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Role of Nutraceuticals in Control of Hypertension: A Review

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Authors' contributions

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Review Article

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ABSTRACT

Nowadays, hypertension is of utmost concern in both developing and developed countries, since it leads to many health problems like cardiovascular disease, heart attack, and stroke. In recent years, many studies were conducted to investigate the effect of nutraceuticals on blood pressure, which are natural food components having pharmacological properties. Nutraceuticals are especially beneficial for pre-hypertensive patients having a little more blood pressure than the normal range, in association with positive lifestyle changes. Even though nutraceuticals have a blood pressure-lowering effect, they cannot replace the conventional method of drug treatment for patients suffering from high blood pressure. Nutraceuticals with blood pressure-lowering activity under different categories like food, nutrients, and non-nutrients are reviewed in this article.

Keywords: Nutraceuticals; blood pressure; BP; hypertension; dietary supplements; cardiovascular disease.

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1. INTRODUCTION

High blood pressure or BP is considered among the most pertinent risk factor that can cause cardiovascular diseases. Patients with hypertension are present all over the world. A person's chances to develop hypertension during their lifetime are as high as 90%. According to the estimates, by 2025 the global share of hypertension is likely to raise up to 1.56 billion affected humans [1]. There are a total of 7.6 million premature deaths caused by suboptimal blood pressure each year globally and it also results in the loss of more than 92 million life years which are disability-adjusted [2]. From many recent studies, it was found that the incidence involving cardiovascular complications can be reduced by maintaining a normal level of blood pressure. This indicates that if the general population has a normal range of blood pressure, then the number of hypertension patients will drastically decrease [3]. There are many risk factors that may contribute to the development of hypertension like increased levels of salt consumption, excessive alcohol consumption, and a lazy lifestyle which are major causes for this condition. Hypertension is also promoted by a deficiency of many food items like vegetables, fruits, oily fish, and dairy products. A deficiency of many micronutrients may also be regarded as a potential risk factor associated with hypertension like vitamin C, folate, vitamin D, and riboflavin [4]. In the Western world, cardiovascular diseases are attributed as one of the leading causes of death because the general population cannot properly control the cardiovascular risk factors [5]. According to the European guidelines, patients with a mild increase in blood pressure or a minor increment in glucose levels or serum lipids are advised to approach nonpharmacological methods like changing their lifestyles and using healthier food alternatives and nutraceutical products. This nonpharmacological strategy is highly efficient for controlling risk factors at the level of the population [6]. It is estimated that in most countries about 30% of the adult population suffers from hypertension and among them, 50 percent are unaware of their condition [7]. There are 2 types of hypertension. The first one is essential hypertension, which is not caused by any known source but occurs because of a combination of many factors such as heredity, body weight, age, environment, and diet. The second one is secondary hypertension, which is caused by other medical conditions such as narrowing arteries, renal diseases, and adrenal cortical diseases [8]. Treating all types of sub-optimal blood pressure with antihypertensive medicine can lead to many problems, so other alternatives are also considered, like changing food and lifestyle [9]. Many large-scale studies have shown that there are many health benefits of changing the diet on levels of blood pressure like dietary approaches to stop hypertension (DASH) as well as Mediterranean Diet studies. There are many different types of dietary supplements available that are supposed to have a blood pressure-lowering activity and these dietary supplements are called nutraceuticals. Nutraceuticals can be described as food or parts of food that have some medical and health values [10].

2. FOODS

Beetroots: A diet containing high amounts of vegetables and fruit has many health benefits, but especially green leafy vegetables provide greater protection against cardiovascular disease. Among all the vegetables, beetroots have the highest concentration of nitrate present in a vegetable in the form of inorganic NO_3^-. Once inorganic NO_3^- is consumed by a person, inorganic NO_3^- is later metabolized in vivo and converted into the active form of nitrate (NO_2^-), which is again later retrieved and finally circulates in the body along with the blood. The effects of NO_2^- exert on the body by its transformation into active nitrogen oxides, which also include nitric oxide (NO) [11]. Generally, the way for the availability of functional nitrogen oxides like NO is the transformation of L-arginine into NO via the process of the NO synthesis pathway. The nitrate that was ingested is now changed into nitrite by commensal Gram-negative bacteria that is found in the oral cavity, which is finally assimilated by the stomach. Now, it is ultimately reduced to bioactive NO in the erythrocytes and vessel wall, which in turn causes vasodilatation [12]. It is found that by consuming a dose of 250 ml beetroot juice in the concentrated form daily, results in a decrease in BP extremely in pre-hypertensive and normotensive patients by bioconversion to produce the vasodilator NO [13]. The beetroots also contain a high amount of betalains, which are color compounds that contain nitrogen which is generally absent in edible plants. Betalains can be categorized into two types, one of which is purple or red beta-cyanins which impart red color to beetroots, and another type is yellow or orange beta-xanthins which impart a yellow color to beetroots. Betalains may also act as

antioxidants because they donate electrons and may possibly have a protective role against protection from diseases related to oxidative stress like hypertension and cardiovascular diseases [14]. In meta-analysis double-blind, placebo-controlled RCTs, it was found that administrating beetroot juice of 5.1 mmol to 45 mmol daily for a time period that varies from 2 hours to 15 days, results in a dose dependant mean reduction of SBP by 4.4 mmHg [15].

Tea: The tea has been extensively investigated for its antihypertensive activity. Tea is in-fact, one of the most commonly consumed and famous beverages. When the chemical properties and manufacturing process of tea are considered, it can be categorized into two types, which are black tea and green tea. The manufacturing process of green tea does not involve fermentation. On the other hand, black tea generally involves fermented products. Since green tea is nonfermented, it contains green tea catechins (GTCs), which belong to a group named, polyphenols present in their original state. Black tea is involved with fermentation, the GTC gets oxidized, which is later polymerized to give rise to pigments named the arubigins (TR) and theaflavins (TF) [16]. When black tea or green tea is consumed regularly for 4-24 weeks with an average of 2 to 6 cups every day, it leads to a prominent decrease in BP, when the baseline values are compared, green tea results in a significant reduction in SBP by a value of 2 mmHg and in the case of DBP by 1.7 mmHg. On the other hand, black tea leads to a reduced SBP by a value of 1.4 mmHg and in the case of DBP by 1.1 mmHg. The antihypertensive effect of tea increases if it is consumed for more than 12 weeks consecutively [17].

Cocoa: There are many dietary flavonoids that have a vascular protective effect and endothelial function. They are anti-inflammatory, improves NO metabolism, and also act as an antioxidant. They also decrease the risk of Cardiovascular diseases (CVD) [18]. Cocoa as well as dark chocolate, both contain a high amount of polyphenols that play an important role in decreasing BP in humans. The flavonoids present in dark chocolate have beneficial effects like protecting the vascular endothelium, elevating NO bioavailability, and reducing the risk factors for CVD [19]. In recent studies, it was found that during hyperglycemia, endothelial functions are disturbed. There were many studies conducted to understand the effects, like reducing BP and increased flow-mediated dilation (FMD) after consuming chocolates [20]. Dark chocolates show BP-reducing effects which are not shown by white chocolates because, unlike white chocolate, dark chocolate has flavanols that allow a strong antioxidant action carried out by epicatechin, when it is released into the bloodstream. There are many additional beneficial effects of dark chocolate like increasing flow-mediated vasodilation in both healthy and hypertensive patients regardless of their glucose intolerance status [21]. In a recent of 20 placebo-controlled, double-blinded RCTs which involved 856 healthy individuals has provided statistically important data to establish the BP-lowering activity of cocoa products that are rich in flavanol. A short-term trial, where the participants are administrated with 3.6-105 g of cocoa supplements every day, which contained about 30 to 1080 mg of flavanol for a period of 2-18 weeks, resulting a mean reduction in the value of SBP by 2.8 mmHg and in the case of DBP by 2.2 mmHg [22]. From the results of two newly conducted meta-analyses, which included 13 trials and 10 trials involving 297 participants, it was found that there was a remarkable decrease in SBP by 3.2 mmHg and DBP by 2.0 mmHg for the first trial and a reduction in SBP by 4.5 mmHg and a reduction in DBP by 3.2 mmHg for the second trial [23]. The BP reduction was found to be comparatively more for those individuals having the highest baseline of BP and also those who consume not less than 50–70% of cocoa products at a daily dose ranging between 6–100 g in their everyday diet. There are also many pieces of evidence that indicate that cocoa may also help to enhance endothelial function and insulin resistance [24].

Pomegranate juice: Recently, pomegranate juice found to possess significant cardioprotective and antihypertensive effects. Pomegranate juice is also rich in polyphenols, which include the hydrolyzable tannins, which are synthesized when gallic acid and/or ellagic acid forms a bond with carbohydrate. The redness of pomegranate juice indicates the high amounts of anthocyanin which is known to have antioxidant effects and includes cyanidin, delphinidin, and pelargonidin glycosides [25]. In a recent meta-analysis, which included 574 participants from 8 RCTs, when administrated with pomegranate juice, showed a remarkable decrease in the mean values of SBP by 4.9 mmHg and in the case of DBP by 2.01 mmHg. Interestingly, pomegranate juice did not significantly affect SBP as the values of SBP were unaffected towards the duration of the treatment and the amount of dose tested. In the

case of DBP, only a borderline notable decrease was observed from the studies of the subset, when subjects were administrated with a daily dose of 240 cm^3 of pomegranate in juice form [26]. Pomegranate juice also showed positive results when given to children suffering from metabolic syndrome as it improved their flow-mediated dilation (FMD). Most of the information presented above is mostly obtained from the Iranian population, so the same data may not be confirmed for different population groups [27].

Sesame: Sesame has antihypertensive properties because of its large amounts of polyunsaturated fatty acid, lignan, fiber, and phytosterol [28]. From a meta-analysis of 8 controlled trials that involved 843 participants, it was found that sesame supplementation can significantly decrease the value of SBP by 7.83 mmHg and the value of DBP by 5.83 mmHg [29]. When a black sesame supplement of 2.52 g per day was given to 15 individuals for a time duration of 4 weeks, a significant decrease was observed in SBP by a value of 8.3 mmHg but no remarkable reduction was observed for DPB, which was of 4.2 mmHg [30]. In addition to antihypertensive activity, sesame was also found to have serum glucose, LDL-C, HgbAIC, and oxidative stress markers lowering activity as well as increasing HDL, SOD, GPx, CAT, glutathione, vitamins A, vitamins C, and vitamins E [31]. The active ingredients present in sesame are natural ACEIs, sesamolin, sesaminol glucosides, and sesamin [32]. All the above mention substances have lower oxidative stress and lower inflammatory effects, they also help in enhancing oxidative defense and as a result, decrease BP [33].

Seaweed: Wakame seaweed is one of the most popular seaweed that is consumed in Japan [34]. In recent trials, it was found that when 3.3 g of wakame seaweed was supplemented every day for a time duration of 4 weeks, there was a remarkable decrease in SBP by 14±3 mmHg and DBP by 5±2 mmHg [35]. The mean arterial pressure (MAP) was found to fall by a value of 11.2 mmHg, particularly for participants who are sodium-sensitive, and a fall by 5.7 mmHg for participants who are sodium-insensitive. Sea vegetables and seaweed have nearly all the 771 minerals that are present in the seawater along with many rare earth elements such as alginate [34]. Major effects of wakame seaweed are due to its angiotensin-converting enzyme inhibitor (ACEI) activity because of their tripeptide as well as dipeptide metabolites, particularly those having amino acid sequences Phe-Tyr, Ile-Tyr, Val-Tyr, Try-Lys in some combinations [36]. The consumption of wakame seaweed in Japan for the long term has provided evidence for its safety. There are many other different varieties of seaweed that can decrease BP in humans. Since, they cause an increase in intestinal potassium assimilation as well as a decrease in sodium assimilation [37].

Garlic: Garlic has played a significant historical role in the fields of both medicine and food [38]. It constitutes of 65% water, and free amino acids, proteins, sulfur compounds, and carbohydrates such as fructose [39]. The medical and dietary properties of garlic are due to the presence of sulfur compounds found in the garlic [40]. In recent studies, it was found that one of the major reasons for the cardiovascular advantages of garlic is because of allicin, which is also called diallyl thiosulfinate [41]. In many clinical trials, it was found that garlic has antihypertensive properties. The average reduction of BP in hypersensitive patients for SBP was found to be 8.4 mmHg and for DBP was found to be 7.3 mmHg [42]. The BP-lowering property of all garlic preparation does not have a similar effect in the reduction of BP, as there are different types of garlic such as cultivated garlic, bear garlic, wild uncultivated garlic, and fresh or aged garlic, with all of them having a variable degree of effects [43]. For a significant amount of BP-reducing effect, a human may consume four cloves of garlic per day, which approximately weighs 4 g. This amount of garlic approximately contains 10,000 milligrams of allicin, which is an active compound of garlic [44].

Table 1. Effects of Foods on Hypertension. Modified and updated [6]

Foods	Expected effect on BP	Clinical evidence
Beetroots	-4.4/1 mmHg	Meta-analysis of 16 RCTs (n = 254)
Tea	-2/-1 mmHg	Meta-analysis of 25 RCTs (n = 1476)
Cocoa	-2.8/-2.2 mmHg	Meta-analysis of 20 RCTs (n = 856)
Pomegranate juice	-4.9/-2 mmHg	Meta-analysis of 8 RCTs (n = 574)
Sesame	-7.8/-5.8 mmHg	Meta-analysis of 8 RCTs (n = 843)
Seaweed	-11.2/-5.7 mmHg	Meta-analysis of 1 RCT (n = 62)
Garlic	-8.4/-7.3 mmHg	Meta-analysis of 1 RCT (n = 50)

Fig. 1. Different types of foods

3. NUTRIENTS

ω-3 polyunsaturated fatty acids: ω-3 polyunsaturated fatty acids, also called PUFA, are known to have a significant effect in lowering BP in humans. The major ω-3 PUFA present in human diet are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [45]. Major ω-3 PUFA-rich sources in the human diet are seafood and oily fish [29]. Many clinical studies have indicated that ω-3 PUFA also contributes to improving cardiovascular health as it carries many different mechanisms to regulate BP in humans. These mechanisms include increasing the production and biosynthesis of relaxing factor (NO) and improving both the activation and regulation of endothelial NO synthase (eNOS), decreasing plasma norepinephrine, increasing parasympathetic nervous system tone, and improving insulin resistance [46]. A lot of data is available regarding the effectivity of ω-3 PUFA against BP. From a meta-analysis of 70 RCTs against a placebo, where the participants were administrated with 0.3-15 grams of ω-3 PUFA every day for a period of 4-26 weeks. It was observed that there was a decrease of SBP by 1.5 mmHg but in the case of DBP, there was a decrease of 1.0 mmHg. The intensity of the effect increased when ω-3 PUFA was given to untreated hypertensive individuals, as for the case of SBP, there was a decrease of 4.5 mmHg, and for DBP, there was a reduction of 3.0 mmHg [47]. From a different meta-analysis, it was observed that if a daily dosage of 900-3000 mg is given for a period of 6-105 weeks, then it leads to improvement in pulse wave velocity as well as in arterial compliance. The only drawback of this meta-analysis involving high dosage was mild gastrointestinal discomfort [48]. In recent studies, it was found that if a mild hypertension patient was given a daily dosage of 500 mg of ω-3 PUFA every day for a long term, then the patient becomes more tolerated to the intervention of lower BP and it also helps to decrease the chances to develop hypertension in healthy individuals [49].

Proteins, peptides, and amino acids: In recent studies, it was found that proteins and peptides which are obtained from plant and animal sources possess various bioactive properties. In a meta-analysis that involved 40 RCTs which included 3277 individuals, in comparison with carbohydrates, it was found that dietary protein intake causes a remarkable decrease in SBP by 1.8 mmHg and a decrease of DBP by 1.2 mmHg. Both animal protein and vegetable protein are found to have BP-lowering activity, where

vegetable protein reduces SBP by a value of 2.3 mmHg, and in the case of DBP by 1.3 mmHg, animal protein reduces SBP by a value of 2.5 mmHg and in case of DBP by 0.9 mmHg [50]. In the case of vegetable protein, the BP lowering effect is due to an additional factor which is soy isoflavones present in it. Soy isoflavones can decrease SBP by 5.9 mmHg and in the case of DBP by 3.3 mmHg when 60-110 mg is consumed every day by hypertensive subjects [51]. Whey and fermented milk protein contain high amounts of angiotensin-converting enzyme inhibitor (ACEI) peptides, which can decrease the BP in humans of SBP by a value of 8 mmHg and of DBP by 2 mmHg when 20 g is consumed every day [52]. Milk peptides specially tripeptides which are Ile-Pro-Pro and Val-Pro-Pro also exhibit ACEI activity and lowers the BP in human, when 5-60 mg is consumed every day for a duration of 4 to 12 weeks [53]. It also results in improved pulse velocity in mild hypertensive patients [54]. Marine fishes which are found in deep seas like tuna and mackerel contain peptides that have antihypertensive activity. It was found that by consuming these marine source peptides at a rate of 1.5 g per day, a significant reduction in BP was recorded which includes a decrease of SBP by a value of 10 mmHg and a decrease in case of DBP by 7 mmHg [55]. In the case of single amino acid like L-arginine, which is a semi-essential amino acid, which leads to the reduction of human BP, when administrated in a dose ranging from 4-24 g per day. Being a natural substrate for NO synthase, L-arginine causes a positive influence on metabolism and hemodynamics because of its positive effect on endothelial function. As a result, a large amount of NO is available on the vessel wall. In a meta-analysis involving 387 participants, who participated in 11 placebo-controlled, double-blind RCTs were administrated with oral L-arginine supplements with a daily dose ranging from 4-24 g for a period of 2-12 weeks. As a result, it was found that, when compared with a placebo, L-arginine decreases the human BP by SBP of 5.4 mmHg and in the case of DBP by 2.7 mmHg. The maximum positive effects were obtained in the 4^{th} week of the treatment period [56].

Magnesium: Magnesium, being one of the important elements in the body to reduce BP, has an inverse relationship with BP. Magnesium affects BP directly by stimulating nitric oxide (NO) and prostacyclin formation [57]. It also controls both types of vasodilation, either endothelium-independent or endothelium-dependent, since it decreases vascular reactivity and tone [58]. The antihypertensive effects of magnesium are increased if associated with a reduced intake of sodium. In a meta-analysis, which involved 20 RCTs, it was discovered that it lowers the SBP by a value of 0.6 mmHg and in the case of DBP by 0.8 mmHg. In a different meta-analysis with 23 trials involving 1173 participants, a remarkable decrease of BP was found with a reduction of SBP by 2-3 mmHg and DBP by 3-4 mmHg, when a daily supplement of 410 mg of Mg was administrated for a period of 11 weeks [59]. The observation from the second meta-analysis was confirmed after getting the results from another meta-analysis that involved 2028 hypertensive and normotensive participants, administrated with a daily supplement of 368 mg of Mg for a period of 3 months [60]. From the results of these studies, it was found that the amount of serum Mg is inversely associated with DBP but not with SBP. The maximum effect of Mg supplements to reduce BP can be obtained by daily administration of 300 mg for a period of one month [61].

Potassium: In recent studies, it was found that a decrease in the amount of dietary intake of potassium leads to an increase in cardiovascular risks as well as a rise in BP. On the other hand, increasing the amount of potassium supplements in food leads to positive cardiovascular effects, especially in hypertension. If an individual consumes a low amount of potassium, like lower than 1 to 2 g daily, particularly in association with an elevation in the consumption of sodium, it causes an increment in the ratio of dietary sodium-to-potassium intake. This results in the rise of BP by 4-5 mmHg. This also raises the risk of developing chronic kidney disease, in addition to the risk of stroke. Low consumption of potassium can enhance tubular reabsorption of sodium, leading to higher sodium retention and lower sodium excretion from the body. As the amount of sodium increases in the body, it leads to a rise in BP in humans. If a hypertensive patient is administrated with a daily dose of 90-120 mEq, it results in a remarkable reduction in the SBP by a value of 7 mmHg and in the case of DBP by 4 mmHg, and a more prominent effect is observed in salt-sensitive individuals [62]. If an individual increases his potassium intake by 42 mmol per day, then it reduces the chances of stroke for that individual by 21% [63].

Calcium: The positive effects of calcium intake are more prominent in younger individuals who

are less than 35 years old. Calcium intake leads to a decrease in BP in younger individuals of SBP by a value of 1.4 mmHg and in the case of DBP by 0.9 mmHg. In recent studies, some controversy has been raised regarding the long-term effects of calcium supplement intake. In larger studies, which include 10 years of follow-up, it was observed that there was a rise in cardiovascular risk and non-cardiovascular death by 17-20% as well as of myocardial infarction, when administrated with calcium supplements above 1 g per day, especially in the case of middle-aged men against some degree of protection, observed in women [64]. Apart from this, many other studies regarding the supplement intake of calcium with a daily dose of 2-2.5 g, showed no signs of harmful effects on the cardiovascular system regardless of its administration in combination with vitamin D [65]. The difference in the effect of calcium supplements may be due to the presence of different factors like divergent effects of diet and external supplements [66].

Zinc: If an individual has a low serum zinc level, then it leads to hypertension and coronary heart disease (CHD) [67]. Metallothionein, which is a low molecular weight protein transporter, transports zinc into vascular muscle, cardiac, and some other tissues. When the deficiencies of intramuscular zinc combine with genetic deficiencies of metallothionein, it may cause increased cardiomyocyte dysfunction, oxidative stress, apoptosis, and mitochondrial dysfunction, which may later cause heart disease or hypertension. If the amount of intercellular calcium increases in the body, it causes a rise in oxidative stress, but this rise in oxidative stress can be reduced by zinc [68]. In a recent study, when zinc levels in 60 hypertensive individuals were compared against the zinc levels of 60 normotensive control subjects, an inverse relationship was observed between serum zinc and BP [67]. A person should maintain 50 mg of zinc in his daily intake either through his diet or by supplements [44].

Vitamin C: There is a reverse relationship between the levels of vitamin C or plasma ascorbate concentration and the levels of BP [69]. Vitamin C also decreases the chances of developing cardiovascular disease (CVA) as well as stroke. If the amount of vitamin C reduces in the body, it leads to an increase in the risk of developing cardiovascular disease [70]. The individual having hypertension has a low plasma ascorbate level which is 40 µmol per liter compared to a normotensive individual having a higher plasma ascorbate level which is 57 µmol per liter. Since there is a reverse relationship between the levels of plasma ascorbate and the levels of BP, so in order to acquire a positive effect on BP, one must maintain at least 100 µmol per liter level of serum ascorbate [71]. In a meta-analysis involving hypertensive patients, when administrated with vitamin C with a supplement of 500 mg per day for a period of around 8 weeks, there was a significant decrease in SBP by 4.8 mmHg but there was no decrease in DBP [72]. The efficiency and performance of amlodipine, which is an antihypertensive drug, increases when administrated in combination with vitamin C [71]. In the case of elderly patients especially those associated with refractory hypertension, when administered with 600 mg of vitamin C every day, resulted in a decrease in SBP by a value of 20±8 mmHg and in the case of DBP by 16±5 mmHg [73].

Vitamin D: Many clinical and experimental investigation indicates a relation between the plasma level of D_3 which is vitamin D in the active form and the levels of BP as D_3 reduces BP in hypertensive patients [74]. Vitamin D may also play an important role in the control of BP directly as well as in insulin metabolism. it is also responsible for the modulating of the renin-angiotensin-aldosterone system [75]. If the amount of vitamin D_3 decreases in the body, then the chances of developing hypertension also increase. In recent studies, it was found that vitamin D_3 can reduce the SBP by 3.6-13.1 mmHg and in the case of DBP by 3.1-7.2 mmHg. The factors responsible for the decrease of BP are serum level of vitamin D_3, vitamin D_3 level in the pretreatment, and dose of vitamin D_3 but the reduction of BP occurs in the case of hypertensive patients. The suggested dose of vitamin D for everyday consumption is 60 ng per ml [76].

Soluble fibre: Normal dietary fiber has a non-significant effect on the reduction of BP, especially when they are included in a Mediterranean diet. But in the case of soluble fiber, there is a remarkable decrease in BP in humans according to many recent RCTs. Soluble fiber also shows a positive effect on lipid and glucose metabolism [77]. After consuming a daily dose of 40 to 50 g of mixed fiber, there was a decrease in SBP by 7.5 mmHg and in the case of DBP by 5.5 mmHg [78]. There are many health benefits to consuming flaxseed, which contains

high amounts of alpha-linolenic acid, fiber, as well as lignans. In a meta-analysis that included 14 RCTs, it was found that administration of flaxseed supplements can reduce SBP by 1.8 mmHg and in the case of DBP by 1.6 mmHg [79]. The maximum positive effect of flaxseed was observed when the trial was conducted for a period of at least 8 weeks [80].

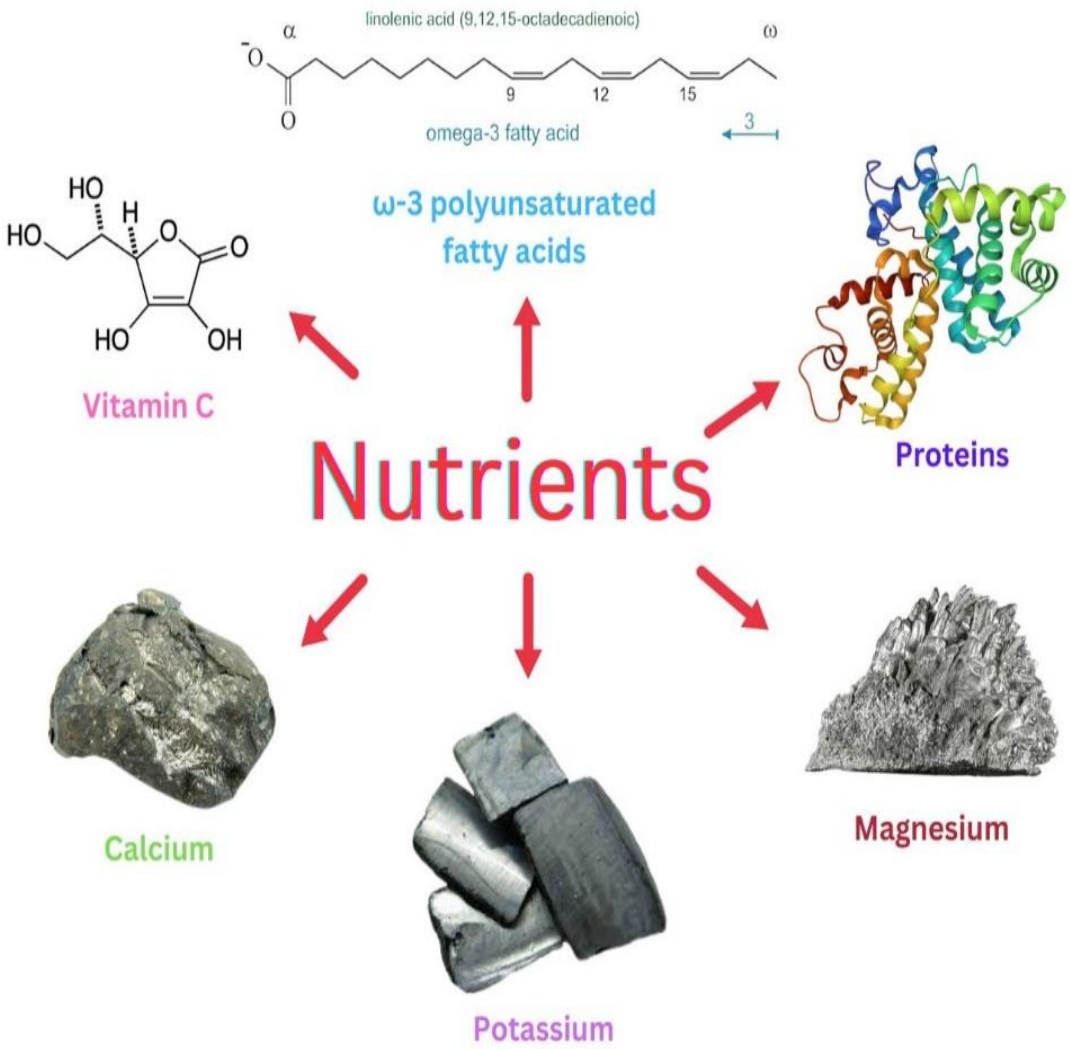

Fig. 2. Different types of Nutrients

Table 2. Effects of Nutrients on Hypertension. Modified and updated [6]

Nutrients	Expected effect on BP	Clinical evidence
ω-3 polyunsaturated fatty acids	-1.5/-1 mmHg	Meta-analysis of 70 RCTs (n = 2250)
Proteins, peptides, and amino acids	-5.4/-2.7 mmHg	Meta-analysis of 11 RCTs (n = 387)
Magnesium	-2.5/-3.5 mmHg	Meta-analysis of 23 RCTs (n = 1173)
Potassium	-7/-4 mmHg	Meta-analysis of 33 RCTs (n = 1829)
Calcium	-1.4/-1 mmHg	Mainly epidemiological data
Vitamin C	-4.8/1 mmHg	Meta-analysis of 21 RCTs (n = 1407)
Soluble fibre	-1.8/-1.6 mmHg	Meta-analysis of 14 RCTs

4. NON-NUTRIENTS

Resveratrol and grape seed extracts: Resveratrol is a polyphenol, which is related to a family of chemical species of polyphenolic compounds called stilbenes. Resveratrol is especially concentrated in grapes as well as red wine. In recent studies, it was found that it possesses antihypertensive activity as well as antioxidant properties. Resveratrol also prevents platelet aggregation, along with the prevention of vascular inflammation [81]. A meta-analysis involving 6 RCTs with 247 participants, administrated with a higher dose of resveratrol, which is more than 150 mg per day, leads to a significant reduction of SBP by 11.9 mmHg [82]. From a different meta-analysis involving 9 placebo-controlled, double-blind RCTs, which included 390 participants, it was found that grape seed extract has various different concentrations of resveratrol along with other polyphenols, decreases SBP by 1.5 mmHg but does not show any reduction in DBP value [83].

Melatonin: Melatonin is released during the night from the pineal gland. It regulates the night and day cycle, which is also known as the sleep-wake cycle. From recent studies, it was found that melatonin reduces BP in humans by regulating both central and peripheral mechanisms like improving NO metabolism, and protecting vessels from oxidation [84]. In a meta-analysis, which involved placebo-controlled, double-blind RCTs, 221 individuals administered with 2-5 mg daily dose of melatonin for a period of 7-90 days. It caused a significant decrease of both night SBP by 6.1 mmHg and in the case of DBP by 3.5 mmHg but the same positive effects were not obtained in the case of fast-release melatonin [85]. When hypertensive patients were administrated with melatonin supplements after providing β-blockers that inhibit melatonin secretion, resulting in better sleep quality [86]. Recent studies have achieved positive results in using melatonin for the treatment of refractory hypertension [87].

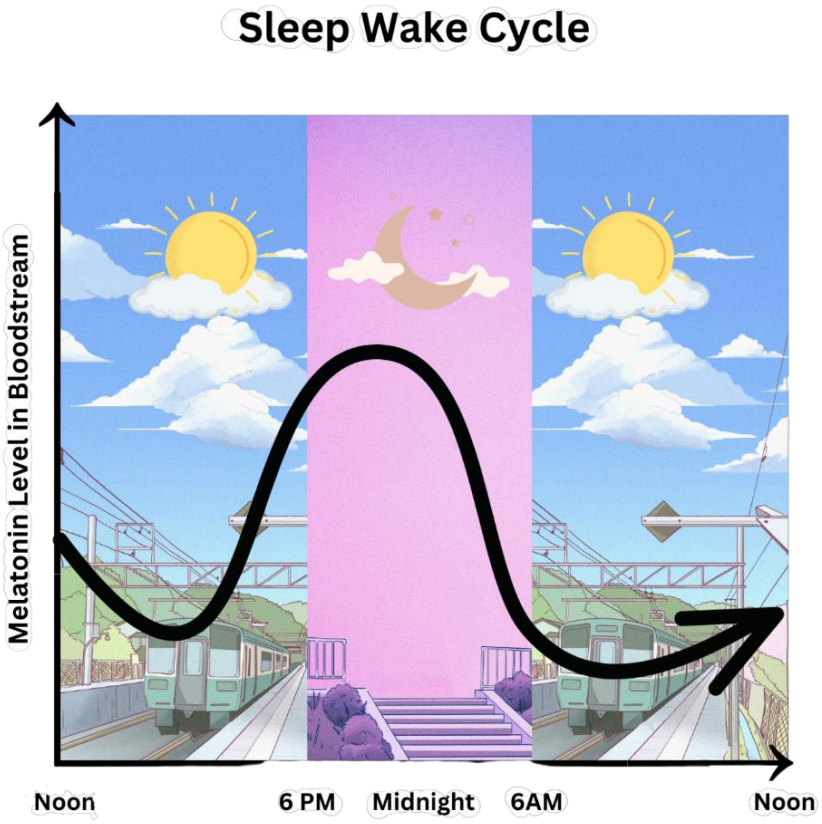

Fig. 3. Melatonin levels in the body throughout the day. From noon to 6 PM, melatonin remains at a low level. From 6 PM to 6 AM, during the night, melatonin levels increase and reached a maximum at midnight and then decrease gradually

Lycopene: Lycopene is a carotenoid, which is present in large amounts in tomatoes and provides tomatoes with their characteristic red-to-pink color. Lycopene has BP-reducing effects but its antihypertensive effects are still under investigation. In a recent meta-analysis involving 6 RCTs, it was observed that by administrating 10-50 mg of lycopene supplement every day for a time duration from 4 to 12 weeks, the mean reduction for SBP was 4.9 mmHg but there was no significant reduction observed for DBP. Later from a subgroup analysis, it was found that antihypertensive effects of lycopene were observed in the Asian population when administrated with a higher dose like more than 12 mg per day with a baseline of SBP of 120 mmHg [88]. One major question that arises here is which one is more effective, providing a lycopene supplement or proving food that is rich in natural sources of lycopene like a tomato. It was found that while considering BP management, lycopene was a better option but to prevent the chances of developing cardiovascular risk, providing whole-food sources of lycopene like a tomato was a better option [89].

Pycnogenol: The extract obtained from the bark of *Pinus pinaster*, commonly known as French maritime pine is generally distributed and marketed under the name of pycnogenol, which is a natural ACE inhibitor. Pycnogenol prevents the cell membrane against oxidative stress and raises NO concentration, which in turn enhances endothelial functions. Pycnogenol also enhances the blood flow of renal cortical, decreases myeloperoxidase activity, and reduces high-sensitive C-reactive protein (CRP) and as a result, it has a beneficial effect on BP for humans [90]. Some clinical trials suggest that if pycnogenol supplements are provided along with other antihypertensive drugs, then it leads to a decrease in the daily dose of antihypertensive for about half of the total patients [91].

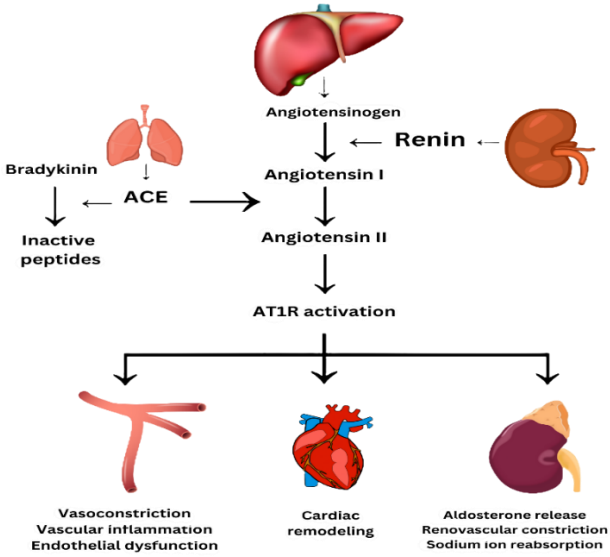

Fig. 4. Regulation of blood pressure by angiotensin Ⅰ-converting enzyme (ACE)

Fig. 4 regulation of blood pressure by angiotensin Ⅰ-converting enzyme (ACE). Firstly, prorenin is converted into renin which hydrolyses plasma angiotensinogen for the generation of angiotensin I. By the activity of ACE, angiotensinogen Ⅰ is quickly hydrolyzed and a shorter peptide containing 8 amino acids is released, which occurs in the lungs. The shorter amino acid peptide is angiotensin Ⅱ, which leads to the activation of the AT1 receptor (AT1R) that ultimately causes a rise in blood pressure and vasoconstriction. Angiotensin Ⅱ increases the retention capacity of both salts and water, which in turn causes an increment in extracellular fluid and leads to an elevation of blood pressure. The angiotensin Ⅱ also results in the release of aldosterone from the adrenal gland, which also contributes to the reabsorption of salt and water in the kidney. Secondly, ACE can inactivate the vasodilator bradykinin leading to an elevation of blood pressure.

Coenzyme Q10: Coenzyme Q10 or CoQ10, commonly known as ubiquinone and is a lipid-soluble, vitamin-like potent antioxidant compound. It is generally present in raw fish and red meat, along with nuts, olives, corn, and soybean [92]. Many investigations suggest that CoQ10 plays an important role in decreasing some cardiovascular risk factors like BP. It regulates mitochondrial respiration by acting as the electron transporter and as a coenzyme and cofactor for the mitochondrial enzymes. It also decreases oxidative stress by acting like a free radical scavenger, which in turn reduces BP in humans [93]. In a recent meta-analysis including placebo-controlled RCTs, it was found that when CoQ10 was administrated in an individual with a baseline of SBP of lower than 140 mmHg or of DBP with a baseline of lower than 70 mmHg with a daily supplement of about 100 mg for a time duration of 4 weeks, it resulted in a decrease in SBP by a value of 11 mmHg and in case of DBP by 7 mmHg [94]. The low availability of CoQ10 is a major problem associated with using it as an antihypertensive supplement but it can be resolved by using CoQ10 nano-emulsion [95].

Aged garlic extract: S-allylcysteine is a polysulfide present in garlic that can induce the synthesis of hydrogen sulfide (H_2S), which improves the control of endothelial NO. It ultimately leads to vasodilation, smooth wall relaxation, and reduction of BP in humans. Some dietary and genetic factors can also influence the efficiency of NO and H_2S signaling pathways and may result in developing hypertension. If an individual has a sulfur deficiency, then it may increase the chances of hypertension, which can be minimized by providing supplements of organosulfur compounds obtained from garlic [96]. The dry-aged garlic can decrease catecholamine sensitivity and enhance arterial compliance by blocking calcium channels and ACEI activity [97]. In a meta-analysis including 9 RCTs in which 482 participants participated, administered with extract of aged garlic for a time period of 8-26 weeks, positive antihypertensive results were observed when compared with placebo. The mean reduction for SBP was by the value of 9.1 mmHg and in the case of DBP by 3.8 mmHg [98]. Even after the high antihypertensive effect of garlic extract, it is not widely used because of its common gastrointestinal side effects [99].

Probiotics: Trillions of microbial cells constitute the human gut microbiota, which includes Gram-positive and Gram-negative as well as aerobic and anaerobic species. From recent studies, it was found that wrong dietary habits and lifestyle can influence the microbiota negatively, which

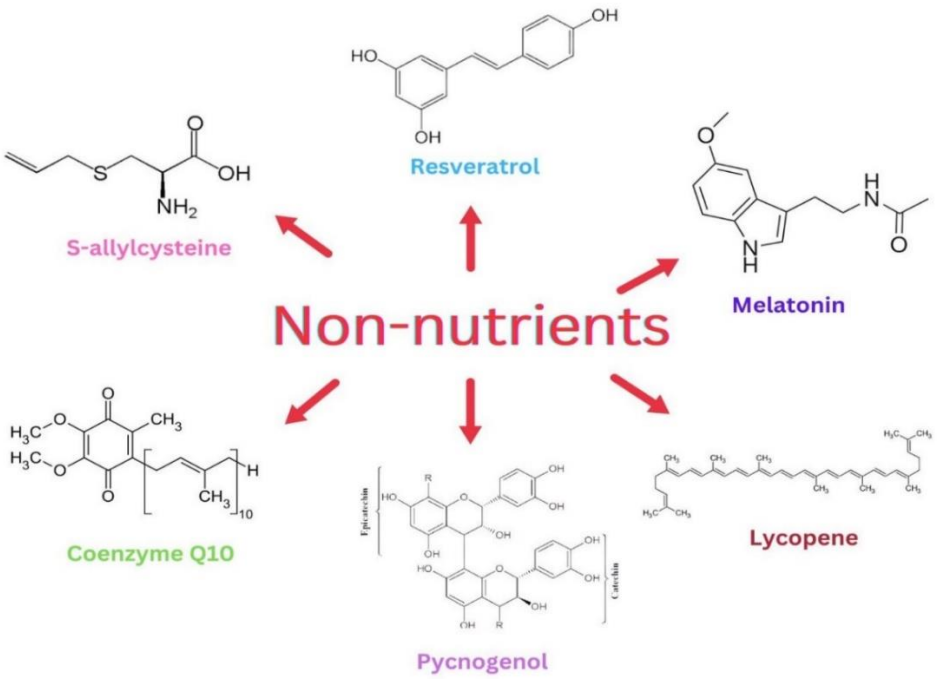

Fig. 5. Different types of Non-nutrients

Table 3. Effects of Non-nutrients on Hypertension. Modified and updated [6]

Non-nutrients	Expected effect on BP	Clinical evidence
Resveratrol and grape seed extracts	-12/1 mmHg	Meta-analysis of 9 RCTs (n = 390)
Melatonin	-6.1/-3.5 mmHg	Meta-analysis of 7 RCTs (n = 221)
Lycopene	-5/1 mmHg	Meta-analysis of 6 RCTs (n = 482)
Pycnogenol	-3/-3 mmHg	Meta-analysis of 9 RCTs (n = 549)
Coenzyme Q10	-11/-7 mmHg	Mainly epidemiological data
Aged garlic extract	-9.1/-3.8 mmHg	Meta-analysis of 9 RCTs (n = 482)
Probiotics	-3.5/-2.3 mmHg	Meta-analysis of 9 RCTs (n = 543)

may lead to cardiovascular diseases. Hypertensive patients with gut dysbiosis have been observed with a rise in Firmicutes/Bacteroidetes ratio, accompanied by a reduction in butyrate-producing bacteria [100]. The synthesis of inflammatory factors and short-chain fatty acids due to these changes, increases which cause a negative influence on kidneys, arteries, and BP in humans [101]. In a recent meta-analysis involving 9 RCTs, it was observed that administrating probiotics in less than 10^{11} colony-forming units for a period of 8 weeks leads to a decrease of SBP by a value of 3.5 mmHg and in the case of DBP by 2.3 mmHg. The antihypertensive effect increases when probiotics belonging to many different species are administrated instead of a single species of probiotics. If an individual is administrated with a daily supplement, which is below 10^{11} colony-forming units, then it does not cause any notable reduction in BP [102].

5. FUTURE PERSPECTIVE

Over the course of time, as new and new nutraceuticals and functional foods are being discovered and we are acquiring more information regarding the mechanism, optimal combination, and doses of nutraceuticals, their role in protection against hypertension, and preventing the risk of developing cardiovascular diseases is also increasing. Different nutraceuticals and functional foods have different degrees of blood pressure-reducing activity based on their efficacy and action mechanism. Usually, nutraceuticals and functional foods reduce blood pressure by regulating NO production, preventing ACE activity, improving endothelial function, and scavenging free radicals. There are also some issues related to the use of nutraceuticals for their effectiveness, regulation, safety, and health claims. Furthermore, there are many technical challenges in the application of these nutraceuticals as food. So, the final products that naturally contain these nutraceuticals have a better scope to be applicable in our everyday lifestyle.

6. CONCLUSION

Hypertension is a clinical condition, which occurs when the force of the blood is too high against the walls of the artery. It is one of the most prominent clinically relevant problems, which still affects a large portion of the population and causes cardiovascular diseases and renal problems. The treatment of hypertension includes a combination of antihypertensive medicines, along with lifestyle changes, which is sufficient to tackle some crucial cardiovascular complications like stroke and coronary artery disease. But this course of action is inappropriate for a larger portion of the population associated with prehypertension. Nutraceuticals and functional foods provide a better course of action in the case of prehypertensive patients as it has none or minor side effects, are cost-effective, and the patient does not have to rely on drugs. The nutraceutical category includes foods, nutrients, and non-nutrients which have BP-reducing abilities. However, there is a further need for investigation on nutraceuticals to determine their long-term effect, effects on higher doses, and effects on combining with other nutraceuticals. This article focuses on the efficacy of different nutraceuticals from the results of various randomized clinical trials. There is a further need for investigation to determine nutraceuticals, which are the best in risk-benefit ratio and cost-effectiveness to be used by the general population.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365:217–23.
2. Lawes CM, Vanders HS, Rodgers A. Global burden of blood pressure related disease, 2001. Lancet. 2008; 371:1513–8.
3. McInnes GT. Lowering blood pressure for cardiovascular risk reduction. J Hypertens Suppl. 2005;23: S3–8.
4. McCartney DM1, Byrne DG, Turner MJ. Dietary contributors to hypertension in adults reviewed. Ir J Med Sci. 2015;84: 81–90.
5. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, et al. Reducing the global burden of cardiovascular disease, Part 1: The epidemiology and risk factors. Circ Res. 2017;121:677–694.
6. Borghi C, Cicero AF. Nutraceuticals with a clinically detectable blood pressure-lowering effect: A review of available randomized clinical trials and their meta-analyses. Br J Clin Pharmacol. 2017; 83:163–171.
7. Chockalingam A. World hypertension day and global awareness. Can. J. Cardiol. 2008;24:441–444.
8. Pere MI, Musini VM. Pharmacological interventions for hypertensive emergencies: a Cochrane systematic review. J. Hum. Hypertens. 2008;22:596–607.
9. Appel LJ, Giles TD, Black HR, Izzo JL Jr, Materson BJ, Oparil S, et al. ASH position paper: dietary approaches to lower blood pressure. J Am Soc Hypertens. 2010; 4: 79 – 89.
10. Domenech M, Roman P, Lapetra J, Garcia de la Corte FJ, Sala-Vila A, de la Torre R, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. Hypertension. 2014;64:69 – 76.
11. Kapil V, Milsom AB, Okorie M, Maleki-Toyserkani S, Akram F, Rehman F, et al. Inorganic nitrate supplementation lowers blood pressure in humans: role for nitrite-derived NO. Hypertension. 2010; 56:274–281.
12. Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, et al. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. Hypertension. 2008; 51: 784 – 90.
13. Kapil V, Khambata RS, Robertson A, Caulfield MJ, Ahluwalia A. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: A randomized, phase 2, double-blind, placebo-controlled study. Hypertension. 2015; 65:320–327.
14. Kanner J, Harel S, Granit R. Betalains—a new class of dietary cationized antioxidants. J Agric Food Chem. 2001; 49: 5178 – 85.
15. Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: A systematic review and meta-analysis. J Nutr. 2013; 143: 818–26.
16. Lin LZ, Chen P, Harnly JM. New phenolic components and chromatographic profiles of green and fermented teas. J. Agric. Food Chem. 2008;56:8130–8140.
17. Liu G, Mi XN, Zheng XX, Xu YL, Lu J, Huang XH. Effects of tea intake on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2014;112:1043–54.
18. Habauzit V, Morand C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: an update for clinicians. Ther Adv Chronic Dis. 2012; 3: 87–106.
19. Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, et al. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. J Nutr. 2008;138:1671–6.
20. Grassi D, Desideri G, Necozione S, Ruggieri F, Blumberg JB, Stornello M, et al. Protective effects of flavanol-rich dark chocolate on endothelial function and wave reflection during acute hyperglycemia. Hypertension. 2012; 60: 827–32.
21. Cesare R. Sirtori, Anna Arnoldi & Arrigo F. G. Cicero. Nutraceuticals for blood pressure control, Annals of Medicine 2015;47(6):447-456.
22. Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP. Effect of cocoa on blood pressure. Cochrane Database Syst Rev. 2012; 8: CD008893.
23. Reid I, Sullivan T, Fakler P, Frank OR, Stocks NP. Does chocolate reduce blood pressure? A meta-analysis. BMC Med. 2010;8:39– 46.

24. Desch S, Kobler D, Schmidt J et al. Low vs higher-dose dark chocolate and blood pressure in cardiovascular high-risk patients. Am. J. Hypertens. 2010;23(6): 694–700.
25. Zarfeshany A, Asgary S, Javanmard SH. Potent health effects of pomegranate. Adv Biomed Res. 2014;3:100.
26. Sahebkar A, Ferri C, Giorgini P, Bo S, Nachtigal P, Grassi D. Effects of pomegranate juice on blood pressure: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2017;115:149–161.
27. Kelishadi R, Gidding SS, Hashemi M, Hashemipour M, Zakerameli A, Poursafa P. Acute and long term effects of grape and pomegranate juice consumption on endothelial dysfunction in pediatric metabolic syndrome. J Res Med Sci. 2011;16:245–253.
28. Pathak N, Rai AK, Kumari R, Bhat KV. Value addition in sesame: A perspective on bioactive components for enhancing utility and profitability. Pharmacogn Rev. 2014;8:147–155.
29. Khosravi-Boroujeni H, Nikbakht E, Natanelov E, Khalesi S. Can sesame consumption improve blood pressure? A systematic review and meta-analysis of controlled trials. J Sci Food Agric. 2017; 97:3087– 3094.
30. Wichitsranoi J,Weerapreeyakui N, Boonsiri P et al. Antihypertensive and antioxidant effects of dietary black sesame meal in prehypertensive humans. Nutr. J. 2011;10(1):82–88.
31. Sankar D, Sambandam G, Ramskrishna Rao M, Pugalendi KV. Modulation of blood pressure, lipid profiles and redox status in hypertensive patients taking different edible oils. Clin. Chim. Acta. 2005; 355(1–2):97–104.
32. Harikumar KB, Sung B, Tharakan ST et al. Sesamin manifests chemopreventive effects through the suppression of NF-kappa-B-regulated cell survival, proliferation, invasion and angiogenic gene products. Mol. Cancer Res. 2010; 8(5):751–761.
33. Nakano D, Ogura K, Miyakoshi M et al. Antihyptensive effect of angiotensin-Iconverting enzyme inhibitory peptides from a sesame protein hydrolysate inspontaneously hypertensive rats. Biosci. Biotechnol. Biochem. 2006;70(5):1118–1126.
34. [34]Suetsuna K, Nakano T. Identification of an antihypertensive peptide from peptic digest of wakame (Undaria pinnatifida). J Nutr Biochem 2000; 11:450–454.
35. Nakano T, Hidaka H, Uchida J, et al. Hypotensive effects of wakame. J Jpn Soc Clin Nutr. 1998; 20:92.
36. Sato M, Hosokawa T, Yamaguchi T, et al. Angiotensin I converting enzyme inhibitory peptide derived from wakame (*Undaria pinnatifida*) and their antihypertensive effect in spontaneously hypertensive rats. J Agric Food Chem. 2002;50:6245–6252.
37. Krotkiewski M, Aurell M, Holm G, et al. Effects of a sodium-potassium ion-exchanging seaweed preparation in mild hypertension. Am J Hypertens. 1991;4:483-488.
38. Lawson LD Garlic: A review of its medicinal effects and indicated active compounds. ACS Symposium Series. 1998;691:177-209.
39. Lawson LD The composition and chemistry of garlic cloves and processed garlic. Garlic: The science and therapeutic applications of Allium sativum L. and related species. 1996; 37-109.
40. Ariga T, Seki T. Antithrombotic and anticancer effects of garlic-derived sulfur compounds: A review. Biofactors. 2006;26:93-103.
41. Bradley JM, Organ CL, Lefer DJ Garlic-derived organic polysulfides and myocardial protection. J Nutr 2016;146:403S-409S.
42. Simons S, Wollersheim H, Thien T. A systematic review on the influence of trial quality on the effects of garlic on blood pressure. Neth J Med. 2009;67:212-219.
43. Reinhard KM, Coleman CI, Teevan C, Vacchani P. Effects of garlic on blood pressure in patients with and without systolic hypertension: A meta-analysis. Ann Pharmacother. 2008;42:1766-1771.
44. Houston MC. Treatment of hypertension with nutraceuticals. Vitamins, antioxidants and minerals. Expert Rev. Cardiovasc. Ther. 2007;5(4):681–691.
45. Mozaffarian D, Wu JH. Omega-3 fattyacids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011;58:2047–2067.
46. Cicero AF, Ertek S, Borghi C. Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and

management. Curr Vasc Pharmacol. 2009;7:330–7.

47. Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. Am J Hypertens. 2014; 27: 885–96.
48. Pase MP, Grima NA, Sarris J. Do long-chain n-3 fatty acids reduce arterial stiffness? A meta-analysis of randomised controlled trials. Br J Nutr. 2011;106:974–80.
49. Cabo J, Alonso R, Mata P. Omega-3 fatty acids and blood pressure. Br J Nutr. 2012; 107 (Suppl 2): S195–S200.
50. Rebholz CM, Friedman EE, Powers LJ, Arroyave WD, He J, Kelly TN. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am J Epidemiol. 2012; 176 (Suppl 7): s27–s43.
51. Liu XX, Li SH, Chen JZ, Sun K,Wang XJ,Wang XG, et al. Effect of soy isoflavones on blood pressure: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2012; 22: 463–70.
52. FitzGerald RJ, Murray BA, Walsh DJ. Hypotensive peptides from milk proteins. J. Nutr. 2004; 134(4), S980–S988.
53. Siltari A, Viitanen R, Kukkurainen S, Vapaatalo H, Valjakka J. Does the cis/trans configuration of peptide bonds in bioactive tripeptides play a role in ACE-1 enzyme inhibition? Biologics. 2014;8:59–65.
54. Cicero AF, Rosticci M, Gerocarni B, Bacchelli S, Veronesi M, Strocchi E, et al. Lactotripeptides effect on office and 24-h ambulatory blood pressure, blood pressure stress response, pulse wave velocity and cardiac output in patients with high-normal blood pressure or first-degree hypertension: a randomized double-blind clinical trial. Hypertens Res. 2011;34: 1035–40.
55. De Leo F, Panarese S, Gallerani R, Ceci LR. Angiotensin converting enzyme (ACE) in hibitoroy peptides: production and implementation of functional food. Curr. Pharm. Des. 2009;15(31):3622–3643.
56. Dong JY, Qin JQ, Zhang ZL, Zhao Y, Wang J, Arigoni F, et al. Effect of oral L-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials. Am Heart J. 2011;162: 959–65.
57. Satake K, Lee JD, Shimizu H, Uzui H, Mitsuke Y, Yue H, et al. Effects of magnesium on prostacyclin synthesis and intracellular free calcium concentration in vascular cells. Magnes Res. 2004;17:20–27.
58. Soltani N, Keshavarz M, Sohanaki H, Zahedi Asl S, Dehpour AR. Relaxatory effect of magnesium on mesenteric vascular beds differs from normal and streptozotocin induced diabetic rats. Eur J Pharmacol. 2005;508:177–181.
59. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur J Clin Nutr. 2012; 66:411–418.
60. Zhang Xi, Yufeng Li, Del Gobbo L, Rosanoff A, Wang J, Zhang W, et al. Effects of magnesium supplementation on blood pressure a meta-analysis of randomized double-blind placebo-controlled trials. Hypertension. 2016; 68:324–333.
61. Iqbal S, Klammer N, Ekmekcioglu C. The effect of electrolytes on blood pressure: a brief summary of meta-analyses. Nutrients. 2019;11:pii: E1362.
62. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013; 346: f1378.
63. D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol. 2011; 57:1210.
64. Anderson JJ, Kruszka B, Delaney JA, He K, Burke GL, Alonso A, et al. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 2016; 5: pii: e003815.
65. Kopecky SL, Bauer DC, Gulati M, Nieves JW, Singer AJ, Toth PP, et al. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults: a clinical guideline from the National Osteoporosis Foundation and the American Society for Preventive

Cardiology. Ann Intern Med. 2016;165: 867–868.
66. Tankeu AT, Ndip Agbor V, Noubiap JJ. Calcium supplementation and cardiovascular risk: a rising concern. J Clin Hypertens. 2017;19:640– 664.
67. Bergomi M, Rovesti S, Vinceti M, Vivoli R, Caselgrandi E, Vivoli G. Zinc and copper status and blood pressure. J. Trace Elem. Med. Biol. 1997;11:166–169.
68. Shahbaz AU, Sun Y, Bhattacharya SK et al. Fibrosis in hypertensive heart disease: molecular pathways and cardioprotective strategies. J. Hypetens. 2010; 28:S25–S32.
69. Block G, Jensen CD, Norkus EP, Hudes M, Crawford PB. Vitamin C in plasma is inversely related to blood pressure and change in blood pressure during the previous year in young black and white women. Nutr J. 2008; 17:35–46.
70. Enstrom JE, Kanim LE, Klein M. Vitamin C intake and mortality among a sample of the United States population. Epidemiology. 1992; 3: 194-202.
71. Houston MC. Nutrition and nutraceutical supplements in the treatment of hypertension. Expert Rev. Cardiovasc. Ther. 2010; 8(6), 821–833.
72. Juraschek SP, Guallar E, Appel LJ, Miller ER 3rd. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012; 95:1079–1088.
73. Sato K, Dohi Y, Kojima M, Miyagawa K. Effects of ascorbic acid on ambulatory blood pressure in elderly patients with refractory hypertension. Arzneimittelforschung. 2006; 56(7), 535–540.
74. Hanni LL, Huarfner LH, Sorensen OH, et al. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens. 1995;8:894-901.
75. Bednarski R, Donderski R, Manitius L. [Role of vitamin D in arterial blood pressure control]. Pol. Merkur. Lekarski. 2007;136:307–310.
76. Bhandari SK, Pashayan S, Liu IL et al. 25-hydroxyvitamin D levels and hypertension rates. J. Clin. Hypertens. 2011;13(3):170–177.
77. Cicero AF, Derosa G, Manca M, Bove M, Borghi C, Gaddi AV. Different effect of psyllium and guar dietary supplementation on blood pressure control in hypertensive overweight patients: a six-month, randomized clinical trial. Clin Exp Hypertens. 2007;29:383–94.
78. Houston MC. Nutrition and nutraceuticals supplements in the treatment of hypertension. Prog Cardiovasc Dis. 2005;47:396–449.
79. Caligiuri SP, Edel AL, Aliani M, Pierce GN. Flaxseed for hypertension: implications for blood pressure regulation. Curr Hypertens Rep. 2014;16:499.
80. He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: A review of epidemiologic evidence. Clin Exp Hypertens. 1999; 21:785–796.
81. Li H, Xia N, Förstermann U. Cardiovascular effects and molecular targets of resveratrol. Nitric Oxide. 2012; 26: 102–10.
82. Liu Y, Ma W, Zhang P, He S, Huang D. Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. Clin Nutr. 2015;4:27–34.
83. Feringa HH, Laskey DA, Dickson JE, Coleman CI. The effect of grape seed extract on cardiovascular risk markers: a meta-analysis of randomized controlled trials. J Am Diet Assoc. 2011;111:1173–81.
84. Rodella LF, Favero G, Foglio E, Rossini C, Castrezzati S, Lonati C, et al. Vascular endothelial cells and dysfunctions: role of melatonin. Front Biosci. 2013; 5:119–129.
85. Grossman E, Laudon M, Zisapel N. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. Vasc Health Risk Manag. 2011;7:577–84.
86. Scheer FA, Morris CJ, Garcia JI, Smales C, Kelly EE, Marks J, et al. Repeated melatonin supplementation improves sleep in hypertensive patients treated with betablockers: a randomized controlled trial. Sleep. 2012; 35:1395–402.
87. Zaslavskaya RM, Lilitsa GV, Dilmagambetova GS, Halberg F, Cornélissen G, Otsuka K, et al. Melatonin, refractory hypertension, myocardial ischemia and other challenges in nightly blood pressure lowering. Biomed Pharmacother. 2004; 58 (S1): S129–34.
88. Li X, Xu J. Lycopene supplement and blood pressure: an updated meta-analysis of intervention trials. Nutrients. 2013; 5:3696–3712.
89. Burton-Freeman B, Sesso HD. Whole food versus supplement: comparing the clinical

evidence of tomato intake and lycopene supplementation on cardiovascular risk factors. Adv Nutr. 2014; 5: 457–85.
90. Maimoona A, Naeem I, Saddiqe Z, Jameel K. A review on biological, nutraceutical and clinical aspects of French maritime pine bark extract. J Ethnopharmacol. 2011;133: 261–77.
91. Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P. Pycnogenol, French maritime pine bark extract, improves endothelial function of hypertensive patients. Life Sci. 2004; 74: 855–62.
92. Pravst I, Zmitek K, Zmitek J. Coenzyme Q10 contents in foods and fortification strategies. Critical Reviews in Food Science and Nutrition. 2010; 50(4):269–280.
93. Langsjoen PH, Langsjoen AM. Overview of the use of CoQ10 in cardiovascular disease. Biofactors. 1999;9:273–84.
94. Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst Rev. 2009;4:CD007435.
95. Ankola DD, Viswanas B, Bhardqaj V, Ramarao P, Kumar MN. Development of potent oral nanoparticulate formulation of coenzyme Q10 for treatment of hypertension: can the simple nutritional supplement be used as first line therapeutic agents for prophylaxis/ therapy? Eur J Pharm Biopharm. 2007;67:361–9.
96. Ried K, Fakler P. Potential of garlic (*Allium sativum*) in lowering high blood pressure: mechanisms of action and clinical relevance. Integr Blood Press Control. 2014;7:71–82.
97. Butt MS, Sultan MT, Butt MS, Iqbal J. Garlic: nature's protection against physiological threats. Crit Rev Food Sci Nutr. 2009;49:538–51.
98. Rohner A, Ried K, Sobenin IA, Bucher HC, Nordmann AJ. A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension. Am J Hypertens. 2015; 28: 414–23.
99. Reid K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomized controlled trial. Maturitas. 2010; 67:144–150.
100. Robles-Vera I, Toral M, Romero M, Jime´nez R, Sa´nchez M, Pe´rez-Vizcaı´no F, et al. Antihypertensive effects of probiotics. Curr Hypertens Rep. 2017;19:26.
101. Antza C, Stabouli S, Kotsis V. Gut microbiota in kidney disease and hypertension. Pharmacol Res 2018; 130:198–203.
102. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: A systematic review and meta-analysis of randomized, controlled trials. Hypertension. 2014; 64:897–903.