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Ameliorative effects of antioxidants on hypertension

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Abstract

Prevention and management of hypertension are the universal public health challenges. It has been revealed that many dietary components may contribute to cardiovascular morbidity and mortality. There has been an expanded focus on ascertaining these natural components of foods, describing their physiological activities and mechanisms of actions. The main bioactive components of herbal plants and foods are polyphenols, vitamins, catechins, anthocyanins, phenolic acids, polyphenols, tannins, polysaccharides, fiber, saponins, sterols, and minerals. They may reduce blood pressure by different mechanisms such as antioxidant, angiotensin converting enzyme (ACE) inhibition effect, vasodilatory and Ca^{2+} channel blocking properties. These functional natural components may provide new therapeutic approach for hypertension management, and contribute to a healthy cardiovascular population. The present review summarizes the antihypertensive micronutrients, food bioactive components, and herbal plants as well as related physiological mechanisms to suppress the high blood pressure in humans.

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Introduction

Hypertension or high blood pressure is one of the risk factors for heart attack, stroke, and heart failure. It is associated with progressive renal dysfunction, renal interstitial fibrosis, decreasing glomerular filtration, and glomerulosclerosis. Prevention and management of hypertension are the major challenges for universal public health. Some condition increase the risk of developing hypertension such as inactive lifestyle, stress, vitamin D deficiency, potassium deficiency, obesity, raise of rennin, renal failure, hyperthyroidism, hypothyroidism, and obesity. Uncontrolled high blood pressure may lead to a reduced life expectancy and a higher morbidity because of a high risk of cardiovascular complications. It is now renowned that the ailing and sclerotic arteries were most often the concern of the hypertension. Specific aspects of the approvals for the pharmacological treatment of hypertension are the treatment of hypertension in adults who are less than 40 years (1-4).

In spite of the fact that the treatment of hypertension has an extended clinical trial indication base, but the effect of bioactive compounds and naturally medicinal plants are not exactly clear. It has been recognized that many dietary components may contribute to human cardiovascular health. There has been an expanded focus on ascertaining these natural components of foods, explaining their physiological activities and mechanisms of actions. Grain, vegetables, fruits, dairy, meat, fish, tea, and lactic acid bacteria are various food sources with prospective antihypertensive effects (2,5-8).

Their main bioactive components include polyphenols, flavonoids, flavanols, vitamins, catechins, anthocyanins, tannins, polysaccharides, fiber, saponins, and sterols. They may reduce blood pressure by different mechanisms, such as antioxidant, angiotensin converting enzyme (ACE) inhibition effect, vasodilatory and Ca^{2+} channel blocking properties. These functional foods may pro-

Core tip

Prevention and management of hypertension are the universal public health challenges. The present review summarizes the antihypertensive micronutrients, food bioactive components, and herbal plants as well as related physiological mechanisms to suppress the high blood pressure in humans.

vide new therapeutic approaches for hypertension prevention and treatment, and contribute to improve cardiovascular patient's status. In addition in the last three decades, a lot of concerted efforts have been focused into researching native plants with antihypertensive curative values. The antihypertensive consequences of some of these medicinal plants have been proved. Thus an important aspect of this review was introduction these compounds with antihypertensive effects that have been scientifically studied up to now (5,9-11).

Materials and Methods

This review article discusses the pathophysiological mechanisms of antioxidant therapy for high blood pressure. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as Angiotensin converting enzyme, ACE-inhibitory activity, antihypertension, renin angiotensin system, medicinal plants derived polyphenols, plants peptides (2,12).

Micronutrients

Carotenoids

A possibility mechanism of hypertension is reactive oxygen species (ROS) which seems to be related to inflammation, vasoconstriction, as well as contributing to vascular hurt in many cardiovascular diseases such as hypertension; hyperlipidemia and diabetes (3,13).

ROS have an important pathophysiological role in hypertension. Numerous natural carotenoids exist in fresh fruits such as carrots and vegetables. Consumption of vegetables enrich in carotenoids was associated with a reduced risk of coronary heart disease. Antioxidants, such as carotenoids inhibit NADPH oxide motivated generation of ROS, recover endothelial function, progress nitric oxide (NO) generation and decrease blood pressure in hypertensive patients. Taxanthin, an oxicarotenoid, has antihypertensive effect by normalization of stimulus of adrenoreceptor sympathetic pathway and decline in oxidative stress and recuperation in NO bioavailability. Lycopene, a carotenoid with red pigment abundant in tomatoes and watermelon has been associated with a decrease in blood pressure (4,14-16).

Vitamin C

Vitamin C (ascorbic acid), a crucial micronutrient that is assimilated primarily through the consumption of fruits, vegetables and supplements, is a powerful aqueous phase antioxidant that lowers oxidative stress and improves endothelial function through effects on NO production by endothelial cells. Vitamin C increases intracellular tetrahydrobiopterin, elaborates NO, increases blood vessels and improves endothelial strength and elasticity. The antioxidant properties of vitamin C are assumed to act synergistically with vitamin E, decreasing the structure of peroxyl radicals and blocking lipid peroxidation (14,17,18).

Vitamin D

Deficiency of vitamin D is associated with arterial hypertension. The antihypertensive effect of vitamin D is incorporated with suppression of renin and parathyroid hormone concentrations. It also has renoprotective, anti-inflammatory and vasculoprotective properties. Vitamin D deficiency stimulates renin angiotensin system to increase blood pressure independent of angiotensin II mediated inflammatory responses and vascular growth. 1,25(OH)2 D3 causes smooth muscle cells vasodilation by stimulation of prostacyclin construction and increasing expression of vascular endothelial growth factor that can up-regulate endothelial NO synthase as a result of stimulating smooth muscle cells proliferation and endothelium vasodilation (3,4,12,17,19).

Vitamin E

Vitamin E is a group of compounds classified as tocopherols and tocotrienols. Nutritional sources rich in vitamin E include nuts, avocados, vegetable, asparagus, and green vegetables. Vitamin E is potent scavenger of free radicals, stimulates activation of NO synthesis activity and increases NO synthesis in endothelial cells which are important molecular envoy accounting for endothelium derived relaxing factors. These effects can contribute to improve vasodilatation in hypertension. Vitamin E inhibits expression of adhesion molecules, which might influence cell/cell interactions and, consequently, vascular structural changes related to hypertension (10,13,14,18,20,21).

Niacin or Vitamin B3

High dosage of niacin, vitamin B3 or nicotinic acid is used for improvement of plasma lipid profile. It prevents atherosclerosis by reduction of hyperlipidemia and hypercholesterolemia. Niacin improves the vascular endothelial cell redox state through preventing vascular inflammatory genes, oxidative stress, and key cytokines (22-24).

Vitamin K

Experimental studies have shown the hypotensive potential of vitamin K in NaCl-sensitive hypertension. The protective effect of K, beside the development of vascular diseases might mainly be due to its influence on blood pressure regulation. The direct influence of vitamin K on blood pressure regulation would be via its effect on natriuresis, baroreceptor sensitivity, the renin–angiotensin system, vasodilatation, and sympathetic nervous system activation. Other mechanisms for the role of vitamin K are inhibition of free radical formation, vascular smooth muscle proliferation and arterial thrombosis. Inadequate vitamin K in the diet has been associated with increased risk of tissue calcification and atherosclerosis. Vitamin K supplementation might demonstrate beneficial in preventing vascular disease in patients with chronic kidney disease or end-stage renal disease (5,14,25).

Magnesium

Epidemiological studies have reported a significant converse relationship between Mg^{2+} intake and the development of hypertension. Previous studies have been reported low cytosolic free Mg^{2+} in hypertensive subjects. The fermentation of Mg^{2+} at pharmacological products causes vasodilation of systemic vasculature and coronary arteries. Also it protects the myocardium beside ischemia/reperfusion injury in investigational animals. An experiment trial has proved that intravenous Mg^{2+} had a protective effect during the treatment of acute myocardial infarction (1,17,26,27).

Several mechanisms suggested for the antihypertensive effect of Mg^{2+}. Magnesium ions decrease levels of intracellular Ca^{2+} by competing with Ca^{2+} or membrane binding sites and modulating Ca^{2+} binding and release from the sarcoplasmic reticulum. Thus, it can make vasodilation as an intracellular Ca^{2+} blocker. By the side of the cell membrane, Mg^{2+} regulates ion flexibility through voltage gated, acetylcholine activated, and ATP activated K^{+} channels. These effects may also have an elaborate role in the cardiovascular system. Cardiac and vascular smooth muscle cells are vulnerable to deficit in the extracellular Mg^{2+} because Mg^{2+} insufficiency causes elevation in the intracellular Ca^{2+} in these cells (25-28).

Calcium

The role of calcium in regulating cellular processes, including vascular tone is reliant upon cellular Mg^{2+}/Ca^{2+} ratio. The variations in cellular ionic balanced state become crucial on the pathophysiology of high blood pressure, and cardiac hypertrophy. Vascular plasma membrane depolarization through decreased K^{+} channel activation produces opening of the voltage-dependent T and L Ca^{2+} channels, with consequent of Ca^{2+} contemporary representing influx into the cytosol of extracellular Ca^{2+}. Increasing in intracellular Ca^{2+} stimulates initiation of specific ryanodine subtle Ca^{2+} release channels in the sarcoplasmic reticulum and extends the initial localized increase in Ca^{2+} more generally through the cytosol. At the contractile site, the increase in Ca^{2+} initiates the cascade of molecular reorganizations of calmodulin and myosin light chain kinase, subsequent myofilament shortening and vasoconstriction. Muscle relaxation is a reversal of the ionic equilibrium through the sarcoplasmic reticulum-mediated reuptake of Ca^{2+} into intracellular storage in addition to the plasma membrane Ca-ATPase and Na^{+}/Ca^{2+} exchange arbitrated Ca^{2+} outlet from the cell. These would result in reducing Ca^{2+} (17,29-31).

Flavonoids

The largest group of polyphenolic compounds in plants such as tea, apples, grapes, and oranges are flavonoids. The biosynthesis of flavonoids is through the shikimic acid and malonic acid pathways. The abilities of flavonoids as ACE inhibitors in controlling blood pressure have been studied during the previous decades and most of them have proved to be effective in defeating the activity of ACE. Flavonoids such as flavanones, and flavanols are able to modulate blood pressure by restoring endothelial function (6,7,11,23).

Quercetin

Quercetin has revealed the most reliable blood pressure lowering effect in animal and human studies. Flavonoids have shown vasodilatory activities through indirect pathways. Epicatechin reduces blood pressure via activation of endothelial NO synthesis and increasing vascular NO synthesis phosphorylation. As result it restores the availability of NO and improves endothelial function in the hypertension. Antihypertensive effect of catechin is due to its inhibition of ACE action, so it can reduce blood pressure in patients. The blood pressure reaction to epicatechin is attributed to its ability to increase both acetylcholine mediated vasodilation and endothelial NO synthase activity, and improving comprehensive endothelial function (7,14,22,32).

Chrysin

Chrysin increases cyclic guanosine monophosphate (cGMP), consequently inhibiting intracellular calcium release and vessel constriction. It also keeps superoxide radical scavenging activity, which prevents the breakdown of NO by superoxide radicals (14).

Myricetin

Myricetin moderates systolic blood pressure and vascular reactivity. Myricetin's antihypertensive activity is assumed to be due to its antioxidant activity, which results in reduced ROS and increased antioxidant enzymes in the heart tissue. Myricetin and epicatechin together inhibit vasoconstrictors such as angiotensin II and endothelin (1,2,19).

Anthocyanins

Anthocyanins have shown ACE inhibition activity in vitro. Delphinidin-3O-sambubiosides and cyanidin-3O-sambubiosides which exist in *Hibiscus* (*Hibiscus sabdariffa*) have shown ACE effects. Cyanidin-3-O-β-glucoside isolated from rose species inhibited ACE in vitro. Bilberry (*Vaccinium myrtillus*) extracts reduced ACE activity in vein endothelial cell culture model. Dietary supplementation of anthocyanins, cyanidin-acyl-glucoside, cyanidin-3-glucosides and peonidin acyl glucoside in purple corn and purple sweet potato have reduced the systolic blood pressure. The decline mechanisms of blood pressure by anthocyanins were described to be due to their antioxidant activity, preservation of endothelial NO, and inhibition of serum lipid oxidation. The observed ACE inhibitory activity of anthocyanins has been explained by the metal chelating ability of flavonoids with hydroxyl groups (6,7,14,19,33).

Coenzyme Q10

Coenzyme Q10, ubiquinone, has a quantity of important physiological functions and has been used for treating various cardiovascular disorders including angina pectoris and hypertension. Numerous trials with supplemental CoQ10 in heart failure found improvement in functional parameters such as ejection fraction, stroke volume and cardiac output. Several epidemiological studies have shown an inverse association between dietary Q10 and blood pressure (1,34).

Omega 3 polyunsaturated fatty acids

Omega 3 fatty acids have cardio-protective effects. The cardio-protective specific effects of omega 3 fatty acids are improving blood pressure, cardiac function, and vascular function via their antiplatelet and anti-inflammatory effects. Seafood as rich sources of long chain omega 3 polyunsaturated fatty acids protect against thrombosis and atherosclerosis. Some studies have indicated that consuming fish or fish oil containing the omega 3 polyunsaturated fatty acids including eicosapentaenoic acid and docosahexaenoic acid is associated with decreased cardiovascular death rate. Various studies proved that low dosage of eicosapentaenoic acid plus docosahexaenoic acid could improve cardiovascular diseases risk factors, including blood pressure, platelet aggregation, inflammation, and vascular reactivity (17,28,29).

Herbal medicine

Alliaceae

The antihypertensive and antioxidative effects of Alliaceae family (garlic) have been observed in patients with hypertension. The results have shown reduction of 8-hydroxy-2-deoxyguanosin, NO, and lipid peroxidation with garlic consumption (35,36).

Annonaceae

The leaf extract of Annonaceae has been confirmed to lower an elevated blood pressure by reducing the peripheral vascular resistance. Aristolochiaceae is being used as a diuretic and antiphlogistic remedy for the cure of edema and rheumatic pain. The extract of this plant has been reported to contain magnoflorine, which causes hypotension (10,11).

Poaceae/Gramineae (Avena sativa)

The family of Poaceae/Gramineae (*Avena sativa*) decreases systolic and diastolic blood pressure. The leaf extract of Caesalpiniaceae has had relaxant effect on the aortic volume. It relaxes smooth muscle and reduces blood pressure via inhibiting Ca^{2+} inflow through receptor operated channel and voltage sensitive channel. Family of Rosaceae effects involve a hypotensive activity through vasorelaxation resulting from nitrous oxide stimulus and antioxidant activity, as well as a tonic action on cardiac myocytes (17,37,38).

Fabaceae (Soybean)

Family of Fabaceae (Soybean) has been reported to cause a reduction in systolic in addition to diastolic blood pressure in a dose-dependent manner. This reduction in blood pressure has been attributed to the saponin fraction and medicagenic acid (5,38).

Linaceae

Family of Linaceae is rich in α-linolenic acid that belongs to a group of substances of omega-3 fatty acids, is beneficial for the heart diseases. Family of Solanaceae (Tomato) contains carotenoids, such as lycopene, beta carotene, and vitamin E. It is an effective ACE inhibitor, calcium channel blocker, and antioxidant (28,39).

Physiological mechanisms to suppress the high blood pressure in humans

The renin angiotensin system

ACE inhibitors make vasodilation through inhibiting the creation of angiotensin II. ACE converts angiotensin I to angiotensin II, which constricts arteries and veins by binding to angiotensin type II receptors located on the smooth muscle, that are coupled to a G-protein and the inositol trisphosphate signal transduction pathway. The angiotensin II enhances sympathetic activity on the heart and blood vessels by accelerating the release of norepinephrine from sympathetic adrenergic nerves and inhibiting norepinephrine reuptake through these nerves. ACE inhibitors are effective in the management of hypertension caused by renal artery stenosis, which causes renin dependent hypertension due to the augmented release of renin through the kidneys. Reducing angiotensin II formation leads to arterial and venous dilation, which decreases arterial and venous pressures. By reducing the effects of angiotensin II on the kidney, ACE inhibitors cause natriuretic and diuretic actions, that decrease blood volume and cardiac output, hence decreases arterial pressure. Studies have indicated that some plant extracts enrich in phytochemicals are effective in ACE inhibition (6,12,19,20).

The sympathetic hyperactivity

One of the causes of sympathetic hyperactivity in patients with metabolic syndrome is leptin which stimulates sympathetic outflow from the hypothalamus. In addition sodium reabsorption raises in the kidney and leading to sodium maintenance because of elevated insulin level in metabolic syndrome. Raised intra-cranial sodium ions increase sympathetic nervous system activity via mineralocorticoid receptors (15,27,37).

Dopamine and dopamine receptor agonists

Dopamine and dopamine receptor agonists play a therapeutic potential role in treatment of hypertension. Dopamine is naturally synthesized in the kidney and plays an important role in the regulation of fluid and electrolyte balance and blood pressure. In addition absence of any of the five dopamine receptor subtypes consequences hypertension (6,35,39-41).

Conclusion

Studies have revealed that some micronutrients, food bioactive components, and herbal plants have antihypertensive effect by different mechanisms such as antioxidant, ACE inhibition effect, vasodilatory and Ca^{2+} channel blocking properties. These functional foods may provide new therapeutic approaches for hypertension prevention and treatment, and contribute to improve cardiovascular patient's status (7,15,19,25,27,35-37).

Authors' contribution

Primary search of the articles; MB, SK and MM. First draft; MK. Edited the final paper; MRK.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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