An Emerging Role of Natural Antioxidants in Hypertension

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Abstract
The prevalence of cardiovascular diseases (CVD) like hypertension (HT) is increasing worldwide at an alarming rate. A direct relationship occurs between blood pressure (BP) and the risk of CVD, with oxidative stress as the prime culprit. The evidence which implicates the role of oxidative stress in the pathogenesis and complications of HT suggests the beneficial role of antioxidants in the treatment and prevention of HT.

1. INTRODUCTION
Several risk factors for cardiovascular diseases (CVD) like coronary heart disease (CHD) and myocardial infarction (MI) have been reported worldwide. Hypertension (HT) represents one of the major factors for the development and progression of CVD. Numbers of evidences suggest that reactive oxygen species (ROS) play an important role in the pathogenesis of HT and along with MI, and thus, the adverse effects of ROS on biological systems have become an important area for focus on current biomedical research. Various reports demonstrated the involvement of oxygen free radicals (OFRs) and lipid peroxides (LP) in the pathogenesis of many diseases, including diabetes mellitus (DM), cancer, HT, rheumatoid arthritis (RA), systemic lupus erythematosus, atherosclerosis and aging. The antioxidant vitamins have been suggested to exert potential effects against the development and progression of various CVD, including HT. In addition, data from several observational epidemiologic studies have reported that the agents with antioxidant properties like dietary antioxidants β-carotene, vitamin C, and vitamin E play a vital role in reducing the risk of CVD by significantly lowering the blood pressure (BP). Moreover, the anti-oxidant enzymes, which dispose, scavenge and suppress the formation of free radicals, have been noted to produce an important defense mechanism against oxidative stress. The present review article aims to discuss the potential role of various antioxidants in the treatment and prevention of HT.

2. PATHOPHYSIOLOGY OF HYPERTENSION
The exact pathophysiology of HT has not been understood completely, but a number of pathophysiological mechanisms have been reported from time to time. The rise in peripheral resistance in established HT has been suggested to be attributed to the structural narrowing of small arteries and arterioles. In addition, decrease in the number and density of capillaries has also been noted to be part of the cause. Further, HT has been linked with reduced peripheral venous compliance, enhancing the venous return and cardiac preload, ultimately causing diastolic dysfunction. Moreover, occurrence of high pulse pressure in geriatric patients presented with HT or isolated systolic HT has been suggested to be caused due to increased arterial stiffness associated with aging. Furthermore, other mechanisms have also been denoted for the development of increased peripheral resistance in HT which includes disturbances in renal salt and water management, particularly abnormalities in the intra-renal renin-angiotensin system, and dysfunctioning of the sympathetic nervous system. Additionally, various evidences have suggested that endothelial dysfunction and vascular inflammation also contribute to enhanced peripheral resistance and vascular damage in HT. (Fig. 1).

3. ROLE OF NATURAL ANTIOXIDANTS (VITAMINS) IN TREATMENT OF HT
Various antioxidant vitamins show antihypertensive effects by different mechanisms, but the mechanisms have not been apparent. A number of antioxidant vitamins have been suggested for the treatment and prevention of the HT which include Vitamin A,
C. E. Coenzyme Q10 (CoQ-10). L-arginine, α-lipoic acid and flavonoids. Vitamin A, commonly known as retinoids, contains a β-ionone ring attached to an isoprenoid carbon chain. Vitamin A is derived from certain plant pigments called carotenoids (Pro-vitamin A). The four components of pro-vitamin A are: α-carotene, β-carotene, γ-carotene and cryptoxanthine. The rich dietary sources of vitamin A includes fish liver oils, sweet potato, cheese, butter, liver, potato, carrot, pumpkin, spinach and broccoli leaf. It has been suggested that free radicals are responsible for the development and progression of CVD such as heart attack, HT, and atherogenesis. Vitamin A has been noted to neutralize the free radicals and prevent these complications by significantly decreasing the enhanced plasma levels in order to decrease BP in a clinical study. However; the adverse mortality data with respect to β-carotene has limited interest in this compound as an effective antihypertensive agent. Lycopene, which is synthesized from vitamin A derivatives, have also been noted to show potent antioxidant effects. This contention is supported by the fact that tomato-extract based invention showed significant decrease in BP in patients presented with stage-I hypertension. Vitamin C, commonly known as ascorbic acid, has been reported to possess potent antioxidant effects. It has a six-carbon lactone ring and a hydroxyl group similar to L-glucose. Good dietary sources of Vitamin C include citrus fruits like lemon and orange; berries; melons; leafy vegetables; cabbages; tomatoes; and rose hips. L-ascorbic acid has been the biologically active form of Vitamin C which represents the primary antioxidant in blood. It has been suggested that Vitamin C reacts with the oxygen species, and terminates free radical chain reactions, and thus, acts as a strong antioxidant agent. In addition, Vitamin C also has crucial interactions with a number of other antioxidants, and is crucial for the regeneration of lipid-bound Vitamin E. Furthermore, the antihypertensive potential of Vitamin C has been evaluated in multiple studies which evidenced the fact that a significant reductions in BP is achieved in both normotensive and hypertensive populations. Moreover, it has been demonstrated that Vitamin C supplementation showed a significant decline in both systolic and diastolic BP which may persist for prolonged period. In addition, Vitamin C has been suggested to act more than an antioxidant and its effects on neurotransmitters lead to its antihypertensive activity. This contention is supported by the fact that Vitamin C interferes with the production of free oxygen radicals and peroxides and stimulates the synthesis of prostaglandins (PGs), which produces a vasodilatory effect, ultimately leading to the treatment and prevention of HT. Other mechanisms supporting the protective antioxidant potential of Vitamin C in HT suggest that the effect is caused by restoring vasodilatory activity of nitric oxide (NO) and by improving Ang II- induced endothelial-dependent vasodilation. Vitamin C has been reported to reduce insulin resistance which in turn causes endothelium-dependent and NO-mediated vasodilation.

Vitamin E, commonly known as tocopherol, is the principal lipid-soluble antioxidant, which was discovered in 1936. The four naturally occurring tocopherols are alpha, beta, gamma and delta consisting of a six-chroman ring or head with a phytol side chain. It has been suggested that dietary Vitamin E is mostly absorbed in the small intestine, and thus, severe pancreatic, biliary dysfunction or fat malabsorption have been noted to affect the absorption of Vitamin E. The rich dietary sources of Vitamin E includes wheat germ oil, milk, butter, rice, salad, cooking oils, peanuts, tree nuts, mayonnaise and other oil based dressings and some vegetables, asparagus, leafy green vegetables, higher derived from fats and oils. Further, the cardio-protective potential of Vitamin E has been attributed to its potent antioxidant action. This contention is supported by the fact that α-tocopherol shows antioxidant potential by donating hydrogen radical to remove the free lipid radicals, reacting with it to form non-radical products, or trapping of lipid radicals. In addition, cardioprotective potential of Vitamin E has been attributed to its possible protective effect against Ang II. In addition, various epidemiological studies have demonstrated that a potential role for neutralizing the eNOS-related antioxidant effects of L-arginine in patients presented with HT. Flavonoids, like quercetin, are polyphenolic compounds, which have been suggested to possess a prime role in the treatment and prevention of HT. Rich dietary sources of quercetin includes apples, onions, berries, red wine, red grapes, dark chocolate, flowers, citrus fruits, capers, and cocoa powder. However; various epidemiological studies denote an inverse relationship between dietary quercetin and CVD. Conversely, other studies have been reported a reduction in BP with quercetin supplementation provided to hypertensive animals and humans. Furthermore; quercetin showed antihypertensive effects by various proposed mechanisms like reduction in oxidative stress, quenching of ACE, and improving endothelial function. Additionally, quercetin has been reported to decrease the prevalence of CVD along with protective effects in a variety of disorders such as allergies, asthma, bacterial infections, arthritis, gout, eye disorders, HT and neurodegenerative diseases. Furthermore; the potential of quercetin in the treatment and prevention of HT is supported by the fact that short duration of dark chocolate therapy found to have BP lowering effects in patients presented with HT. Moreover, in certain population, tea intake has been noted to show BP lowering effects, which further evidenced the potential of flavonoids in the treatment and prevention of HT. In addition; various epidemiological studies have suggested that other potential natural antioxidants such as garlic, glutamate, N-acetylcysteine, sour milk, and vitamin D show antihypertensive effect by quenching the sources of excessive ROS through antioxidant mechanisms.  

4. CONCLUSION

The wide-reaching prevalence of chronic CVDs like HT is on an all-time rise, resulting in increased mortality and morbidity. Moreover, it constitutes the major cause of death globally, mainly associated with oxidative stress. Thus, the antioxidant vitamins find the ceiling scope in prevention and treatment of HT. Numbers of dietary antioxidants such as vitamin C, vitamin E and beta carotene have been suggested to might play a potential role in decreasing BP. However, the studies investigating the effect of natural antioxidants on oxidative stress in HT have been at a relatively early stage, and hence further studies are needed to completely explore the benefits of other potent antioxidants in the treatment and prevention of patients presented with HT.

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