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# Oxidative Stress and Essential Hypertension

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## Abstract

Experimental evidence supports a pathogenic role of free radicals or reactive oxygen species (ROS) in the mechanism of hypertension. Indeed, vascular ROS produced in a controlled manner are considered important physiological mediators, functioning as signaling molecules to maintain vascular integrity by regulating endothelial function and vascular contraction-relaxation. However, oxidative stress can be involved in the occurrence of endothelial dysfunction and related vascular injury. Thus, ROS activity could trigger pathophysiological cascades leading to inflammation, monocyte migration, lipid peroxidation, and increased deposition of extracellular matrix in the vascular wall, among other events. In addition, impairment of the antioxidant capacity associates with blood pressure elevation, indicating potential role of antioxidants as therapeutic antihypertensive agents. Nevertheless, although increased ROS biomarkers have been reported in patients with essential hypertension, the involvement of oxidative stress as a causative factor of human essential hypertension remains to be established. The aim of this chapter is to provide a novel insight into the mechanism of essential hypertension, including a paradigm based on the role played by oxidative stress.

**Keywords:** essential hypertension, oxidative stress, antioxidants, endothelial dysfunction, nitric oxide

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## 1. Introduction

Hypertension is a major risk factor for cardiovascular disease [1]. Recently, a growing body of evidence has involved oxidative stress in the mechanism of development of hypertension. Indeed, reactive oxygen species (ROS) contribute to regulating the biological processes occurring in the vascular wall, both in normal physiological conditions, as well as in the occurrence of hypertension [2–4]. Available evidence of the contribution of oxidative stress in

the pathogenesis of human hypertension includes enhancement of ROS production, together with decreased bioavailability of both nitric oxide (NO) and antioxidants. The first-formed ROS is superoxide anion radical, which is produced from NADPH oxidase (NOX), an enzyme subjected to regulation by hormones such as angiotensin II (AT-II), endothelin-1 (ET-1), and urotensin II (UT-II), among others. Furthermore, mechanical stimuli known to occur in blood pressure elevation further contribute to increased ROS production. It is of interest to mention that increased intracellular calcium concentration may result from ROS-induced vasoconstriction, thus enhancing the development of hypertension [2]. The regulation of vasomotor tone depends upon a delicate balance between vasoconstrictor and vasodilator forces, the latter being likely to be modulated by oxidative stress. This view has stimulated the interest for searching novel antihypertensive therapies aimed to decrease ROS generation and/or increase NO bioavailability. The present study was aimed to present an update of the available studies related to the role of oxidative stress in the mechanism of development of blood pressure elevation, as well as the role of antioxidants in the prevention or treatment of this derangement.

## **2. Pathophysiology of hypertension**

### **2.1. Endothelial dysfunction**

The response to cardiovascular risk factors is expressed in alterations of endothelial function, a chronic inflammatory process characterized by loss of antithrombotic factors and an increase in vasoconstrictor and prothrombotic products, thus elevating the risk of cardiovascular events. Consequently, an impairment of the ability of endothelium to induce vasodilation leads to hypertension. Recently, it has been argued that ROS play a key role in this pathological process.

### **2.2. Role of vascular oxidative stress in hypertension**

The occurrence of oxidative stress is due to an imbalance between ROS generation and the antioxidant potential in the body, the latter being overwhelmed by the increased ROS concentration in the steady state. It should be noted that although ROS are mediators of normal biological effects related to vascular function at the cell level, the increased levels of these species can give rise to pathological changes, as those observed in cardiovascular disease. ROS behave as redox-sensitive blood pressure modulators [5–7]. Accordingly, increased ROS concentration has been demonstrated both in patients with essential hypertension and in various animal models of hypertension [8–12]. In addition, this derangement is accompanied by a decreased antioxidant potential [13]. Therefore, these data provide evidence of the involvement of vascular oxidative stress in the mechanism of development of essential hypertension [2, 3, 14]. Furthermore, a strong association between blood pressure and oxidative stress-related parameters has been found, such as plasma 8-isoprostane levels [15]. Interestingly, studies performed in mice models having genetic deficiency in ROS-generating enzymes showed that these animals had lower blood pressure than control with wild-type

mice [16, 17]. Moreover, at the cellular level, it has been reported that ROS production is enhanced in cultured vascular smooth muscle cells (VSMC) isolated from both hypertensive rats and isolated arteries of hypertensive human patients; these findings are associated with amplified, redox-dependent signaling and reduced antioxidant bioactivity [18]. These reports could support the view that the modulation of oxidative stress could be expressed in blood pressure lowering in the case of known antihypertensive agents, such as  $\beta$ -adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and calcium channel blockers [19, 20].

### 2.2.1. Vascular ROS sources

There are various ROS sources formed in blood vessels, from both enzymatic and non-enzymatic origin. Together with the mitochondrion, the major enzymatic sources comprise NADPH oxidase (NOX), xanthine oxidase (XO), and uncoupled NO synthase.

#### 2.2.1.1. NADPH oxidase

In the vascular wall, as well as in the kidney, superoxide anion is mainly produced enzymatically through NOX activity; consequently, the upregulation of this enzyme exerts an important pathogenic role in the development of renal dysfunction and vascular damage [12, 21]. The enhanced activity of NOX in hypertension is achieved through mechanical and humoral signals, with AT-II being the most studied stimulus. However, it is important to remark that ET-1 and UT-II cooperatively participate in NOX activation. In addition, NOX-derived superoxide anion is able to inactivate NO, thus producing peroxynitrite anion. The latter induces downregulation of prostacyclin synthase, further allowing the development of hypertension. Finally, oxidative stress leads to eNOS uncoupling [16, 22]. Therefore, several effects contribute to the impairment of endothelial function related to oxidative stress. In summary, increased superoxide anion, decreased NO bioavailability, and decreased prostacyclin synthesis contribute to the impairment of endothelium-dependent vasodilation. Thus, NOX activation in the vascular wall results in several effects contributing to the mechanism of development of hypertension [23].

#### 2.2.1.2. Uncoupled endothelial NO synthase

The vascular tone is modulated by vasoconstriction-vasodilation balance, and NO bioavailability constitutes an important component of the latter process. The NO production is partly dependent upon the activity of eNOS. However, other factors, such as L-arginine and tetrahydrobiopterin (BH<sub>4</sub>) availability, are also required as substrate and coupling factor, respectively. Deficiency or oxidation of either of these two factors will result in decreased NO production. The initial ROS source is NOX-dependent superoxide generation. Furthermore, peroxynitrite is formed through the reaction between NO and superoxide [24]. The activity and function of eNOS are changed due to the peroxidant ability generated by peroxynitrite, and this enzyme produces more superoxide instead of NO [22, 25]. This vicious cycle results in BH<sub>4</sub> oxidation, thereby promoting eNOS uncoupling and enhancement in ROS production.

#### 2.2.1.3. *Xanthine oxidase*

This enzyme system provides an important endothelial source of superoxide in the vascular wall [23, 26]. XO-catalyzed reactions lead to oxygen reduction to produce superoxide from purine metabolism. It has been reported that spontaneously hypertensive rats demonstrate increased levels of both endothelial XO activity and ROS production, together with increased arteriolar tone [21]. Furthermore, it was suggested that XO may contribute to end-organ damage in hypertension [27].

#### 2.2.1.4. *Mitochondrial dysfunction*

The mitochondrion could behave as both a ROS source and target. Superoxide is produced in the intermembrane space, but it is rapidly carried to the cytoplasm [28]. Either ubiquinol or coenzyme Q could be a source of superoxide when these mitochondrial components are partially reduced; but these molecules behave as antioxidants when they are fully reduced [29]. Superoxide produced by mammalian mitochondria in vitro mostly comes from complex I. This high rate of complex I-dependent superoxide production can be very effectively decreased through mild uncoupling. In addition, it was found that patients with hypertension show reduced activity of antioxidant enzymes [30].

### 2.2.2. *Role of vascular wall components*

In response to mechanical and hormonal stimuli, the endothelium releases agents participating in the regulation of vasomotor tone. Particularly relevant is the ability of endothelium to exert a protective role through the generation of vasorelaxing factors. In addition, pathophysiological conditions result in increased released of endothelium-derived vasoconstricting factors, such as ET-1, AT-II, UT-II, superoxide anions, vasoconstrictor prostaglandins, and thromboxane A<sub>2</sub>, all of them capable of producing vasoconstrictor effects. It should be mentioned that VSMC contribute to modulating blood pressure not solely in short-term regulation of the blood vessel diameter, but also in the structural remodeling occurring during long-term adaptation, both processes being mediated by ROS. It is of interest considering that the adventitia can also participate in the development of hypertension, which is achieved through ROS contribution in either reduction of NO bioavailability or vascular remodeling.

### 2.2.3. *Role of vascular hormones and factors*

#### 2.2.3.1. *Nitric oxide*

NO plays a key role as a paracrine regulator of vascular tone. It is involved in the physiological regulation responsible for the maintenance of the health of vascular endothelium through processes such as inhibition of leukocyte-endothelial cell adhesion, VSMC proliferation and migration, and platelet aggregation. The effect of decreased NO bioavailability is particularly relevant, leading to reduction of vasodilatory capacity in the vasculature, thereby providing a mechanism of hypertension. The formation of NO from the substrates oxygen and L-arginine is catalyzed by the enzyme eNOS, being the predominant isoform of NOS family in the vascular



wall. This enzyme can be rapidly activated by receptor-mediated agonist stimulation, shear stress, and allosteric modulators [31]. It is of interest to mention that NO diffuses easily to the adjacent VSMC, thus binding to receptors such as soluble guanylyl cyclase. The numerous NO biological properties include not only vasorelaxing and antiproliferative actions but also antagonizing the effects of AT-II, endothelins and ROS, among other vasoconstrictors. Though L-arginine, a substrate for eNOS, could be considered as a promising factor in preserving NO formation, it failed to prevent blood pressure elevation and left ventricle remodeling in a model based on chronic treatment with the methyl ester of N-nitro-L-arginine (L-NAME), an inhibitor of eNOS [32]. Furthermore, NO-deficient hypertension was completely prevented by the ACE inhibitor captopril, yet without improving NOS activity. Another reported effect for NO consists of its ability to exert an ACE downregulation effect. NO half-life can be prolonged by thiols, as these compounds protect NO from oxidation and are able to form nitrosothiols [33, 34]. It should be remarked that reduced NO levels can be the result of its combination with superoxide to form peroxynitrite, a compound capable of enhancing oxidative stress by oxidizing BH<sub>4</sub>, destabilizing eNOS, and producing more superoxide [22, 24, 25]. The importance of the balance between NO and AT-II in the regulation of the sympathetic tone has been reported.

#### 2.2.3.2. Renin-angiotensin system

There is cumulated evidence supporting that the renin-angiotensin system (RAS) contributes to the development of cardiovascular disease. The production of AT-II, a potent vasoactive peptide, occurs in vascular beds having important ACE activity. Increased AT-II production above normal levels is able to induce vascular remodeling and endothelial dysfunction, as well as increases in levels of blood pressure. At the cell level, AT-II acts as a potent NOX activator, thus leading to enhancement of ROS production [35, 36]. It was reported that the expression of NOX subunits, oxidase activity, and ROS production are all increased in rat and mice models of hypertension achieved by AT-II infusion [37]. In addition, the effect of AT-II is not only confined to increasing NADPH oxidase activity but also upregulating SOD, likely as a compensation mechanism against ROS increase. Consequently, ROS levels and oxidative stress biomarkers may appear normal despite the occurrence of an oxidative challenge. However, the consequences of oxidative stress will be apparent when ROS production becomes overwhelming and the compensatory mechanisms are inadequate, thus explaining the pathophysiological consequences [38]. Pharmacological inhibition of ACE by captopril and enalapril prevented blood pressure rise in young spontaneously hypertensive rats. The hypotensive effect of captopril is higher than that of enalapril, which could be due to the antioxidant role of its thiol group [39]. Interestingly, NO not only antagonizes the vascular effects of AT-II on blood pressure, cell growth, and renal sodium excretion but also downregulates the synthesis of ACE and AT1 receptors. In addition, upregulation of eNOS expression has been reported as a consequence of ACE inhibition [40]. Recently, a relationship through Ca<sup>2+</sup>/calmodulin-dependent protein kinase II has been proposed to link the actions of AT-II and ROS in cardiovascular pathological conditions [41].

#### 2.2.3.3. *Acetylcholine*

The endothelium-dependent vasodilation by acetylcholine (ACh) in vascular vessels occurs mainly via NO production. NO rapidly diffuses to the underlying VSMC, thereby inducing relaxation in these cells. Under oxidative stress conditions, a diminution in NO bioavailability should be expected, thus leading to significantly reduced ACh-mediated vasodilation [40].

#### 2.2.3.4. *Endothelin-1*

Vascular endothelium, among others vascular tissues, produces potent vasoconstrictor isopeptides known as endothelins. ET-1 is the major endothelin generated by endothelial cells, and is probably the most important in cardiovascular physiology and disease. It has been demonstrated that large concentration of exogen ET-1 acts as potent vasoconstrictor capable of altering arterial pressure. ET-1 mediates its effect through two receptors, ETA and ETB. ETA exerts its effects via activation of NOX, XO, lipoxygenase, uncoupled NOS, and mitochondrial respiratory chain enzymes. ETB induces relaxation on endothelial cells [42]. The vasoconstricting action of ET-1 is counteracted by vasodilators such as prostacyclin (PGI<sub>2</sub>) and/or NO, and it has been seen that many factors that stimulate ET-1 synthesis (e.g. thrombin, AT-II) also cause the release of the vasodilators above mentioned. Several studies reported in primary hypertension demonstrate an increased ET-1 vasoconstrictor tone, apparently dependent on decreased endothelial ETB-mediated NO production, contributing to NO bioavailability impairment.

#### 2.2.3.5. *Urotensin-II*

UT-II is the most potent vasoconstrictor identified [43]. It acts through the activation of NOX. UT receptors have been identified in several other organs besides vascular bed, suggesting that vasoconstriction is not its only effect [44, 45]. UT-II has also been shown to act as a potent vasodilator in some models [46]. Nevertheless, the role of UT-II in disease is not fully elucidated yet.

#### 2.2.3.6. *Norepinephrine*

VSMC is innervated primarily by the sympathetic nervous system through three types of adrenergic receptors:  $\alpha_1$ ,  $\alpha_2$  and  $\beta_2$ . VSMC proliferation is stimulated by norepinephrine. Interestingly, blood pressure is increased by over-expression of inducible nitric oxide synthase (iNOS) through central activation of the sympathetic nervous system, mainly mediated by an increase in oxidative stress [5].

#### 2.2.3.7. *Prostaglandins*

PGI<sub>2</sub> is considered one of the most important vasodilators depending on the endothelium and relaxes the vascular musculature. A large amount of substances that generate an increase in PGI<sub>2</sub> release have been described, such as thrombin, arachidonic acid, histamine, and serotonin. Prostaglandin H<sub>2</sub> is formed by the prostaglandin H<sub>2</sub> synthase, which uses arachidonic acid as a substrate. Then, prostaglandin H<sub>2</sub> is converted to PGI<sub>2</sub>, a vasoactive molecule.

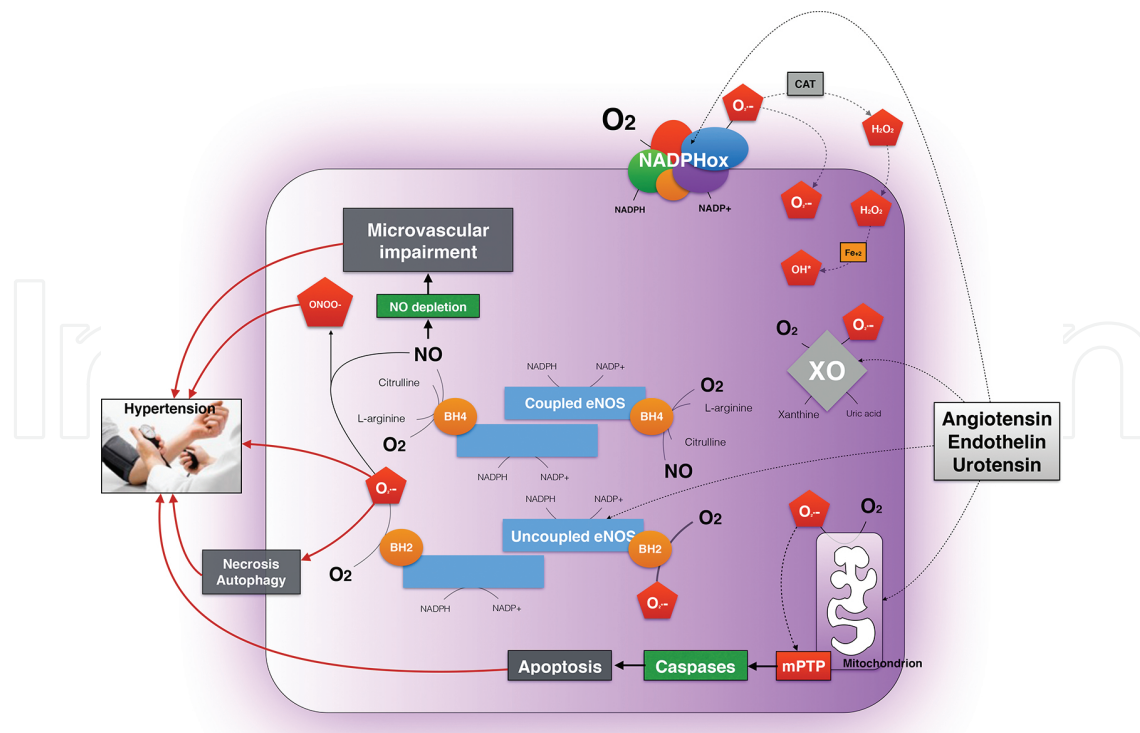
Oxidative stress-related conditions, such as hypertension, impair the PGI<sub>2</sub>-mediated vasodilation. It has been demonstrated that peroxynitrite inhibits the enzymatic activity of prostacyclin synthase. Thus, the isoform prostaglandin H<sub>2</sub> synthase-2 may mediate vascular dysfunction under such conditions.

#### 2.2.3.8. Homocysteine

It has been proposed that homocysteine plays an important role in the pathophysiology of primary hypertension [3]. An increase in homocysteinemia augments the proliferation of VSCM, thus altering the elasticity of vascular wall; it generates an oxidative stress state and diminishes NO bioavailability, thus impairing vasodilation. All the mechanisms exposed contribute to elevated blood pressure [47]. Homocysteine could also lead to endothelium oxidative damage [3]. The administration of vitamins B<sub>6</sub>, B<sub>12</sub>, and folic acid has been proposed as a potential adjuvant treatment in hypertension, probably by correcting the increased homocysteinemia [3, 48]. Despite the above mentioned, further randomized controlled trials are required to establish the efficacy of these therapeutic agents in the treatment of hypertension.

A hypothesis for the role of vascular oxidative stress in hypertension is depicted in **Figure 1**.

Besides the key role of ROS production in the vasculature and its relation to hypertension, it has been demonstrated that hypertensive stimuli, such as high salt and AT-II, also increase the production in the kidney and the central nervous system, contributing either to generate hypertension or to the untoward sequels of this disease [49, 50]



**Figure 1.** Schematic summary of the role of vascular oxidative stress in the pathogenesis of hypertension. NO: nitric oxide, eNOS: nitric oxide synthase, BH<sub>4</sub>: tetrahydrobiopterin, and mPTP: mitochondrial permeability transition pore.



### 3. Antioxidants in hypertension

This section refers to the antihypertensive role of endogenous and exogenous antioxidants that have demonstrated their ability to alter the blood vessels' function and to participate in the main redox reactions involved in the pathophysiology of hypertension.

#### 3.1. Vitamin C

Vitamin C (or ascorbate) is a potent and widely used antioxidant, characteristically water-soluble. It has been described that this antioxidant could act as an enzyme modulator on the vascular wall, upregulating eNOS and downregulating NOX [51]. An inverse relationship between vitamin C plasma levels and arterial pressure in both healthy and hypertensive population has been demonstrated in several studies [15]. Antioxidant supplementation improves vascular function and reduces blood pressure in both experimental models [52, 53] and in patients [54, 55]. Ascorbate may improve vasodilation, probably by increasing NO bioavailability [56–58]. Vitamin C could protect BH4 from oxidation, which leads to an increase in the enzymatic activity of eNOS.

Despite the rationale of using vitamin C as an antihypertensive molecule, several clinical trials with methodological differences (including number of patients and follow-up) have yielded inconsistent outcomes [59–64]. The absence of antihypertensive effect observed in trials using the administration of ascorbate could be due to the lack of consideration of its pharmacological characteristics, mainly pharmacokinetics. It was determined in experimental conditions that the antihypertensive effect of ascorbate is reachable at a plasma concentration of 10 mM [57]. This concentration allows ascorbate to efficiently compete against the reaction between NO and superoxide, which is increased in oxidative stress-related conditions such as hypertension. The plasma level mentioned earlier is not reachable through oral administration of vitamin C. Daily oral doses of vitamin C between 60 and 100 mg are sufficient for the renal ascorbate threshold to occur. Plasma is completely saturated at doses of 400 mg daily, leading to a steady state level of 80  $\mu$ M [65]. Therefore, it is plausible to propose that the antihypertensive effect of ascorbate would only be reachable with a high-dose infusion.

#### 3.2. Vitamin E

Vitamin E is a lipid-soluble antioxidant which has received significant attention during the last decades. An epidemiological association between high dietary vitamin E intake and a lower incidence of cardiovascular disease has been established [58]. A growing body of evidence indicates that vitamin E, besides its antioxidant properties, could act as a biological modifier and is also capable of regulating mitochondrial generation of free radicals in a dose-dependent manner.

Interestingly, some studies fail to demonstrate the beneficial effects of vitamin E in cardiovascular disease patients [66–69]. Moreover, one trial proving vitamin E supplementation showed an increase in blood pressure and cardiac frequency in type 2 diabetes patients [70]. Probably,

vitamin E by itself is unlikely to achieve enough levels to counteract all components of oxidative stress acting in primary hypertension [71].

### 3.3. Association of vitamins C and E

Alfa-tocopheroxyl radical is reduced in vivo by ascorbate; therefore vitamin C may be needed for achieving the beneficial effects of vitamin E [72]. In fact, both antioxidants may act synergistically to generate appropriate conditions for NO synthesis in endothelium [73]. Therefore, the association between vitamins C and E provides a reinforcement of their biological properties in a synergistic manner and could lead to a significant antihypertensive effect; however, further studies are required [74].

Despite the fact that some short-term studies have demonstrated that the supplementation of both antioxidants reduces blood pressure [60, 63, 64, 75], long-term clinical trials have failed to support this hypothesis. However, most of these studies have some serious methodological bias, mainly lack of rigorous exclusion criteria [76].

### 3.4. Allopurinol

XO has been proposed as an important enzymatic source of free radicals in the endothelium [24]. It produces uric acid by catalyzing the two final steps of purine metabolism. It has been demonstrated that XO activity is positively correlated with arteriolar tone and blood pressure [77, 78]. Moreover, allopurinol, an XO inhibitor, is capable of improving endothelial function in some experimental models. Treatment with allopurinol decreased blood pressure in a young people-based study [79], hypertensive murine models [80], and CKD patients [81]. Despite the evidence supplied by small studies, a small number of randomized controlled trials have not demonstrated benefit using XO inhibitors [82].

### 3.5. Selenium

Selenium is an essential trace element and a key part of several proteins. Its antioxidant properties are carried out mainly by selenocysteine residues, which are an integral constituent of glutathione peroxidase (GSH-Px), thioredoxin reductases (TR), and selenoprotein P [83]. It has been proposed that the maintenance of full GSH-Px and TR activity by proper selenium dietary intake could be useful for the prevention of cardiovascular disease. From a molecular point of view, selenium is capable of preventing the activity of nuclear factor kappa B (NF- $\kappa$ B) [84], conferring selenium anti-inflammatory and antioxidant properties. The inhibition of NF- $\kappa$ B is probably the result of the binding of selenium to the factor thiols [85].

Several trials have proved the antioxidant properties of selenium [84, 86–91]. Low-dose selenium showed to provide significant protection of coronary endothelium against oxidative damage in humans [83]. In spontaneously hypertensive rats, selenium supplementation was associated with an increased antioxidant response and protection against cardiac oxidative injury, as well as a reduction in disease severity and mortality [92]. Besides, in hypertensive pregnancies, reduced selenium levels are associated with a decrease in GSH-Px activity [93].

Therefore, it is plausible to propose that selenium deficiency could be an independent risk factor of cardiovascular disease, including hypertension [94].

3.6. N-acetylcysteine

N-acetylcysteine (NAC) is a sulfhydryl group donor that holds great attention for its antioxidant properties and potential benefits in cardiovascular disease. In salt-sensitive hypertension, NAC is capable of improving renal dysfunction and decreasing blood pressure [95]. The antihypertensive effect of NAC is mainly due to NO-dependent mechanisms and is probably mediated by the inhibition of oxidative stress [96]. NAC effectively prevents BH4 oxidation by the increased superoxide present in primary hypertension [97]. Besides this, NAC can protect against oxidative injury directly by scavenging ROS and inhibiting lipid peroxidation [98, 99].

3.7. Polyphenols

Polyphenols have been defined as the most abundant antioxidants in human diet. They exert several protective mechanisms, including ROS scavenging, iron chelating and modulation of antioxidant enzymes [100, 101]. NAC also possibly increases the endothelium-NO production [102, 103]. In this regard, NO levels increase after the consumption of polyphenols by humans [104]. Polyphenols improve endothelial function by increasing glutathione and inhibiting pro-oxidant enzymes such as NOX and XO [105]. Despite this, some studies using polyphenols and antioxidant vitamins have shown an increase in blood pressure [106]. Therefore, the evidence is still insufficient to establish polyphenols as a first-line treatment in hypertension.

A summary of the antioxidant approaches as clinical interventions on essential hypertension is presented in **Table 1**.

Details of study	Results	Reference
Intrabrachial vitamin C (2.4 mg/100 mL forearm tissue per minute). Randomized, placebo-controlled trial	In hypertensive patients but not in control subjects, vitamin C increased the impaired vasodilation to acetylcholine	[107]
Intra-arterial infusion of vitamin C at 24 mg/min for 10 minutes. Randomized trial	Forearm blood flow response to acetylcholine was significantly enhanced with intra-arterial infusion of vitamin C in hypertensive group before antihypertensive treatment	[108]
Oral administration of 500, 1000, or 2000 mg of vitamin C once daily. Randomized, double-blind, placebo-controlled trial	Significant diminution of mean systolic blood pressure and diastolic blood pressure, with no differences between the increasing doses of vitamin C	[109]
Chronic supplementation of 600mg/daily of vitamin C. Randomized, placebo-controlled trial	Reduced systolic blood pressure and pulse pressure in ambulatory elderly patients, but not in adult group	[110]
Included 29 trials of vitamin C supplementation. Meta-analysis	In short-term trials, vitamin C supplementation reduces systolic and diastolic blood pressure	[111]

Details of study	Results	Reference
Oral supplementation: 1g vitamin C + 400 UI vitamin E or placebo for 8 weeks. Randomized double-blind placebo-controlled trial	Specific association between oxidative stress-related parameters and blood pressure. Patients with essential hypertension had significantly lower systolic, diastolic, and mean arterial blood pressure	[112]
ACE inhibitors + NAC (600 mg t.i.d.) or ACE inhibitors only. Randomized, controlled trial, crossover study	Significant decrease in systolic and diastolic blood pressure with the combination of ACE inhibitors and NAC compared to ACE inhibitors-only	[113]
Intra-arterial administration: NAC (48 g/min) or vitamin C (18 mg/min). Cross-over randomized study	Intra-arterial administration of NAC had no effect on endothelium-dependent vasodilation. Intra-arterial vitamin C improved endothelium-dependent vasodilation	[114]
Vitamin C supplement daily. Either 50 or 500 mg, for 5 years. Randomized double-blind controlled trial	Neither systolic nor diastolic blood pressure was significantly related with the serum vitamin C concentration	[115]

**Table 1.** Clinical trials accounting for strategies using antioxidants in essential hypertension.

## 4. Conclusions and perspectives

There is a growing amount of evidence supporting the view that oxidative stress is involved and plays a key role in the pathophysiology of primary hypertension. In this regard, ROS act as mediators of the major physiological vasoconstrictors, increasing intracellular calcium concentration. In this review, we propose an integrative view of how oxidative stress is involved in the genesis of hypertension, mainly by reducing bioavailability of NO.

Antioxidant therapy can curtail the development of hypertension in animal models, but remains controversial in humans. Possible confounding factors in patients include co-existing pathologies and treatments and lack of selection of treatments according to ROS levels, among others. However, the dietary intake of antioxidants and polyphenols could have an effect on the primary prevention or reduction of hypertension. Though existing molecular basis and in-vitro evidence support the use of diverse antioxidants, clinical evidence continues to be controversial. It is necessary to perform basic/clinical trials that augment the current findings, which could eventually help to elucidate the role of antioxidants as novel therapy for essential hypertension. It is important to mention that the potential role of antioxidants in treatment of hypertension probably is reachable only at early stages of the disease, when endothelial dysfunction predominates over structural vascular damage.

In summary, oxidative stress plays a key role in the pathophysiology of hypertension, and antioxidants appear to be a promising treatment or co-adjuvant therapy, but further well-designed and conducted trials are required to establish them as a major alternative of pharmacology agents.

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