 mg of calcium alone. HR fell 5.4% ($p = 0.02$), but DBP was not changed [75].

Vitamin B6

Low serum vitamin B6 levels are associated with hypertension in humans [76]. One human study by Aybak *et al.* suggested that high-dose vitamin B6 significantly lowered BP [77]. This study compared nine normotensive men and women with 20 hypertensive subjects, all of whom had significantly higher BP, plasma norepinephrine and HR compared with control normotensive subjects. Subjects received 5 mg/kg/day of vitamin B6 for 4 weeks. The SBP fell from 167 ± 13 to 153 ± 15 mmHg, an 8.4% reduction ($p < 0.01$), and the DBP fell from 108 ± 8.2 to 98 ± 8.8 mmHg, a 9.3% reduction ($p < 0.005$).

Flavonoids

Over 4000 naturally occurring flavonoids (flavonols, flavones and isoflavones) have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy and licorice [78]. Flavonoids are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation and have antihypertensive properties [78]. In addition, they reduce stroke and provide cardioprotective effects that reduce CHD morbidity and mortality [79].

Resveratrol is a potent antioxidant and antihypertensive found in the skin of red grapes and in red wine. Resveratrol administration to humans reduces augmentation index, improves arterial compliance and lowers central arterial pressure [80]. Human subjects were administered 250 ml of either regular or dealcoholized red wine. There was a significant reduction in the aortic augmentation index of 6.1% with the dealcoholized red wine and 10.5% with regular red wine. The central arterial pressure was significantly reduced by dealcoholized red wine at 7.4 and 5.4 mmHg by regular red wine.

Lycopene

Lycopene is a non-provitamin A carotenoid, potent antioxidant found in tomatoes and tomato products, guava, pink grapefruit, watermelon, apricots and papaya in high concentrations [81–85].

Box 6. Natural antihypertensive compounds categorized by antihypertensive class.

Diuretics	
Hawthorne berry	Mg^{2+}
Vitamin B6 (pyridoxine)	Ca^{2+}
Taurine	Protein
Celery	Fiber
GLA	Coenzyme Q-10
Vitamin C (ascorbic acid)	L-carnitine
K^+	
β-blockers	
Hawthorne berry	
Central α agonists (reduce sympathetic nervous system activity)	
Taurine	Vitamin C
K^+	Vitamin B6
Zinc	Coenzyme Q-10
Na^+ restriction	Celery
Protein	GLA/DGLA
Fiber	Garlic
Direct vasodilators	
Omega-3 FAs	Flavonoids
MUFA (omega-9 FAs)	Vitamin C
K^+	Vitamin E
Mg^{2+}	Coenzyme Q-10
Ca^{2+}	L-arginine
Soy	Taurine
Fiber	Celery
Garlic	ALA
Calcium channel blockers	
ALA	Hawthorne berry
Vitamin C (ascorbic acid)	Celery
Vitamin B6 (pyridoxine)	Omega-3 fatty acids (EPA and DHA)
Mg^{2+}	Calcium
N-acetyl cysteine	Garlic
Vitamin E	
Angiotensin converting enzyme inhibitors	
Garlic	Geletin
Seaweed – various (e.g, wakame)	Sake
Tuna protein/muscle	Essential fatty acids (omega-3 FAs)
ACE inhibitors (cont.)	
Sardine protein/muscle	Chicken egg yolks
Hawthorne berry	Zein
Bonito fish (dried)	Dried salted fish
Pycnogenol	Fish sauce
Casein	Zinc
Hydrolyzed whey protein	Hydrolyzed wheat germ isolate
Sour milk	
ARBs	
K^+	Vitamin B6 (pyridoxine)
Fiber	Coenzyme Q-10
Garlic	Celery
Vitamin C	GLA and DGLA

ALA: α lipoic acid; Ca^{2+}: Calcium; EPA: Eicosapentaenoic acid; DGLA: Dihomo-γ-linoleic acid; DHA: Docosahexanoic acid; FA: Fatty acid; GLA: γ-linolenic acid; K^+: Potassium; Mg^{2+}: Magnesium.

Lycopene has recently been shown to produce a significant reduction in BP, serum lipids and oxidative stress markers [81–85]. Paran *et al.* evaluated 30 subjects with Grade I hypertension, age 40–65 years, and taking no antihypertensive or anti-lipid medications treated with a tomato lycopene extract for 8 weeks [85]. The SBP was reduced from 144 to 135 mmHg (9-mmHg reduction; $p < 0.01$) and DBP fell from 91 to 84 mmHg (7-mmHg reduction; $p < 0.01$). A similar study of 35 subjects with Grade I hypertension showed similar results on SBP, but not DBP [81]. Englehard gave a tomato extract to 31 hypertensive subjects over 12 weeks demonstrating a significant BP reduction of 10/4 mmHg [81]. Patients on various antihypertensive agents had a significant BP reduction of 5.4/3 mmHg over 6 weeks when administered a standardized tomato extract [83]. Other studies have not shown changes in blood pressure with lycopene [84].

Coenzyme Q10

Coenzyme Q10 (Co-Q10) is a potent lipid-phase antioxidant, free radical scavenger, cofactor and coenzyme in mitochondrial energy production and oxidative phosphorylation that lowers systemic vascular resistance and BP, and protects the myocardium from ischemic reperfusion injury [1,86–88]. Co-Q10 improves mitochondrial energy production, enhancing myocardial infusion with improved diastolic function, left ventricle (LV) function, left ventricle wall tension (LVWT) and New York Heart Association class for CHF [1,86–88].

Serum levels of Co-Q10 decrease with age and are lower in patients with diseases characterized by oxidative stress such as hypertension, CHD, hyperlipidemia, diabetes mellitus, atherosclerosis, and in those who are involved in aerobic training, patients on total parenteral nutrition (TPN), those with hyperthyroidism and patients who take statin drugs [1]. Enzymatic assays showed a

deficiency of Co-Q10 in 39% of 59 patients with essential hypertension versus only 6% deficiency in controls ($p < 0.01$) [1]. There is a high correlation between Co-Q10 deficiency and hypertension.

In hypertensive subjects following oral administration of 100–225 mg per day of Co-Q10 the blood pressure fell about 15/10 mmHg [1,86–90]. Co-Q10 is a lipid soluble nutrient and is best absorbed with a fatty meal. However, newer formulations with emulsification and nanoparticles will improve intestinal absorption and serum levels [91].

In summary, Co-Q10 has consistent and significant antihypertensive effects in patients with essential hypertension. The major conclusions from *in vitro*, animal and human clinical trials indicate the following:

- Compared with normotensive patients, essential hypertensive patients have a high incidence of Co-Q10 deficiency documented by serum levels;
- Doses of 120–225 mg per day of Co-Q10, depending on the delivery method and concomitant ingestion with a fatty meal, are necessary to achieve a therapeutic level of over 2 µg/ml. This dose is usually 1–2 mg/kg/day of Co-Q10. Use of a special delivery system allows better absorption and lower oral doses;
- Patients with the lowest Co-Q10 serum levels may have the best antihypertensive response to supplementation;
- The average reduction in BP is approximately 15/10 mmHg based on reported studies;
- The antihypertensive effect takes time to reach its peak level, usually at approximately 4 weeks, then BP remains stable. The antihypertensive effect is gone within 2 weeks after discontinuation of Co-Q10;
- Approximately 50% of patients on antihypertensive drugs may be able to stop between one and three agents. Both total dose and frequency of administration may be reduced;
- Even high doses of Co-Q10 have no acute or chronic adverse effects.

Other favorable effects on cardiovascular risk factors include improvement in the serum lipid profile and carbohydrate metabolism, with reduced glucose and improved insulin sensitivity, reduced oxidative stress, reduced HR, improved myocardial LV function, and oxygen delivery and decreased catecholamine levels.

α-lipoic acid

α-lipoic acid is a potent and unique thiol compound-antioxidant that is both water and lipid soluble [1]. α-lipoic acid helps to recirculate tissue and blood levels of vitamins and antioxidants in both lipid and water compartments such as vitamin C and vitamin E, glutathione and cysteine [1].

The only human study published to date evaluated α-lipoic acid and acetyl-L-carnitine in combination in 36 patients with CHD and hypertension, with or without the metabolic syndrome [92]. The brachial artery diameter increased by 2.3% ($p = 0.008$). BP was decreased in the overall group but significantly in those with BP above the median (151 ± 20 to 142 ± 18 mmHg; $p = 0.03$) and in the subgroup with the metabolic syndrome (139 ± 21 to 130 ± 18 mmHg; $p = 0.03$) [92].

L-arginine

L-arginine is the primary precursor for the production of nitric oxide (NO), which has numerous cardiovascular effects mediated through conversion of L-arginine to NO by eNOS to increase cyclic GMP levels in vascular smooth muscle, improve ED, and reduce vascular tone and BP [1,93]. Patients with hypertension, hyperlipidemia and atherosclerosis have elevated serum levels of asymmetrical dimethylarginine, which activates NO [94].

Human studies in hypertensive and normotensive subjects of parenteral and oral administrations of L-arginine demonstrate an antihypertensive effect [93,94]. The BP decreased significantly on 10 g L-arginine per day by 6.2/6.8 mmHg. L-arginine produces a statistically and biologically significant decrease in BP and improved metabolic effect in normotensive and hypertensive humans that is similar in magnitude to that seen in the Dietary Approaches to Stop Hypertension (DASH)-I diet [93]. This reduction in BP was seen whether L-arginine was provided through natural foods or as a pharmacologic supplement when given at approximately a twofold dietary increase (dose: 10 g/day). Although these doses of L-arginine appear to be safe, no long-term studies in humans have been published at this time and there are concerns of a pro-oxidative effect in patients who may have a dysfunctional endothelium, or advanced atherosclerosis, CHD or MI.

L-carnitine

L-carnitine is a nitrogenous constituent of muscle primarily involved in the oxidation of fatty acids in mammals. Human studies on the effects of L-carnitine are small and limited with minimal to no change in blood pressure [95]. L-carnitine may be useful in the treatment of essential hypertension, Type 2 diabetes mellitus with hypertension, hyperlipidemia, cardiac arrhythmias, CHF and cardiac ischemic syndromes [1,95].

Taurine

Taurine is a sulfonic β-amino acid that is considered a conditionally essential amino acid. It is not utilized in protein synthesis, but is found free or in simple peptides with its highest concentration in the brain, retina and myocardium [96]. In cardiomyocytes, it represents about 50% of the free amino acids and has roles as an osmoregulator and inotropic factor, and has been used to treat hypertension [97].

Human studies have noted that essential hypertensive subjects have reduced urinary taurine as well as other sulfur amino acids [1,96,97]. Taurine lowers BP and HR, decreases arrhythmias, CHF symptoms and sympathetic nervous system activity, increases urinary Na^+, and decreases plasma renin activity, aldosterone, plasma norepinephrine, plasma and urinary epinephrine [1,96–98]. A study of 31 Japanese males with essential hypertension placed on an exercise program for 10 weeks showed a 26%

increase in taurine levels and a 287% increase in cysteine levels. The BP reduction of 14.8/6.6 mmHg was proportional to both taurine level elevations and plasma norepinephrine reduction [99]. Fujita *et al.* reduced BP by 9/4.1 mmHg ($p < 0.05$) in 19 hypertension subjects given 6 g of taurine for 7 days [97]. Taurine has numerous beneficial effects on the cardiovascular system and blood pressure [98]. The recommended dose of taurine is 2–3 g per day at which no adverse effects are noted, but higher doses may be needed to reduce BP significantly [1,96–99].

Pycnogenol

Pycnogenol, a bark extract from the French maritime pine, at doses of 200 mg/day resulted in a significant reduction in SBP from 139.9 to 132.7 mmHg ($p < 0.05$) in 11 patients with mild hypertension over 8 weeks. DBP fell from 93.8 to 92.0 mmHg (p = NS). Serum thromboxane concentrations were significantly reduced ($p < 0.05$) [100]. Other studies have shown reductions in BP, reduced ET-1, reductions in hemoglobin A1c and fasting glucose and reductions in LDL-C [101,102].

Natural antihypertensive compounds categorized by antihypertensive class

As has been discussed previously, many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants and minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than the antihypertensive drug, when used in combination with other nutrients and nutraceuticals the antihypertensive effect is magnified. In addition, many of these nutrients and nutraceuticals have varied, additive or synergistic mechanisms of action in lowering BP. **Box 6** summarizes these natural compounds into the major antihypertensive drug classes such as diuretics, β-blockers, central α-agonists, calcium channel blocker, ACE-I and ARBs.

Expert commentary & five-year view

The prevention and treatment of hypertension and its cardiovascular consequences with all of the lifestyle changes discussed in this article has the potential to reduce blood pressure, decrease the need for antihypertensive medications, improve cardiovascular health, reduce morbidity and mortality and save on healthcare expenditure. The integration of pharmacologic treatments with a nutrition and nutraceutical supplement program, exercise and weight reduction will become the new standard of care in the management of hyperertension in the future.

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Key issues

- Vascular biology (endothelial and vascular smooth muscle dysfunction) plays a primary role in the initiation and perpetuation of hypertension, cardiovascular disease and target organ damage.
- Nutrient–gene interactions are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension.
- Nutrition (natural whole food and nutraceuticals) can prevent, control and treat hypertension through numerous vascular biology mechanisms.
- Oxidative stress initiates and propagates hypertension and cardiovascular disease.
- Antioxidants can prevent and treat hypertension.
- Whole food and phytonutrient concentrates of fruits, vegetables and fiber with natural combinations of balanced phytochemicals, nutrients, antioxidants, vitamins, minerals, and appropriate macronutrients and micronutrients are generally superior to single-component or isolated artificial or natural substances for the prevention and treatment of hypertension and cardiovascular disease.
- There is a role for the selected use of single-component nutraceuticals, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional dietary intake from food and other lifestyle modifications.
- Exercise, weight reduction, smoking cessation, alcohol and caffeine restriction, as well as other changes in lifestyle, should be incorporated.

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