



Antioxidant therapy for hypertension; a mini-review on the recent findings

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ABSTRACT

Oxidative stress is a key mechanism underlying hypertension. Therefore, antioxidant therapy is an attractive concept for hypertension. Antioxidant therapy has been shown to have a significant impact on blood pressure reduction in various studies. The duration of treatment before observing results can vary depending on the specific antioxidant used, the dosage, and the individual's health status. Antioxidant therapy by reducing oxidative stress and improving endothelial function reduces the high blood pressure. Antioxidants may achieve their antihypertensive effects by reducing the formation of advanced glycation end products and aldehydes that impair vascular function and improving insulin resistance and endothelial function and also by normalizing calcium channels and peripheral vascular resistance.

Implication for health policy/practice/research/medical education:

Antioxidant therapy leads to reduce oxidative stress, leads to the improvement of endothelial function, and decreasing superoxide production and renal dysfunction and also cardiac damage.

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Introduction

Hypertension is a complex condition that often requires a multifaceted approach, including lifestyle modifications (such as diet and exercise), medications, and sometimes other interventions. Antioxidants are compounds that help neutralize harmful free radicals in the body, which can cause damage to cells and contribute to various health conditions, including hypertension. This treatment has been studied as a potential treatment for hypertension, as oxidative stress is believed to play a role in the development and progression of high blood pressure (1,2). Antioxidant therapy for hypertension targets the molecular mechanisms underlying oxidative stress, which is a key contributor to the development and progression of hypertension. Therefore, targeting oxidative stress through antioxidant therapies may be a promising approach to prevent or treat this condition (3). Previous studies showed that oxidative stress plays a significant role

in the development and progression of various chronic diseases (2,3). Oxidative stress can contribute to the development of atherosclerosis, hypertension, and other cardiovascular diseases by promoting inflammation, endothelial dysfunction, and vascular damage. Oxidative stress is also involved in the pathogenesis of diabetes by impairing insulin secretion, promoting insulin resistance, and contributing to the development of diabetic complications (4). Moreover, oxidative stress can impair kidney structure and function which can contribute to the development of chronic kidney disease. The mechanisms by which oxidative stress contributes to chronic diseases include direct damage to cellular macromolecules like DNA, proteins, and lipids, across with activation of redox-sensitive signaling pathways, promotion of inflammation and induction of apoptosis and cell death and finally, impairment of mitochondrial function along with disruption of cellular homeostasis (5). In this mini-

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review we aimed to discuss the impact of oxidative stress on the emerge or aggravation of hypertension (HTN) and potential antioxidant therapy of this disease.

Search strategy

For this study, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including; Oxidative stress, reactive nitrogen species, hypertension, antioxidant therapy and reactive oxygen species.

Contribution of oxidative stress to hypertension

Oxidative stress reduces nitric oxide (NO) bioavailability, impairing endothelium-dependent vasodilation and promoting vasoconstriction (6). Reactive oxygen species (ROS) can also modify proteins involved in redox signaling, further contributing to endothelial dysfunction. Excessive ROS production leads to vascular smooth muscle cell hypertrophy, hyperplasia, and migration, resulting in structural changes and increased vascular stiffness. Moreover, oxidative stress also promotes extracellular matrix deposition and fibrosis (7). Likewise, ROS activate redox-sensitive transcription factors like NF- κ B, leading to the upregulation of pro-inflammatory genes and the recruitment of inflammatory cells to the vascular wall. This inflammatory response further exacerbates vascular damage. Besides, ROS can directly induce vasoconstriction by increasing intracellular calcium levels in vascular smooth muscle cells (8). Oxidative stress also enhances the vasoconstrictor effects of angiotensin II, endothelin-1, and urotensin II. Finally, ROS can induce post-translational modifications of proteins, altering their function and contributing to vascular dysfunction²⁵. Redox proteomics has identified specific proteins that undergo oxidative modifications in hypertension (9,10).

Molecular mechanisms of antioxidant therapy of HTN

Antioxidant therapy works by neutralizing ROS and reactive nitrogen species (RNS), which are generated in excess during hypertension. This imbalance between ROS/RNS production and antioxidant defense mechanisms leads to oxidative and nitrosative stress, promoting vascular damage and hypertension (11). Antioxidants neutralize excess ROS/RNS, preventing oxidative damage to cellular components. Strategies that combat oxidative stress by targeting Noxs, which are the primary sources of ROS in the vasculature, have shown promise in reducing oxidative stress and hypertension. Antioxidants can protect mitochondria from oxidative damage, which is a key mechanism underlying hypertension (12).

Antioxidant therapy for the treatment of HTN

Antioxidant therapy can enhance endothelial function, which is crucial for maintaining healthy blood vessels and regulating blood flow. Antioxidants also defend against

oxidative stress, which is a key factor in the development and progression of hypertension. By reducing oxidative stress, antioxidants may protect against vascular damage and other complications associated with hypertension (13). Accordingly, antioxidants can improve NO bioavailability, a molecule essential for vasodilation and maintaining healthy blood pressure levels. Moreover, antioxidant therapy prevents cardiovascular complications associated with hypertension by targeting oxidative stress and improving overall vascular health (14). Finally, antioxidants may possess anti-inflammatory properties, which can further benefit individuals with hypertension by reducing inflammation in the cardiovascular system. These additional benefits highlight the multifaceted role of antioxidant therapy in managing hypertension beyond just lowering blood pressure (14, 15). However, the evidence on the effectiveness of antioxidant therapy for hypertension is mixed, with some studies showing positive results while others have found no significant benefit. In a study by Vaziri et al using the potent antioxidant desmethyl tirilazad, significant amelioration of hypertension was observed after 3 weeks of administration. They suggest that antioxidant therapy can have a relatively rapid effect on blood pressure reduction (16). Though, the translation of antioxidant strategies from animal studies to human hypertension has been disappointing. Factors like trial design, type of antioxidants used, and the presence of irreversible oxidative damage may account for the differences (14,16).

Among antioxidants, vitamin D is emerging as a promising anti-hypertensive agent through activation of antioxidant mechanisms. Hence, maintaining adequate levels of vitamin D through sunlight exposure, diet, and possibly supplementation may have benefits in managing blood pressure, especially in individuals with vitamin D deficiency (17). Some antihypertensive drugs like celiprolol, carvedilol and nebivolol also have antioxidant properties in addition to their blood pressure lowering effects (18). However, some studies deny the beneficial effects of antioxidant to improve the high blood pressure. This disparity in results highlights the complexity of antioxidant therapy in hypertension and the need for further research to determine the optimal treatment duration and dosage (17,19). The examples of antioxidant-rich foods that can help reduce oxidative stress in hypertension include berries such as blueberries, strawberries, and raspberries, citrus fruits like oranges and grapefruits, and tropical fruits such as mangoes and papayas are rich in antioxidants like vitamin C and flavonoids that can help combat oxidative stress (17,20,21). Additionally, dark leafy greens such as spinach and kale, bell peppers, broccoli, and tomatoes are excellent sources of antioxidants like vitamins A, C, and E, as well as phytonutrients that can support cardiovascular health and reduce oxidative damage in hypertension (22). Moreover, Whole grains like quinoa, brown rice,

oats, and whole wheat contain antioxidants, fiber, and other nutrients that can help lower blood pressure and reduce oxidative stress in the body. Accordingly, almonds, walnuts, chia seeds, and flaxseeds are rich in antioxidants, omega-3 fatty acids, and minerals like magnesium that can help protect against oxidative stress and inflammation in hypertension (22,23). Likewise, turmeric, ginger, cinnamon, and garlic are known for their antioxidant and anti-inflammatory properties, which can help reduce oxidative stress and support cardiovascular health in individuals with hypertension (24). Finally, it should remember that antioxidants may have some potential benefits for hypertension; however, they should not be used as a standalone treatment. Lifestyle changes such as maintaining a healthy diet, regular exercise, managing stress, and medication therapy are still the cornerstone of managing high blood pressure (14,25).

Conclusion

Oxidative stress has a significant impact on blood vessels in hypertension, contributing to endothelial dysfunction, vascular remodeling, and inflammation. Antioxidant therapy can have a significant impact on blood pressure reduction in hypertension, however the duration of treatment before observing results varies depending on the specific antioxidant, dosage, and individual health status. Hence, incorporating the antioxidant-rich foods into the diet can help lower blood pressure, reduce oxidative stress, and promote overall cardiovascular well-being in individuals with hypertension.

Authors' contribution

Conceptualization: Mohammad Memarian, Rahimeh Eskandarian.

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Investigation: Rahimeh Eskandarian.

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Supervision: Mohammad Memarian, Rahimeh Eskandarian.

Validation: All authors.

Visualization: All authors.

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Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

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

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