

# Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants

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Hypertension is a major risk factor for myocardial infarction, heart failure, stroke, peripheral arterial disease, and aortic aneurysm, and is a cause of chronic kidney disease. Hypertension is often associated with metabolic abnormalities such as diabetes and dyslipidemia, and the rate of these diseases is increasing nowadays. Recently it has been hypothesized that oxidative stress is a key player in the pathogenesis of hypertension. A reduction in superoxide dismutase and glutathione peroxidase activity has been observed in newly diagnosed and untreated hypertensive subjects, which are inversely correlated with blood pressure. Hydrogen peroxide production is also higher in hypertensive subjects. Furthermore, hypertensive patients have higher lipid hydroperoxide production. Oxidative stress is also markedly increased in hypertensive patients with renovascular disease. If oxidative stress is indeed a cause of hypertension, then, antioxidants should have beneficial effects on hypertension control and reduction of oxidative damage should result in a reduction in blood pressure. Although dietary antioxidants may have beneficial effects on hypertension and cardiovascular risk factors, however, antioxidant supplementation has not been shown consistently to be effective and improvement is not usually seen in blood pressure after treatment with single or combination antioxidant therapy in subjects thought to be at high risk of cardiovascular disease. This matter is the main focus of this paper. A list of medicinal plants that have been reported to be effective in hypertension is also presented.

**Key words:** Antioxidant, hypertension, oxidative stress

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## INTRODUCTION

Hypertension (HTN) is a chronic medical condition that is rarely accompanied by any symptoms. It is usually identified through screening or when the patient is seeking for an unrelated problem. Hypertension is a major risk factor for myocardial infarction, heart failure, stroke, peripheral arterial disease, aortic aneurysm, and is a cause of chronic kidney disease.<sup>[1-4]</sup> Elevation of arterial blood pressure is associated with a shortened life expectancy.<sup>[1,5,6]</sup>

In 2000, nearly one billion people of the adult world population had hypertension. The rate of blood pressure is increasing, so that in 1995, 43 million people (22%) in the United States suffered hypertension or were taking antihypertensive medication,<sup>[7]</sup> in 2006, 76 million US adults (34% of the population) had hypertension.

Hypertension is often associated with metabolic abnormalities such as diabetes and dyslipidemia and the rate of these diseases is increasing too. It is estimated

that 30-60% of diabetic patients have associated hypertension.<sup>[8]</sup>

Recently it has been hypothesized that oxidative stress is a key player in the pathogenesis of hypertension.<sup>[9,10]</sup> Endothelial cells play a major role in arterial relaxation. Nitric oxide is released by the endothelium and causes vascular relaxation.<sup>[11]</sup> Nitric oxide is rapidly degraded by the oxygen-derived free radical superoxide anion. Superoxide anion acts as a vasoconstrictor and is a major determinant of nitric oxide (NO) biosynthesis and bioavailability. It, therefore, can modify the endothelial function. Human hypertension is associated in a decrease in NO bioavailability and an increase in oxidative stress.<sup>[12]</sup> Decreased catalase and/or superoxide dismutase and reduced levels of reactive oxygen species (ROS) or reactive nitrogen species (RNS) scavengers such as glutathione, and vitamins C and E also contribute to oxidative stress.<sup>[13,14]</sup> Activation of reduction-oxidation (redox)-dependent signaling cascades and NADPH oxidase-driven generation of ROS are involved in the role of angiotensin-II-induced hypertension.<sup>[15]</sup> Angiotensin II stimulates nonphagocytic NADPH

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oxidase, causing the accumulation of hydrogen peroxide, superoxide, and peroxynitrite.<sup>[16]</sup>

In obesity and diabetes that are usually associated with hypertension, chronic oxidative stress is present.<sup>[17-20]</sup> In this regard, caloric restriction in fasting and obese subjects leads to a marked reduction in ROS generation and other indices of oxidative stress.<sup>[17]</sup>

A reduction in superoxide dismutase and glutathione peroxidase activity have been observed in newly diagnosed and untreated hypertensive subjects, which are inversely correlated with blood pressure. Hydrogen peroxide production is also higher in hypertensive subjects.<sup>[21]</sup> Furthermore, hypertensive patients have higher lipid hydroperoxide production. Oxidative stress is also markedly increased in hypertensive patients with renovascular disease.<sup>[22]</sup>

Furthermore, there is a correlation between renin activation and elevated oxidative stress which may suggest that angiotensin II is a stimulus for oxidant stress in renovascular disease.<sup>[23]</sup> The role of oxidative stress in hypertension and the possible mechanisms involved are well documented in a couple of recently published original and review papers<sup>[9,10]</sup> and are further discussed in this paper. If oxidative stress is indeed a cause of hypertension, then, these all suggest that antioxidants should have beneficial effect on hypertension control. Hence, reduction of oxidative damage may result in a reduction in blood pressure. This matter is the main focus of this paper. Other than further discussing about oxidative stress and its importance in hypertension, a list of medicinal plants which have been reported to be effective in hypertension is also presented.

### Oxidative stress and its importance in hypertension

Oxidative stress (OS) is believed to be involved in many types of disease processes. Oxidative stress occurs when there is an imbalance between the generation of ROS and the antioxidant defense systems [Figure 1]. The ROS comprises many molecules with different effects on the cellular function. ROS and RNS are regularly formed as the result of excess oxidative stress or even normal organ functions. In any biological system there should be an important balance between the formation of ROS and RNS, and their removal.<sup>[11]</sup> The reactive species including

superoxide ( $O_2^-$ ), hydroxyl radical ( $HO\bullet$ ), hydrogen peroxide ( $H_2O_2$ ), peroxynitrite ( $ONOO^-$ ), nitrogen oxide ( $NO\bullet$ ), and hypochlorous acid ( $HOCl$ ) are produced in normal metabolic pathways and scavenged by antioxidants, however, in excess amounts, they can exert harmful reactions. In the vascular system, superoxide and hydrogen peroxide are particularly important. Superoxide, one of the most important sources of initiating radicals in the body, is produced in mitochondria and leaks outside of the mitochondria. To maintain an oxido/redox balance, organs protect themselves from the toxicity of excess ROS/RNS in different ways, including the use of endogenous and exogenous antioxidants [Figure 1].<sup>[12]</sup>

As was mentioned earlier, there is a strong association between blood pressure and some oxidative stress-related parameters. Genetic deficiencies in ROS-generating enzymes have also been shown to be lower in blood pressure compared with their wild-type counterparts.<sup>[24]</sup> Furthermore, in isolated arteries from hypertensive humans and animals, antioxidant bioactivity is reduced, redox-dependent signaling is amplified and ROS production is enhanced.<sup>[25]</sup> The beneficial effects of antihypertensive agents, such as angiotensin I converting enzyme inhibitors, angiotensin-II receptor antagonists,  $\beta$ -adrenergic, and calcium channel blockers might be mediated, at least in part, by decreasing vascular oxidative stress.<sup>[26-30]</sup>

Different sources of ROS might exist in blood vessels. One of the best characterized sources of ROS is NADPH oxidase. Several other enzymes including NO synthase, xanthine oxidase, and mitochondrial enzymes may also contribute to ROS generation. The vasculature and kidney are the rich sources of NADPH oxidase-derived ROS, having important role in vascular damage and renal dysfunction under.<sup>[31]</sup> This system functions as an electron donor and catalyses the reduction of oxygen by NADPH which increases the generation of superoxide upregulation of NADPH oxidase in hypertensive patients.<sup>[31]</sup>

The function of NADPH oxidase-derived superoxide is inactivation of NO in the reaction that forms peroxynitrite, leading to impaired endothelium dependent vasodilation. The activation of NADPH oxidase has been strongly associated with hypertension.<sup>[32]</sup> Oxidation or deficiency of tetrahydrobiopterin (BH4) and L-arginine which are two cofactors for endothelium-derived NO synthase (eNOS) action are associated with the uncoupling of the L-arginine-NO pathway that results in increased eNOS-mediated generation of superoxide and decreased formation of NO.

NADPH oxidase is the initial source of ROS. Superoxide combines with NO, which is synthesized by eNOS, to form peroxynitrite. In turn, peroxynitrite oxidizes and

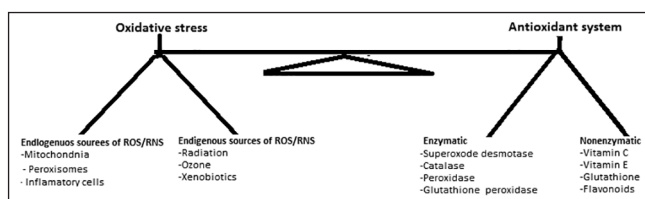


Figure 1: The balance between oxidative stress and antioxidant defence system

destabilizes eNOS to produce additional superoxide.<sup>[33]</sup> BH4 is highly sensitive to oxidation and upper oxide leads to BH4 oxidation, which promotes eNOS uncoupling and further ROS production. Xanthine oxidase that is believed to be involved in hypertension is another important source of ROS in the vascular endothelium. It catalyzes the last two steps of purine metabolism and reduction of oxygen to superoxide.<sup>[32]</sup> Hypertensive rats have demonstrated increased ROS production and elevated levels of endothelial xanthine oxidase, which is associated with increased arteriolar tone.<sup>[31]</sup> Xanthine oxidase may also have a function in end-organ injury in hypertensive patients.<sup>[34]</sup>

The endothelium is also greatly involved in ROS production and furthermore releases agents that regulate vasomotor function. Under some pathophysiological circumstances, endothelium-derived vasoconstricting factors, such as angiotensin-1 and -II, vasoconstrictor prostaglandins and thromboxane A2, urotensin II, and superoxide anions, can be released and contribute to the paradoxical vasoconstrictor effects.<sup>[34]</sup>

As was described, NO has an important role in vascular tone. The decrease in bioavailability of NO in the vasculature reduces hypertension by increasing in vasodilation capacity. The NO is synthesized by NOS from oxygen and arginine. NO, in addition to its antiproliferative and vasorelaxing roles, has an important role in antagonizing the effects of endothelins, AT-II, and ROS.<sup>[35]</sup>

Reduced NO levels can be attributed to elevated levels of ROS. Superoxide combines with NO to form peroxynitrite that oxidizes BH4 and destabilizes eNOS to produce more superoxide and enhancing the development of oxidative stress.<sup>[33]</sup>

Angiotensin-II also, as a potent activator of NADPH oxidase, contributes to the production of ROS. Angiotensin-II not only increases NADPH oxidase activity but also upregulates the activity of superoxide dismutase, possibly to compensate the increased levels of ROS.<sup>[36]</sup>

Captopril and enalapril prevented increases in blood pressure in young, spontaneously hypertensive rats by inhibiting ACE. The ability of angiotensin-II to induce endothelial dysfunction is also due to its ability to downregulate soluble guanylyl cyclase, thereby leading to impaired NO/cGMP signaling. The decrease in NO will also lead to reduced acetylcholine-mediated vasodilation, and an overall increase in ROS is associated in the reduction in the bioavailability of NO.<sup>[37]</sup>

Urotensin-II which is the most potent identified vasoconstrictor also acts through the activation of NADPH

oxidase.<sup>[31]</sup> In addition, overexpression of inducible NOS increases blood pressure via central activation of the sympathetic nervous system, which is mediated by an increase in oxidative stress.<sup>[38]</sup>

In general, although there are multiple sources producing ROS, the most potential sources of excessive ROS in hypertension are as follows: NADPH oxidase, eNOS, mitochondria, xanthine oxidase, cytochrome P450 epoxygenase, cyclooxygenase 1 and 2, transition metals (e.g. Iron).<sup>[38-40]</sup>

### Effects of antioxidants on hypertension

Antioxidants are compounds that are able to trap ROS and thus may be capable of reducing oxidative damage and possibly blood pressure.<sup>[26-33]</sup> Antioxidants terminate the chain reactions of ROS by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such as ascorbic acid, vitamin E or polyphenols that act by different mechanisms [Table 1].<sup>[41-43]</sup>

As was mentioned earlier, there might be a correlation between stress oxidative and arterial hypertension<sup>[9,10]</sup> This matter has led to the use of exogenous antioxidants to reduce blood pressure.<sup>[44]</sup>

Polyphenols that are widespread antioxidants in vegetables and fruits in some studies have demonstrated their beneficial role in prevention and therapy of hypertension. Polyphenols inhibit ROS-producing enzymes such as NADPH and xanthine oxidases, activate, and enhance eNOS expression and increase glutathione. These have improved endothelial function, subsequent normalization of vascular tone, and an overall antihypertensive effect.<sup>[45]</sup>

The antioxidants vitamins C and E and other antioxidants have been considered as possible therapy for decreasing

**Table 1: Exogenous antioxidants and their mechanisms in hypertension<sup>[34]</sup>**

Antioxidant	Mechanisms
Vitamin C	eNOS upregulation, NADPH oxidase downregulation, Protection against BH4 oxidation, ROS scavenging
Vitamin E	eNOS upregulation, NADPH oxidase downregulation, Regulation of mitochondrial ROS synthesis, ROS scavenging
N-acetylcysteine	Protection against BH4 oxidation, ROS scavenging
Polyphenols	Production of NO, ROS scavenging, Iron chelation, Enzyme modulation
Allopurinol	Inhibition of xanthine oxidase
Selenium	Cofactor of glutathione peroxidase, thioredoxin reductases and selenoprotein P, Inhibition of nuclear factor kappa-B activation

eNOS = Endothelial nitric oxide synthase; NADPH = Nicotinamide adenine dinucleotide phosphate; ROS = Reactive oxygen species; BH4 = Tetrahydrobiopterin; NO = Nitric oxide

oxidative stress and thereby lowering blood pressure. Additionally vitamins C and E down-regulate NADPH oxidase, a major source of ROS in the vascular wall, and up-regulate eNOS, both of these effects lower blood pressure.<sup>[46]</sup> In this regard, a randomized double-blind clinical trial other than demonstrating a specific association between oxidative-stress-related parameters and blood pressure, documented enhancement of antioxidant status by supplementation with antioxidants vitamins C and E and their hypotensive properties.<sup>[47]</sup>

Combination supplement with vitamin C, vitamin E, beta-carotene, and zinc also resulted in a significant reduction in systolic blood pressure and a nonsignificant reduction in diastolic blood pressure.<sup>[48]</sup>

The diets rich in fruits and vegetables reduce blood pressure in hypertensive and normotensive patients.<sup>[49]</sup> The modification in diet results in an increase in serum antioxidant capacity and a decrease in malondialdehyde, an *in-vitro* marker of lipid peroxidation, suggestive of a reduction in oxidative stress.<sup>[49-53]</sup> In a study, increase of fruit and vegetable intake for a period of 6 months to the diet of hypertensive subjects, increased blood antioxidant capacity and decreased in systolic and diastolic blood pressure.<sup>[49]</sup>

Large clinical trials examining the effects of antioxidants specifically on blood pressure are rare. Moreover, the majority of large clinical trials did not find any antihypertensive effects of antioxidants.<sup>[53]</sup> A large study reported no improvement in blood pressure after treatment with a combination of vitamin C, vitamin E, and beta carotene versus placebo after 5 years in subjects thought to be at high risk of cardiovascular disease.<sup>[54]</sup> Furthermore, a meta-analysis has revealed no clear benefit after antioxidant supplementation in cardiovascular mortality.<sup>[55]</sup>

In general, long-term clinical trials have failed to consistently support the antihypertensive effects of antioxidants. Results of studies showing that supplemental antioxidants intake lowers blood pressure in short-term trials are inconsistent. Most of such studies have looked at all-cause or cardiovascular mortality, rarely focusing on blood pressure as a primary end point.<sup>[49,50,56]</sup>

Possible reasons for these disappointing outcomes might also be relate to 1) the trial design, 2) the type of antioxidants used, and 3) Patient cohorts included in trials. With respect to antioxidants, it is possible that dosing regimens and duration of therapy were insufficient or agents examined were ineffective and nonspecific. It is also possible that the antioxidants administered are inaccessible to the source of free radicals, particularly if ROS are generated in intracellular organelles and compartments.<sup>[9]</sup>

Furthermore, antioxidants do not inhibit ROS production and antioxidant vitamins do not scavenge H<sub>2</sub>O<sub>2</sub>, which may be more important than •O<sub>2</sub><sup>-</sup> in cardiovascular diseases.<sup>[9]</sup>

Regarding cohorts included in large trials, most subjects had significant cardiovascular disease, in which case damaging effects of oxidative stress might be irreversible. Moreover, not all hypertension are related to oxidative stress and there are not any large clinical trials in which patients be recruited based on evidence of elevated ROS formation. Also, none of the large clinical trials were designed to examine effects of antioxidants specifically on blood pressure.

However, most therapeutic guidelines suggest that the general population consumes a diet emphasizing antioxidant-rich fruits and vegetables and whole grains.<sup>[46]</sup>

From the literature review we may conclude that the diets high in antioxidants (fruits and vegetables) are capable of reducing blood pressure and cardiovascular diseases, but this is not the case for diet supplementations.<sup>[56-59]</sup>

The possible explanation is that, in the diet, there is a mix of antioxidants and it is well recognized that they work as a continuous chain, while supplementation is usually given using one or two substances. Therefore, the antioxidant chain is not completely available.

Moreover, it is well known that after scavenging free radicals, if an antioxidant is not restored by the following antioxidant in the chain, it begins to be a pro-oxidant. In this situation, the final effect of such supplementations would be no effect or a damaging effect.<sup>[60-63]</sup>

Other than beneficial effects of fruits and vegetables, there are some medicinal plants that are believed to ameliorate blood pressure. Some of these plants are presented in the following.

### Medicinal plants effective in blood pressure

Clinical trials of the plant extracts in human being have shown reliable evidence of antihypertensive effects. Even small diet changes such as cooking with garlic and savory herbs instead of salt can have beneficial effects in reduction of hypertension.<sup>[64]</sup>

When considering medicinal plant therapy for hypertension, although medicinal products have advantages over synthetic drugs, however, lessons from prior disappointing attempts to reduce blood pressure and cardiovascular risks with antioxidants and these products should be considered. Some advantages of natural antioxidants and medicinal products are as follows:<sup>[65]</sup>



Good safety profile with limited side effects, good oral bioavailability, patient-friendly dosing regimen (once or twice daily dosing, concentrating in relevant tissues (brain, kidney, and/or vasculature), limited potential for pro-oxidative activity and secondary cell signaling that may limit their effectiveness, mostly inhibition of ROS production rather than quenching ROS post-production, efficacious for hypertension originating from disparate etiologies, pleiotropic effects that go beyond blood pressure lowering and translate into reversal or prevention in progression of end organ damage, and finally limited interactions with the metabolism of concomitant antihypertensive therapies.<sup>[65]</sup>

It seems that antioxidant activity is not the sole cause of these plants in hypertension reduction. Because most of medicinal plants have antioxidant activity but it does not seem to be a correlation between antioxidant activity and their capacity in reduction of hypertension.

Daily consumption of green tea or hibiscus, a delicious red tea, has been shown in studies to reduce high blood pressure. Herbal diuretics such as Buchu and Cornsilk tea can also help by eliminating water. Angelica contains compounds that act much like calcium channel blockers, which are often prescribed for high blood pressure and heart health.

Some medicinal plants with antihypertension activity are discussed in the following.

#### *Garlic or Allium sativum*

Garlic is from Alliaceae family or Liliaceae. Garlic has been shown to have antioxidant activity<sup>[66]</sup> and antihypertension effects. It has long been used for a variety of diseases including hypertension and hyperlipidemia. It increases nitric oxide production that results in smooth muscle relaxation and vasodilatation. Meta-analysis of data has demonstrated that garlic decreases BP in patients with increased systolic pressure.<sup>[11]</sup>

#### *Annona muricata or Prickly custard apple*

*Annona muricata* is a member of the family of Annonaceae and a species of the genus *Annona*, known mostly for its edible fruits *Annona*. The leaf extract of the plant has been reported to lower an elevated BP by decreasing the peripheral vascular resistance.<sup>[70]</sup>

#### *Apium graveolens or Celery*

Celery is from Apiaceae family, effective against hypertension. It acts on liver and one type of hypertension is associated with liver. In a study in which the juice was mixed with equal amount of honey and about 8 ounces were taken orally three times each day for up to 1 week was useful in reducing HTN in 14 of 16 patients.<sup>[69]</sup> It has

also been reported to reduce systolic and diastolic BP. The difference of BP in human beings before and after treatment has been found to be significant. It is also administered in HTN associated with pregnancy and climacteric.<sup>[70]</sup>

#### *Avena sativa or Green Oat*

*Avena sativa* is from Poaceae/Gramineae family. It contains soluble fibers that can control hypertension. It improves blood lipid and glucose, too.<sup>[71]</sup> The addition of oat cereals to the normal diet of patients with HTN has been found to significantly reduce both systolic and diastolic BP.<sup>[72]</sup>

#### *Blond psyllium or Indian plantago*

*Indian plantago* is from Plantaginaceae family. It has been shown that daily consumption of 15 g Indian plantago can lower both systolic and diastolic blood pressure.<sup>[73]</sup>

#### *Cassia absus or Chaksu*

*Cassia absus* is from Caesalpiniaceae family. This plant is found in the tropical region of India. It has been shown that 1-30 mg/kg of crude extract of *C. absus* dose dependently decreases the BP. Repeated injections of the same dose of the crude extract have been seen to produce tachyphylaxis.<sup>[74]</sup>

#### *Cassia occidentalis or Coffee weed*

Coffee weed is from Caesalpiniaceae family. *In-vitro* studies of the leaf extract of coffee weed have been shown to have a relaxant effect on the aortic rings. It is used in local folk medicine as an antihypertensive agent. The studies revealed that cassia extract may be relaxing smooth muscle and reducing BP by inhibiting Ca<sup>2+</sup> influx through receptor-operated channel and voltage-sensitive channel, showing its nonselectivity on these Ca<sup>2+</sup> channels.<sup>[75]</sup>

#### *Camellia sinensis or Tea*

*Camellia sinensis* is from Theaceae family. Population research links consumption of green tea and oolong tea with a decreased risk of developing HTN. Research on black tea shows no effect on BP in people with HTN. It has also good effects in a wide range of other complications. Black bean is also from Fabaceae family. Crude extract of *C. australe* (1-100 mg/kg) has been shown to reduce both systolic and diastolic blood pressure in a dose-dependent manner. This fall in BP has been attributed to the saponin fraction and medicagenic acid glucoside present in the crude extract.<sup>[76,77]</sup>

#### *Commelina virginica or Virginia dayflower*

Virginia dayflower is from Commelinaceae family; it is native to the mideastern and southeastern United States. Whole plant extract has been reported to decrease the tension of phenylephrine-stimulated isolated guinea pig aorta rings by 15% to 35%; however, its antihypertension has not been investigated, yet.<sup>[78]</sup>

***Daucus carota or Carrot***

Carrot is from Umbelliferae family. It has been used in traditional medicine to treat HTN. Isolation of two coumarin glycosides coded as DC-2 and DC-3. Intravenous administration of these compounds indicate that DC-2 and DC-3 may be acting through blockade of calcium channels, and this effect may be responsible for the BP-lowering effect of the compounds observed in the *in vivo* studies.<sup>[79]</sup>

***Glycine max or Soybean***

Soybean is from Fabaceae family. Soybean has been found to be effective as a hypertensive agent.<sup>[80]</sup>

***Gossypium barbadense or Pima cotton***

Pima cotton is from Malvaceae family. It has been shown that the leaf extract of Pima cotton decreases the tension of phenylephrine-stimulated isolated guinea pig aorta rings by 15% to 35%. In Suriname's traditional medicine, the leaves of the plant are used to treat HTN and delayed/irregular menstruation.<sup>[68,78]</sup>

***Hibiscus sabdariffa or Roselle***

Roselle is from Malvaceae family. The leaves of Roselle have been used traditionally as antihypertensive agent. Its antihypertensive has been reported in a couple of studies.<sup>[78,79]</sup> The antihypertensive effects of the crude extract of the HS have been attributed to mediation through acetylcholine and histamine like dependent mechanism through direct vasorelaxant effects.<sup>[79]</sup> The chronic administration of aqueous extract of HS has been reported to reverse cardiac hypertrophy in renovascular hypertensive rats.<sup>[80]</sup>

Clinical trials of the plant extract in human being have shown reliable evidence of antihypertensive effects.<sup>[81]</sup>

***Lavandula stoechas or French Lavender***

French Lavender is from Lamiaceae family. Crude extract of *L. stoechas* has been reported to produce a fall in BP and HR in anesthetized rats. Pretreatment of atropine abolished the cardiovascular responses, suggesting that the antihypertensive and bradycardia effects of the crude extract may be mediated through mechanism(s) similar to that of acetylcholine.<sup>[82]</sup>

***Linum usitatissimum or Linseed, Flaxseed***

Linseed, Flaxseed is from Linaceae family. Flaxseed oil is rich in  $\alpha$ -linolenic acid, an essential fatty acid that that is belonged to a group of substances called omega-3 fatty acids. Several studies suggest that diets rich in omega-3 fatty acids lower BP significantly in people with HTN. Daily consumption of 15 to 50 g/day of ground flaxseed can modestly reduce total cholesterol and low-density lipoprotein concentrations without altering triglycerides or high-density lipoprotein cholesterol. However, the exact mechanism is unclear.<sup>[82]</sup>

***Lycopersicon esculentum or Tomato***

Tomato is from Solanaceae family. Its extract contains carotenoids, such as lycopene, beta carotene, and vitamin E, which are known as effective antioxidants, to inactivate free radicals and to slow the progress of atherosclerosis. The tomato extract of tomato has been shown to reduce BP in patients with mild HTN.<sup>[83]</sup> Tomato extract when added to patients treated with low doses of ACE inhibition, calcium channel blockers, or their combination with low-dose diuretics had a clinically significant effect-reduction of BP by more than 10 mmHg systolic and more than 5 mmHg diastolic pressure.<sup>[84]</sup>

***Ocimum basilicum or Basil***

Basil is from Lamiaceae family. Crude extract of Basil has been shown to reduce systolic, diastolic, and mean BP in a dose-dependent manner with median effective dose of 30 mg/kg. The cardiovascular effect of the extract has been attributed to eugenol, which exerts its effect by blocking the calcium channels.<sup>[85]</sup>

***Peganum harmala or Harmal***

Harmal is from Nitrariaceae family. The crude extract fraction and all pure compounds: Harmine, harmaline, tetrahydroharmine, harmol, and harmaloi from Harmal produced antihypertensive effects in anesthetized rats in a dose-dependent manner.<sup>[86,87]</sup>

***Punica granatum or Pomegranate***

Pomegranate is from Lythraceae family. Researches have shown pomegranate juice reduces the activity of angiotensin converting enzymes (ACE) by about 36%. One study shows modest reduction in systolic BP after drinking 50 ml/day of pomegranate juice for a year. Another study shows no benefit after drinking 240 ml/day of the juice for 3 months.<sup>[88]</sup>

***Rauwolfia serpentina or Rauwolfia***

Rauwolfia is from Apocynaceae family. Extracts of its different parts considered to be the most powerful hypotensive plant medicine. Reserpine, the purified alkaloid of *R. serpentina*, was the first potent drug widely used in the long-term treatment of HTN. Only a small dose is required to achieve results and to avoid side effects. Nasal congestion is the most common side effect. In 1952, reserpine was introduced under the name Serpasil in the treatment of HTN, tachycardia, and thyrotoxicosis. The combination of reserpine, dihydroergocristine, and a diuretic is still on the market. However, I may cause depression.<sup>[89]</sup>

***Sesamum indicum or Sesame***

Sesame is from Pedaliaceae family. Alcoholic extract of seeds (1-30 mg/kg) in a dose-dependent manner decreased blood pressure. Atropine (2 mg/kg) was reported to abolish the cardiovascular responses, indicating the presence of

acetylcholine-like substance in the seeds. Sesamin and sesaminol are the major phenolic constituents of sesame oil. A study in hypertensive patients indicated that sesame oil consumption remarkably reduced oxidative stress and simultaneously increased glutathione peroxidase, superoxidase dismutase, and catalase activities. These results support the hypothesis that sesame oil consumption may help to enhance antioxidant defense system in human beings. The investigators suggested that sesamin is a useful prophylactic treatment in HTN and cardiovascular hypertrophy.<sup>[90,91]</sup>

#### *Solanum sisymbriifolium* or Wild Tomato

Wild Tomato is from Solanaceae family. The root of *S. sisymbriifolium* has been used as a traditional medicine possessing diuretic and antihypertensive properties. The intravenous administration of the extract (50 and 100 mg/kg) produced a significant decrease in BP in anesthetized hypertensive (adrenal regeneration HTN + deoxycorticosterone acetate) rats. Oral administration of the extract (10, 50, 100, and 250 mg/kg) also produced a dose-dependent hypotensive effect in conscious hypertensive animals. The results suggested that nuatigenosido may play an important role in the therapeutic effects of this herb.<sup>[92]</sup>

#### *Theobroma cacao* or Cocoa Butter

Cocoa Butter is from Malvaceae family. Cocoa powder, enriched with flavonoid constituents, is used for preventing cardiovascular disease. Flavonoids, contained in chocolate, stimulate formation of nitric oxide, increase vasodilatation, and reduce endothelial dysfunction. A growing body of clinical research also shows that daily consumption of dark or milk chocolate (*T. cacao*), 46 to 105 g daily, providing 213 to 500 mg of cocoa polyphenols, can lower systolic BP by about 5 mmHg and diastolic by about 3 mmHg.<sup>[93]</sup>

#### *Uncaria rhynchophylla* or Cat's Claw herb

Cat's Claw herb is from Rubiaceae family. It has been used to lower BP and to relieve various neurological symptoms. The hypotensive activity has been attributed to an indole alkaloid called *hirsutine*<sup>[85]</sup> that reduces intracellular Ca<sup>2+</sup> level through its effect on the Ca<sup>2+</sup> store as well as through its effect on the voltage-dependent Ca<sup>2+</sup> channel.<sup>[94]</sup> Alteration in HR, possibly involves sympathetic mechanism, too.<sup>[95]</sup>

#### *Vitex doniana* Black plum

Black plum is from Verbenaceae family. The extract was found to exert hypotensive effect. Both the systolic and diastolic BPs were significantly reduced within 45 min after oral administration of the extract. The BP began to return to normal after 2 h.<sup>[96]</sup>

#### *Zingiber officinale* or Ginger

Ginger is from Zingiberaceae family. Ginger root dose-dependently (0.3-3 mg/kg) induced a fall in the arterial BP

of anesthetized rats. Human trials for hypotensive effect of ginger have been few and generally used a low dose with inconclusive results.<sup>[97,98]</sup>

#### Cautions in the use of medicinal plants

The renewed interest in the search for new drugs from natural sources, especially from plant sources, has gained global attention during the last two decades. This attention is primarily due to the rich biodiversity, which promises a high diversity of chemicals with the potential novel structures and promising effects.<sup>[99-103]</sup> However, of this rich biodiversity, only a small portion has been studied for its medicinal potential.<sup>[104,105]</sup> Thus, natural plants and herbs can be our source of drugs, with fewer side effects and better bioavailability for treatment of HTN in future. However, it should be noted that the use of medicinal plants is not guaranteed to be nontoxic. For example ginseng is contraindicated for those in whom high blood pressure is dangerous, because high blood pressure has been reported in some ginseng consumers. This is because conflicting reports are about the effect of this medicinal plant on hypertension. It is not known yet whether ginseng is a cure for high blood pressure, or worsens it. Maintaining electrolyte balance is also important; for instance licorice (*Glycyrrhiza glabra*) can decrease potassium levels, cause sodium and water retention, and increase blood pressure.<sup>[106,107]</sup>

#### CONCLUSIONS

There is a proposed hypothesis relating the pathogenesis of hypertension and cardiovascular diseases to oxidative stress of arterial wall. However, antioxidant therapy has not been shown to be consistently beneficial. It seems that fruits and vegetables due to having a large variety of antioxidants are more effective than supplementation therapy with a limited number of antioxidants. Nevertheless, large clinical trials are needed to document the role of oxidative stress in hypertension and the possible treatment of hypertension with antioxidants.

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