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Review Article

Pathophysiological and Clinical Evidence of the Effectiveness of Antioxidant Compounds as a Single or Adjunct Therapy for Hypertension

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Abstract

High blood pressure is a highly prevalent condition affecting 1.13 billion people worldwide. Its pathophysiology is not yet fully understood, but evidence shows an important role of oxidative stress in its development and maintenance, being responsible for phenotypic changes in blood vessels that increase blood pressure. Focusing therapy on reducing oxidative stress has been an objective tested in both animal and human models with diverse and sometimes contradictory results. The origin of this controversy lies, among other things, in the different antioxidant doses, inclusion methods, and criteria present in the studies. A deep analysis of these antioxidant compounds could generate evidence for their combined and targeted use in key regulators of ROS production. Moreover, analyzing current evidence from already existing studies, with a focus on those performed in humans, can elucidate the suitability of this treatment. We present the pathophysiological bases and existing evidence for a new proposal aimed to improve the effectiveness of antihypertensive therapy based on the use of widely known and used antioxidants compounds as a single or adjunct therapy with other antihypertensive drugs.

Keywords: Antioxidants; Antihypertensive drugs; Hypertension; N-Acetylcysteine; Oxidative stress; Reactive oxygen species; Resveratrol; Vitamin C; Vitamin E

Introduction

Hypertension is a chronic medical condition defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg according to several guidelines, although ACC/AHA guidelines 2017 now define hypertension stage 1 as a systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg [1]. The global prevalence of this condition is increasing, mainly due to a significant increase in low income countries where habits such as reduced physical activity and unhealthy diets are combined with limited healthcare resources and progressive population aging [2]. According to the World Health Organization, the prevalence of hypertension was 1.13 billion people worldwide in 2015, relating to one in four men and one in five women. Unfortunately, less than one in five people had this medical condition under control [3].The pathophysiology of essential hypertension (i.e., hypertension without a known secondary cause) is still not fully understood. One of the first modern proposals about the mechanisms of essential hypertension was the Mosaic Theory of hypertension, first proposed in 1949 by Dr. Irvine Page. He stated that the etiology of essential hypertension is multifactorial including genetic, humoral, anatomical, environmental, adaptive, endocrine, neural, humoral and hemodynamics factors [4]. In the following years, various other theories appeared. Remarkably, Arthur Guyton stated that hypertension is a result mainly of alterations at the renal level, and involves a shift in the pressure natriuresis curve, causing sodium retention and consequently blood pressure elevation [5]. Moreover, Dr. Guyton mentioned that extrarenal factors such as the renin-angiotensin-aldosterone system, increased sympathetic tone, changes in electrolytes concentration, or antidiuretic hormone levels could have an important role in the pathogenesis of essential hypertension. There are still many uncertainties about the mechanisms implicated and only a small number of patients (~10%) have a secondary cause of hypertension (e.g., glomerulonephritis, primary aldosteronism, Cushing's syndrome) [6]. In this context, many studies have emerged pointing to oxidative stress as a central mechanism in the pathogenesis of essential hypertension [7-10].Oxidative stress can be defined as an imbalance between the production of reactive oxygen species (ROS) and the ability of the antioxidant system to detoxify these molecules or repair the resulting damage [10]. Considering the central role of oxidative stress in hypertension several therapeutic agents have been studied. Such is the case of vitamins C and E, selenium, Nacetylcysteine, allopurinol, polyphenols, and certain diets [12]. The objective of this review is to explore the pathophysiological role of oxidative stress in essential hypertension and the results of some of the most well-known antioxidant compounds in hypertension treatment. Several studies have

addressed their effectiveness, often with controversial results. Thus, one of the main problems is to elucidate the origin of the discrepancies in the results of the different clinical trials. Demonstrating the effectiveness of antioxidant therapy can lead to the use of lowcost pharmaceutical compounds with minimal adverse effects for the treatment of this condition, which is also very useful to reduce the polypharmacy to which patients with chronic diseases are exposed, especially in people with resistant hypertension where therapies with minimum adverse interactions are desirable. It is also important to notice that combined antioxidant therapy has not been properly addressed, and previous local experiences have shown positive results with the combined treatment of vitamin C and E [13], suggesting possible synergistic or additive effect between different antioxidants.

Case Presentation

General Perspectives

To understand why the supplementation with antioxidants could be beneficial in essential hypertension treatment, it is necessary to explore the known facts in the relationship between oxidative stress and hypertension. The reactive species involved in oxidative stress are found under physiological conditions and are necessary for many cellular functions, such as the ROS burst produced by neutrophils to control infections as part of the innate immune system. Another example are endothelial cells, where superoxide can be dismutated to produce hydrogen peroxide, this reactive specie can act as a second messenger and activate ion channels, tyrosine kinase receptors, and phosphatases to do certain cellular functions [9]. Nevertheless, excessive production of ROS and reactive nitrogen species (RNS) can be deleterious, as they have a central role in atherosclerosis, vascular inflammation, and endothelial dysfunction. These processes are related to hypertension which is a major risk factor in adverse vascular events (e.g., acute myocardial infarction, stroke, ischemia-reperfusion damage, and chronic kidney disease, among others) [14]. Our group previously established the relationship between oxidative stress and hypertension, demonstrating that oxidative stress markers (e.g., F2-isoprostanes) correlate positively with systolic blood pressure and negatively with plasma antioxidant capacity (e.g., FRAP) [15, 16]. Also, increased levels of ROS and decreased circulating antioxidants and nitric oxide, an important vasodilator described later, have been found in hypertensive humans [17]. It is well known that vascular tone is regulated by a fine balance between vasoconstrictor and vasodilator molecules derived from the vascular wall and circulating agents, and both can be affected by ROS. There are multiple enzymatic and non-enzymatic sources of ROS in the vascular wall. Among the enzymatic ROS sources, one of the most important and best described is NADPH oxidase (NOXs), but many other enzymes also contribute, including xanthine oxidase (XO), uncoupled endothelial nitric oxide synthase (eNOS) and the mitochondrion [12].

ROS, Vasoconstriction, and Hypertensive Phenotype

Oxidative stress can also induce major changes in the vascular wall. In vascular smooth muscle cells (VSMCs) and endothelial cells, high ROS levels can induce DNA damage, lipid peroxidation, and protein oxidation [18]. Reactive oxygen species constitute molecules with intracellular signaling capacity, they act via mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), and phospholipase C (PLC) signaling pathways to induce cell proliferation, survival, and differentiation. Also, low to moderate levels of ROS are thought to induce Nrf2 pathway, which promotes the expression of intracellular antioxidant enzymes. However, high levels of ROS activate cellular apoptosis and necroptosis [19, 20, 21]. Furthermore, ROS induces phenotypical changes in the vascular wall that contribute to the pathogenesis of hypertension. The main phenotypical changes are observed in VSMCs where ROS can induce their growth via proliferation and hypertrophy mainly through mentioned growth signaling pathways. Angiotensin II hypertrophy and platelet-derived growth factor (PDGF) and thrombin proliferation of VSMCs are also mediated by ROS signaling [22]. ROS can also cause VSMCs migration; in this process, vascular endothelial growth factor (VEGF) overexpression induced by ROS is involved. VEGF stimulates matrix metalloproteinases (MMPs) in response to vascular injury, which facilitates VSMCs migration through matrix degradation [23]. Not only activity, but also expression of MMPs have shown to be sensitive to ROS. In VSMCs, MMP-2 and MMP-9 are activated by ROS, and genetic deletion of these enzymes decreases VSMCs migration [24]. In addition, ROS induces direct vascular contraction in VSMCs increasing inositol triphosphate and cytoplasmic calcium concentration. They also inhibit the calcium reuptake pump and decrease cyclic GMP (cGMP) production [25]. These effects result in an increase in cytoplasmic calcium released mainly from the endoplasmic reticle, which causes vasoconstriction, and a reduced cytoplasmic concentration of cGMP, which is a second messenger that induces vasodilation.

ROS Production in the Vascular Wall

In the vascular wall, ROS is produced in various processes, both pathological and physiological. An example of ROS physiological production is the synthesis of nitric oxide (NO), which is one of the main regulators of vascular tone in endothelial cells. Nitric oxide is produced through the endothelial nitric oxide synthase (eNOS) and has an effect in VSMCs activating soluble guanylyl cyclase (sGC) and increasing cyclic guanosine monophosphate (cGMP), an important mediator of vasodilation in VSMCs [26]. Endothelial NOS function can become pathological when tetrahydrobiopterin (BH4), an important cofactor of this enzyme is oxidized by ROS, inducing eNOS uncoupling. As a result, electron flow from the reductase domain to the oxygenase domain is diverted to O2. Uncoupled eNOS produces superoxide anions that can form peroxynitrite by binding with NO, and peroxynitrite leads to further eNOS uncoupling constituting a vicious circle [27]. Another major source of ROS in the cardiovascular system are NOX enzymes. Endothelial cells express NOX1, NOX2, NOX4, and NOX5; VSMCs express NOX1, NOX4, and NOX5, all of them involved in superoxide production. It has been seen that NOX1 and NOX4, located in the plasma membrane and endoplasmic reticulum respectively cause increased basal ROS generation. The NOX4 was even associated with an endoplasmic reticulum stress response. These findings identify a novel mechanism in vascular dysfunction in hypertension [28]. Also, NOX2 seems to generate considerably large amounts of ROS and inhibition or deletion of NOX2 reduces oxidative stress in the vasculature [29]. Thus, targeting these enzymes seems promising. However, lack of specificity of current drugs in targeting isoforms of NOX could lead to a disfunction in their physiological roles. As an example, NOX 2 has a crucial role in the innate im-

mune response to invading pathogens [29]. Another relevant enzyme is xanthine oxidase which plays an important role in the catabolism of purine. It is expressed in endothelial cells, among many other cells, oxidizing hypoxanthine to xanthine and xanthine to uric acid. In normal conditions, XO generates low amounts of superoxide via electron leak. Nevertheless, this reaction increases under ischemic or hypoxic conditions, producing significant levels of ROS [30]. XO activity is increased by angiotensin II, TNF-alfa, IL-6, and hypoxia [31,32]. Vascular cells also produce ROS in physiological conditions through the mitochondrial electron transport chain. The ROS produced by this organelle normally fulfill intracellular signaling functions, but in high quantities can also contribute to the pathogenesis of cardiovascular diseases. In fact, mitochondrial superoxide production is related to endothelial dysfunction, impaired acetylcholine-dependent vasodilation, and infarct size in myocardial ischemia/reperfusion [30,33]. All this ROS production within the vascular wall configures the hypertensive vascular phenotype characterized by an impaired endothelium-dependent vasorelaxation, increased vasoconstriction, inflammation, arterial stiffness, and vascular remodeling [7]. In addition to the production of ROS within the vascular wall and their role in this phenotypical shift, several vasoactive factors are capable of inducing vasoconstriction and remodeling of vascular smooth muscle cells mainly through inducing the production of free radicals. The most reviewed of these factors are angiotensin II (Ang II), endothelin-1 (ET-1), and currently urotensin II (UII) [34].

Vasoactive Factors Involved in ROS Production and Hypertension

Angiotensin II

The renin-angiotensin-aldosterone (RAS) system plays a fundamental role in modulating cardiovascular homeostasis and the classic axis is composed of angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and angiotensin II receptor type 1 (AT1R). Angiotensin II is a crucial part of this axis and one of the most relevant vasoactive factors, it regulates NADPH oxidase, inducing its expression and activation, which increases ROS production on the vascular level [35]. As mentioned, ROS is increased with high levels of Ang II as well as endothelin-1 and urotensin-II. Considering ROS may also be generated through unidirectional laminar and oscillatory shear stress during high blood pressure it could be considered a vicious cycle [11]. As a result, angiotensin 1 receptor blockers and aniotensin-converting enzyme inhibitors (ACEI) produce their antihypertensive action at least in part due to inhibition of NOX and consequently decreased ROS production [36]. The AT1R and angiotensin II receptor type 2 (AT2R) are the most studied subtypes of Ang II receptors, and both have vascular effects and expression, being AT1R the one involved in vasoconstriction and vascular remodeling. It has been seen that in aged mice there is an elevated ratio of AT1R:AT2R in the mesenteric arteries exhibiting a higher maximal contractile response to Ang II infusion, which could explain part of the hypertensive phenotype in aged subjects. There was also more superoxide production in the same arteries [37]. Furthermore, mice deficient in NOX-1 do not produce ROS in response to Ang II infusion and showed reduced blood pressure compared to non-deficient NOX-1 mice, highlighting the relevance of ROS in mediating the cardiovascular effects of Ang II [38]. On the other hand, there is a RAS axis composed of angiotensinconverting enzyme 2 (ACE2), angiotensin 1-7 (Ang-(1-7)), and Mas receptor. This pathway has been the focus of intensive research, mainly due to its opposite effects to those of AII. ACE2 (recently popularized due to serve as the entry point into cells for the new SARS-CoV-2) acts through conversion of Ang II to Ang-(1-7), reducing circulating levels of Ang II and, therefore, decreasing the induction of the fibrotic and hypertrophic phenotype on the vessels and the heart [39]. Supporting this, a study in mice showed that the loss of one of the coding alleles for ACE2 produced a greater tendency to pressure overload of the left ventricle of the heart, systolic and diastolic dysfunction, and an increase in the production of free radicals by myocardial NOX. Likewise, an increase in fibrosis and oxidative stress at the level of the vascular wall was observed [40]. Ang-(1-7) also has a crucial role in regulating blood pressure, some studies in murine models showed a protective effect of Ang-(1-7) against hypertension, lowering SPB and DBP. These studies also showed a reduction in cardiac fibrosis, hypertrophy, and Ang II-induced oxidative stress [39,41]. Angiotensin 1-9 (Ang-(1-9)) is another recently studied peptide related to RAS axis, which is also produced by ACE2, but in this case from angiotensin I. Recent data on Ang-(1-9) suggest a protective action over the hearth and vessels in animal models, avoiding remodeling and preventing hypertension, this through his union to AT2R [42, 43]. Moreover, it also has been observed an anti-inflammatory and anti-fibrotic role of Ang-(1-9) in the heart, arteries, and kidneys not mediated by AT2R [44]. It is important to notice that Ang-(1-9) can be transformed to Ang-(1-7) through Angiotensin-converting enzyme (ACE), but their actions are independent of those of Ang- (1-9), exhibiting its own cardioprotective role [45].

Endothelin-1

Endothelin-1 (ET1) is another vasoconstrictor that acts by binding to endothelin receptors in vascular smooth muscle cells. Elevated levels of ET1 have been found in early stages of hypertension and in pre-hypertensive subjects, as well as diminished plasmatic concentrations of NO [46, 47]. ET-1 performs its functions in the vasculature through its union with two different receptors: endothelin type A (ETA) and endothelin type B (ETB). Binding to ETA and ETB on VSMCs leads to activation of phospholipase C-inositol triphosphate signaling pathway causing elevated intracellular calcium and therefore vasoconstriction. On the other hand, activation of ETB receptors on endothelial cells leads to eNOS activation and vasodilation [48,49]. The actions of ET-1 are ligated to ROS production. Activation of both ETA and ETB induces oxidative stress signaling that activates NOX in endothelial cells and VSMCs, producing more superoxide [50]. Moreover, inhibition of NOX in young mice causes a significantly reduced response to ET-1 in the renal artery and aorta [51]. Both ETA and ETB receptors are upregulated by angiotensin II, suggesting a synergistic effect of Ang II and endothelin-1 in the development of hypertension indicating the multiple effects of high levels of Ang II, mediated mainly by ROS [52]. Based on these findings, it could be hypothesized that the reduction of oxidative stress in the vasculature could reduce high blood pressure induced by mechanisms such as high angiotensin II and endothelin-1 levels.

Urotensin II

Urotensin II (UII) is the most active vasoconstrictor identified in humans; it is ten times more active than ET-1 [53].

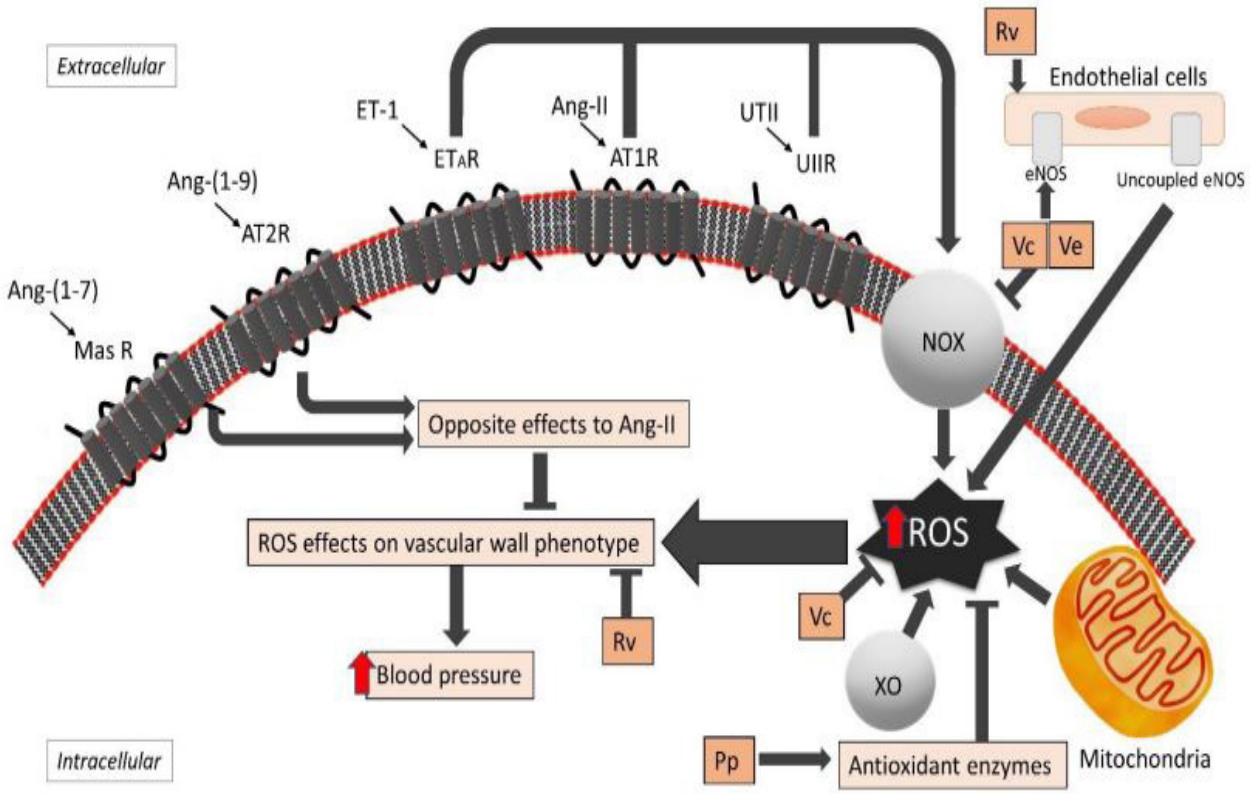

Figure 1: *ROS production in the vascular wall and some of the antioxidant targets. Oxidative stress raises as a central mechanism in the elevation of arterial pressure, susceptible to being intervened. NOXs: NADPH oxidases (isoforms 1,2,4,5). ETAR: ET-1 receptor isoform A. AT1R: Ang II receptor isoform 1. UIIR: urotensin II receptor. XO: Xanthine oxidase. eNOS: endothelial nitric oxide synthase. AT2R: Ang II receptor isoform 2. Mas R: Mas receptor. Rv: Resveratrol. Vc: Vitamin C. Pp: Polyphenols. Ve: Vitamin E.*

Urotensin receptors are found in VSMCs, and their activation leads to vasoconstriction, activation of NOX, and expression of plasminogen activator inhibitor-1 [54]. Studies have been found UII plasmatic levels to correlate positively with systolic bloodressure in patients with essential hypertension [55, 56]. Interestingly, high levels of UII are associated with high blood pressure and reduced cardiac inotropism in healthy subjects, but in chronic kidney disease, UII could act as a vasodilator. Moreover, low UII in these patients appears linked to adverse cardiovascular events and death [57, 58]. This remarks the relevance of the type of patient in which we apply the antioxidant therapy. There are many uncertainties about the function of UII, but it remains clear that part of its function is exerted through the production of oxygen free radicals and that in subjects without terminal chronic diseases it is positively correlated with hypertension. According to evidence, there could be beneficial to intervene in the ROS mediated pathway of UII in subjects with new-onset hypertension.

Antioxidant Therapy

As previously stated, ROS are central mediators of vasoconstrictor response and the generation of a hypertensive phenotype in the vascular wall. Therefore, multiple molecules with antioxidant properties have been tested in the last few years with controversial results. Among them, vitamins C and E are one of the most interesting due to their low rate of adverse effects and their low cost. But multiple other molecules could be beneficial in hypertension treatment that also acts mainly by reducing ROS. Those with more evidence in the literature will be analyzed in this section with a focus on clinical results.

Vitamin C

Vitamin C or ascorbic acid is an essential vitamin found in fruits, vegetables, supplements, and some cereals. It is a known non-synthesizable exogenous antioxidant that scavenges toxic free radicals and other reactive oxygen species derived from cellular metabolism [59]. Vitamin C also modifies the functioning of certain enzymes, such as eNOS and NOXs, enhancing the function of the first one and diminishing the activity of the second one [60]. There is not fully understood how vitamin C produces these effects, but the main theory regarding eNOS activity is that Vitamin C increases intracellular concentrations of BH4 preventing eNOS decoupling [61]. This behavior suggests a beneficial role in hypertensive subjects since it would increase NO production and reduce its degradation, the latter being mediated both by acting as a ROS scavenger and by inhibiting superoxide production by decoupled eNOS. Some studies have addressed this hypothesis with contradictory results, probably due to different subject selection criteria and vitamin C dose. A recent meta-analysis of eight randomized controlled trials, showed that there is a significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in vitamin C supplemented subjects [61]. This meta-analysis also states that the major differences between SBP and DBP between the observation and control group were in the ≥60-year-old subgroup. Is important to notice that with age there is an increased ROS production resulting in a pro-oxidant basal state. Vitamin C pharmacokinetics are usually not considered in the design of the study, resulting in confusing results. Vitamin C exhibits a sigmoidal dose concentration

relationship [62]. This implicates that in patients depleted of vitamin C small doses of supplementation will only increase modestly the plasmatic vitamin C concentration, but slightly higher doses will increase it much more before reaching a plateau. Thus, to obtain reproducible results, the study must consider the plasma concentrations of vitamin C in patients and decide the doses considering the pharmacokinetics of this vitamin. The exact dose of vitamin C supplementation is variable, it depends on the subject's baseline plasma level, sex, body area, and smoking habit. In non-smoking men, metabolic losses of 50 mg/day are assumed, with an absorption rate of 80% and urinary excretion of 25% of vitamin C intake [63]. In oral administration, there is a dose-dependency type curve for vitamin C plasma levels with a maximum level of 70-80 μmol/L [64]. In the NIH depletion repletion study, there was observed that in man a daily vitamin intake of 30mg showed plasmatic vitamin C concentrations of 8.7 μmol/L. An intake of 100mg increased plasmatic levels to 56 μmol/L, and for a daily intake of 400mg, the plasma values were 70 μmol/L. In women, there was a slightly higher plasmatic concentration with the same daily oral dose intake, probably due to differences in body area [65, 66]. Based on this evidence a proper dose of vitamin C supplementation will be something between 200-400mg daily to get saturation plasmatic levels, being this much more effective in people with depleted levels of vitamin C.

Vitamin E

Vitamin E is an important lipid-soluble antioxidant. It decreases lipid peroxidation and exerts part of its actions by down-regulating NADPH oxidase and upregulating eNOS, leading to an increase in NO levels [67]. However, randomized controlled clinical trials results have been disappointing and often contradictory, with many of them showing no effect of vitamin E in preventing major adverse cardiovascular events [68, 69]. Nevertheless, in a meta- analysis conducted by Jayedi et al. on prospective observational studies, higher α-tocopherol concentration was associated with a decreased risk of cardiovascular mortality. Although, this association did not appear with a higher dietary vitamin E intake [70]. Attending specifically to hypertension, Boshtam et al., already in 2002 found a significant decrease in systolic blood pressure after 27 weeks of treatment with 200IU/day of vitamin E and a minor decline in diastolic blood pressure. All subjects were mildly hypertensive and without any other cardiovascular risk factor [71]. A recent meta-analysis on the effects of vitamin E on blood pressure involving 839 patients also found a decrease in SBP, but no significant effect on DBP [72]. There are different forms of vitamin E being α-tocopherol is the most active one, and it is available in its natural form as RRR-αtocopherol. The other available form is all-rac-α-tocopherol, which is a synthetic mixture of the eight possible stereoisomers of α-tocopherol [73]. Of all these stereoisomers RRR-αtocopherol is likely the one with the greatest effects on health outcomes. Some bioavailability studies suggest a 2:1 ratio of bioavailability between RRR-α-tocopherol and all-rac- tocopherol and the US food and drug administration modify the labeling regulations assuming the expressed ratio. Despite this, the biopotency ratio is still under discussion, but the biopotency of RRR-α-tocopherol is probably higher than the all-rac-α-tocopherol [74, 75]. This must be considered when supplementation of vitamin E is chosen for study purposes. Also, the exact dosage of vitamin E is difficult to assess. Plasmatic levels are not a good indicator of the required oral dose, principally because vitamin E distributes in several lipophilic environments. Although, a dose over 400 IU/day has been associated with increased mortality, so it is not recommended to exceed this [76]. The combination of vitamin C and vitamin E in previous studies have demonstrated to decrease SBP and DBP with a synergic effect [13]. Both compounds can induce up-regulation of eNOS, and down-regulation of NOX as previously stated.

Also, Vitamin E can induce oxidative stress through oxidation of α-tocopherol to α-tocopheroxyl in plasma membrane, which may be reduced by the vitamin C supplementation, avoiding lipid peroxidation.

Resveratrol Polyphenols are compounds available in many fruits, cereals, vegetables, and beverages. Among their properties, an antioxidant effect has been described, being capable of acting as scavengers, modulators of ROS-producing enzymes, regulators of the inflammatory cascade, and some could even activate the transcription factor Nrf2, involved in the transcription of antioxidant response element (ARE) enhancer sequence [77]. Resveratrol is a natural polyphenolic compound found in grapes, peanuts, and wine, especially red wine. It is one of the most studied polyphenols and its main actions have been described around the treatment of hypoxic pulmonary hypertension, showing an anti-inflammatory and antioxidant effect [78]. It even inhibits the proliferation of smooth muscle cells in the pulmonary vasculature and prevents cardiac hypertrophy [79], which could suggest a beneficial effect on the change in vascular phenotype associated with arterial hypertension. In endothelial cells, resveratrol enhances NO production through upregulating eNOS expression, enhancing eNOS enzymatic activity, and preventing its uncoupling due to resveratrol antioxidant properties [80]. It also reduces the proliferation of VSMCs induced by advanced glycation end products (AGEs) in VSMCs cultures of spontaneously hypertensivemice [81]. VSMCs excessive proliferation with low cell differentiation is involved in vascular atherosclerosis, restenosis, and pulmonary and systemic hypertension [80]. Moreover, resveratrol can promote VSMCs differentiation via stimulation of SirT1 and AMPK, varying according to the administered resveratrol dose [82]. Like other compounds mentioned, resveratrol has also had conflicting results as a treatment for high blood pressure. Liu et al., published a meta-analysis in 2015 on the effect of resveratrol on arterial hypertension, not finding a significant reduction in SBP or DBP [83]. Although, it is suggested that high doses of resveratrol could be useful in reducing SBP, probably due to the strong first-pass liver metabolism suffered by this compound, according to the authors. Among the limitations of this evidence is the low number of quality studies, since out of a total of 96 non-duplicated articles analyzed, only 6 met the inclusion criteria of the meta-analysis. In 2019, Fogacci et al., published another meta-analysis [84] including a total of 17 studies, selected from a pool of 205 records screened. They also did not find a significant reduction in SBP or DBP between subjects treated with resveratrol and controls. However, a more significant reduction was observed in patients with type 2 diabetes or obesity, and in groups treated with high doses of resveratrol (≥300 mg/day). None of the studies reviewed reported significant adverse effects from resveratrol use. More research is required to determine the therapeutic potential of resveratrol, especially as an addition to standard therapy for arterial hypertension in the early stages, where it could be more useful.

N-Acetylcysteine

N-acetylcysteine (NAC) is a drug commonly known for its use as an antidote in acetaminophen overdose. Its current applications are justified in its antioxidant and mucolytic properties. NAC scavenge ROS and acts as a precursor of cysteine in glutathione synthesis [85]. Generally, glutathione participates in reduction and conjugation reactions preventing intracellular ROS damage, being one of the main cellular defenses against oxidative stress. Glutathione gets depleted under conditions of high oxidative stress, in which it may be useful to increase its synthesis through NAC. NAC effects on blood pressure have been tested. A study on Dhal salt-sensitive rats with high sodium intake showed a protective role of NAC (dose of 4 g/kg per day) in preventing renal damage and rise in blood pressure [86]. In humans, Khaledifar et al., conducted a cross-sectional study with 126 hypertensive patients, comparing ACE inhibitors treatment alone and ACE inhibitors + NAC (dose of 600mg/12 hours) for two months resulting in a significant decrease in mean blood pressure, with both SBP and DBP reduction in the group receiving combined therapy [87]. No significant adverse effects were listed in either of the two studies. In patients with chronic kidney disease (CKD), NAC had no effect so far on lowering blood pressure at a dose of 1200 mg/day as an additional therapy to the usual nephroprotection with RAAS blockers [88]. More studies are needed to extract conclusions on the effectiveness of NAC therapy for hypertension, either in monotherapy or as an addition to usual antihypertensive therapy.

Others

Beta-carotene is an organic pigment found in many fruits and vegetables such as carrots, pumpkin, sweet potatoes, spinach, kale, among others. It has antioxidant properties in low oxygen conditions, although in high oxygen conditions it can undergo autoxidation generating carotenoid peroxyl radical, which may be harmful in some situations [89]. Most of the studies that analyze the relationship between beta-carotene and blood pressure are based on serum levels of this compound or on dietary interviews, so the analysis of the level of evidence should be cautious. A model on spontaneously hypertensive rats (SHR) conducted by Fiorelli et al., showed that supraphysiological supplementation of beta-carotene is associated with lower blood pressure levels. The study did not have any side effects, apart from a transitory change in the rats' hair color [90]. In the human population, recent research on the United States population in which data from National Health and Nutrition Examination Study (2007-2014) was analyzed, found a significantly lower risk of hypertension in subjects who consume at least 100 µg/kg per day of total carotenoids, which was similar for the analysis of beta-carotene alone [91]. There is a lack of randomized clinical trials with controlled doses of betacarotene to make more appreciations about its effect on blood pressure. It is relevant that beta-carotene supplementation in heavy smokers increases lung cancer incidence according to randomized controlled trials data. However, this evidence is inconsistent, and some studies shows no effect. Nevertheless, in heavy smokers, it is not recommended to supplement with beta-carotene. In never smokers or former smokers there is a neutral or lower risk for lung cancer when this therapy is given [92]. Vitamin B6 supplementation is another potential strategy for lowering blood pressure. It has antioxidant effects that could be related to its role in scavenging free radicals. Also, its active form pyridoxal 5'-phosphate coenzyme participates in the transsulfuration pathway that transforms homocysteine to cysteine, causing the deficiency of this coenzyme to result in the accumulation of homocysteine [93]. Hyperhomocysteinemia (i.e., higher than normal levels of homocysteine in plasma) is an independent risk factor for cardiovascular disease. The mechanisms behind this increased cardiovascular risk could relate to endothelial disfunction induced by homocysteine, which inhibits NO synthesis [94]. Thus, vitamin B6 supplementation could prevent homocysteine accumulation and therefore prevent NO synthesis from being disrupted and result in lower blood pressure. Some studies in rats have been conducted to test vitamin B6 effects on blood pressure, resulting in a reduction of both SBP and DBP [95, 96]. In humans, Aybak et al., conducted a clinical trial with 29 participants resulting in significantly reduced systolic and diastolic blood pressure [97]. A more recent randomized clinical trial in older adults showed that lowering plasmatic homocysteine with vitamins B6 (10 mg), B12, and folic acid did not affect blood pressure [98]. This could be related to permanent phenotypic alterations in the arteries of older adults. Another recent cross- ectional study in Japanese children aged between 3-6 years suggested that a diet high in vitamins B12 and folic acid was associated with lower blood pressure in this population. Although, the intake of vitamin B6 supplements showed no association [99]. There is a lack of quality randomized clinical trials to clarify the role of this vitamin in blood pressure and the exact dose needed for that effect. Allopurinol, commonly used to decrease high blood uric acid levels, also acts as an antioxidant through scavenging ROS in a dose-dependent manner and by inhibiting XO activity in much lower doses [100, 101, 102]. A recent meta-analysis of randomized controlled trials confirmed the antioxidant effect of allopurinol finding a significant reduction of the serum concentration of malondialdehyde in patients with allopurinol treatment [103]. Despite its antioxidant effects, the decrease in blood pressure appears to be small. Two meta-analyses from the last decade obtained similar reductions in SBP and DBP, being 3.3 mmHg in one research and 1.3 mmHg in the other [104, 105]. One of these studies included 10 randomized controlled trials and the other 15. More evidence in this matter is required.

Concluding Remarks and Future Perspectives

Hypertension is a major cardiovascular risk susceptible to being modified. It is considered the main risk factor along with smoking-related to premature death and disability according to the Global Burden of Disease Study of 2017 [106]. There is robust evidence supporting the role of ROS in the development and maintenance of blood pressure elevation, constituting a proven central factor in hypertension development, so using it as a therapeutic target could be effective. In this review, we found that compounds that scavenge ROS and inhibit pathways leading to oxidative stress generation are beneficial in many hypertension models. Nevertheless, in humans the evidence is limited, and the compounds listed in this document have varying results on the treatment of hypertension. This may be due to the lack of high-quality randomized clinical trials analyzing these therapies and the high variability in study design. One of the least explored topics regarding antioxidant therapy is its association with conventional antihypertensive therapy. Most conventional drugs currently indicated to hypertensive patients demonstrate antioxidant properties associated with their phar-

macological action [107-109]. Also, evidence reported a synergistic effect between some antioxidant compounds [13]. It is reasonable that an enhanced pharmacological effect against blood pressure elevation should be expected when including natural antioxidants to reinforce the antihypertensive effect of conventional drugs. In addition, supplements of natural antioxidants lack biological effects that could cause adverse events in patients, are easily available, have low pharmacological cost and provide further beneficial effects related to their properties against other oxidative stress-induced pathological processes. Novel randomized, controlled, double-blind clinical trials with the associations of natural antioxidants alone or combined with antihypertensive drugs have not been performed. Therefore, we propose the design of translational studies including the research of association of two or more antioxidants (including antihypertensive drugs) as an adjunct therapy in protocols aimed to treat patients having high blood pressure.

Conflicts of interest statement

The authors declare no conflicts of interest statement.

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