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NUTRACEUTICAL INTERVENTIONS FOR HYPERTENSION: A CONTEMPORARY EXPLORATION OF PREVENTION AND MANAGEMENT STRATEGIES

Harmanjot Kaur[1], Dr. Nancy[1], Dr. Shivam Choudghal[2]* and Pardeep Kumar[3]

[1]Assistant Professor, PCTE Group of Institutes.

[2]Clinical Pharmacologist, Shri Mata Vaishno Devi Narayan Superspeciality Hospital, Kakryal, Katra, J&K.

[3]Research Scholar, School of Pharmaceutical Sciences, CT University, Ludhiana, Punjab.

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***Corresponding Author**
Dr. Shivam Choudghal
Clinical Pharmacologist, Shri Mata Vaishno Devi Narayan Superspeciality Hospital, Kakryal, Katra, J&K.

ABSTRACT

High blood pressure, often known as hypertension, is a major risk factor for cardiovascular conditions like heart disease and stroke. Although medication and lifestyle changes are the mainstays of conventional hypertension treatment, there is growing interest in investigating the possible advantages of nutraceuticals, or bioactive molecules obtained from natural sources, in the prevention and management of this condition. Numerous nutraceuticals, such as polyphenols, omega-3 fatty acids, vitamin C, vitamin E, minerals, and compounds derived from plants, have shown promise in reducing hypertension via mechanisms like vasodilation, antioxidant activity, and modulation of inflammatory pathways. Nutraceuticals offer a comprehensive and individualized strategy to support cardiovascular health and show potential as stand-alone or complementary treatment options in the management of hypertension. This article reviews the current state of research on various nutraceuticals and their role in hypertension prevention and treatment.

KEYWORDS: Hypertension, Omega-3 fatty acids, Coenzyme Q10, Garlic, Green tea, L-Arginine.

INTRODUCTION

High blood pressure, or hypertension, is a serious worldwide health concern that has far-reaching effects on general public health. It is a long-term medical condition marked by persistently elevated blood pressure that can cause major cardiovascular issues if neglected.[1] A significant section of the world's population suffers from hypertension, which is associated with a higher risk of heart disease, stroke, and kidney issues, among other illnesses.[2] A multimodal approach is required to treat hypertension, which involves lifestyle modifications and, in certain cases, pharmaceutical interventions.[3] Nutraceuticals are becoming more and more popular as a means of controlling hypertension because of their potential to improve cardiovascular health.[4] People of all ages, races, and socioeconomic status can suffer from hypertension, which is a common health problem. Because it is asymptomatic in the early stages, it is frequently referred to as a "silent killer" and its prevalence has been gradually rising. If hypertension is not addressed, it can result in major side effects like heart attacks, strokes, heart failure, and kidney issues.[5]

Hypertension is defined as when the diastolic blood pressure, which is the lower number, is consistently equal to or higher than 90 mm Hg, and/or the systolic blood pressure, which is the higher number, is consistently equal to or higher than 140 mm Hg.[6] There are two basic types of hypertension: primary (essential) hypertension, which has no known cause and is frequently linked to lifestyle variables and secondary hypertension, which is brought on by an underlying medical illness.[5][6]

In 1989, Stephen DeFelice, the founder and head of the Foundation for Innovation in Medicine, coined the word "nutraceuticals." "Food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease" is the definition of a nutraceutical.[7] Bioactive substances called nutraceuticals are extracted from plants and other natural sources and are thought to have positive health effects. They could be seen as a link between conventional diets and medications.[8] Nutraceuticals are a broad category of materials that are sold on the basis of their possible ability to improve health. These substances consist of dietary supplements, botanical extracts, vitamins, and minerals.[9] The potential of these drugs to prevent or treat chronic illnesses, such as cardiovascular conditions like hypertension, has been studied. They might be advantageous for several physiological systems.[10] The ability of nutraceuticals to complement traditional therapy for disorders like hypertension and other illnesses makes them important. Numerous nutraceuticals contain

bioactive ingredients that are vasodilatory, antioxidant, anti-inflammatory, and blood pressure regulators.[8,11]

PATHOPHYSIOLOGY OF HYPERTENSION

Controlling blood pressure is a multifaceted process involving several physiological systems. The following are the primary systems that control blood pressure:

- **Renin-Angiotensin-Aldosterone System (RAAS):** In order to maintain fluid balance and control blood pressure, this system is essential. Renin is an enzyme that the kidneys' specialized cells release when blood pressure drops. Angiotensinogen, which is made by the liver, is acted upon by renin to produce angiotensin I, which is then transformed into angiotensin II by the angiotensin-converting enzyme (ACE). Strong vasoconstrictor angiotensin II raises blood pressure and causes the hormone aldosterone to be released, which encourages the kidneys to retain water and salt.[10]

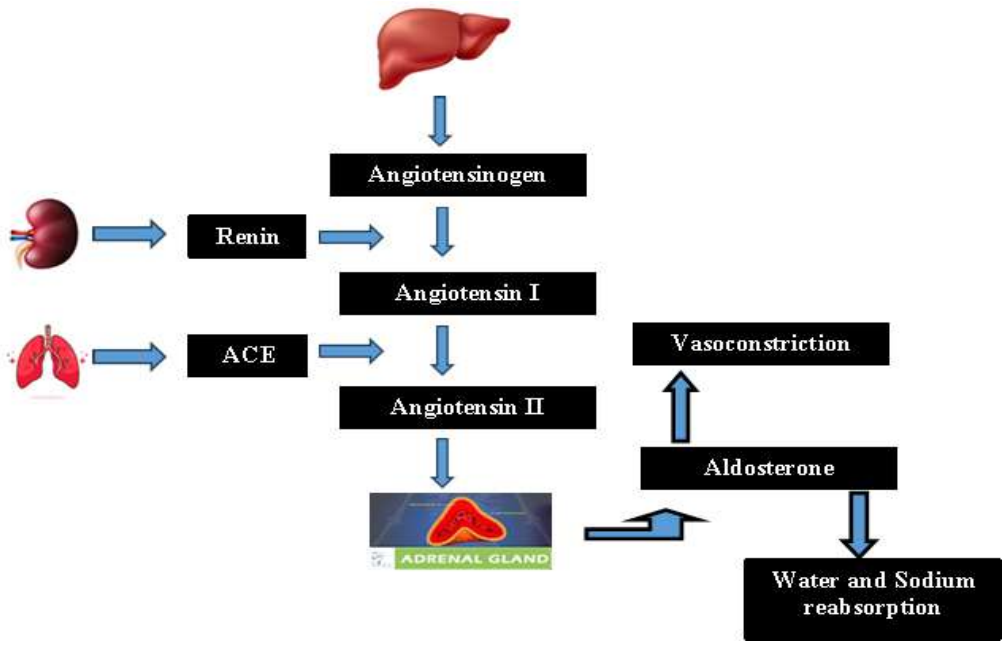

Figure 1: Renin-Angiotensin-Aldosterone System (RAAS).

- **Sympathetic Nervous System (SNS) Activation**: The "fight or flight" reaction is a function of the sympathetic nervous system. It raises blood pressure by causing vasoconstriction and an increase in heart rate.[11]
- **Baroreceptor Reflex:** Specialized sensors called baroreceptors are located in the walls of major arteries, such as the carotid arteries. These receptors detect changes in blood pressure and send signals to the brainstem, which then adjusts heart rate and blood vessel diameter to maintain stable blood pressure.[12]

- **Kidney Regulation:** Through their ability to regulate the amount of water and salt discharged in urine, the kidneys are essential in the long-term regulation of blood pressure. Renal function changes can affect blood volume and, in turn, blood pressure. The kidneys maintain extracellular fluid volume (ECFV) equilibrium by balancing salt and water, which in turn controls circulatory volume.[13]

ROLE OF LIFESTYLE FACTORS IN HYPERTENSION

Lifestyle plays a major role in the development and treatment of hypertension. Several important lifestyle elements include:

- **Physical Activity**: Exercise has been shown to have positive benefits on blood pressure, glucose homeostasis, blood lipids, body fatness, smoking behavior, and endothelial function, among other parameters, in randomized controlled trials and/or observational studies.[14] While some research found no significant independent connections, others came to the conclusion that participants who were fitter and more active had lower blood pressure.[15]
- **Smoking:** The key variables associated with smoking that determine the commencement and acceleration of the atherothrombotic process, which leads to cardiovascular events, include impaired endothelial function, arterial stiffness, inflammation, lipid modification, and an adjustment of prothrombotic and antithrombotic factors. Smoking cigarettes has an immediate hypertensive impact, mostly due to sympathetic nervous system activation.[16]
- **Stress**: Stress's effect on the development of hypertension is thought to be a result of a sympathetic nervous system reaction, in which elevated heart rate, cardiac output, and blood pressure are caused by the release of catecholamines. Although the sympathetic response to acute stress is well established, it is unclear how stress leads to long-term, persistent blood pressure increase. The development of hypertension may be caused by repetitive activation of this system, failure to recover to resting levels after stressful events, inability to become used to repeated stressors of the same kind, or a combination of these factors.[17]

DIET'S PART IN THE DEVELOPMENT OF HYPERTENSION

The diet can have a significant impact on the development of hypertension. Here are some food components that might affect blood pressure:

- **Dietary sodium intake**: In addition to lowering blood pressure and the prevalence of hypertension, a decrease in dietary salt is linked to a lower rate of morbidity and death

from cardiovascular illnesses. Irrespective of gender and ethnicity, a sustained, moderate decrease in salt consumption causes a significant drop in blood pressure in both hypertensive and normotensive people, with greater drops in systolic blood pressure associated with greater salt reductions.[18] High sodium consumption and elevated blood pressure are linked to various health issues such as water retention, elevated systemic peripheral resistance, modified endothelial function, altered structure and function of large elastic arteries, altered sympathetic activity, and autonomic neuronal modulation of the cardiovascular system.[19]

- **Potassium Intake**: Due to its vasodilatory effects on the peripheral vasculature and its role in promoting urine sodium excretion, which helps to maintain an optimum amount of circulating sodium, potassium is an important regulator of blood pressure.[20] Elevated blood pressure is independently linked to both low potassium and high sodium levels, thus lowering blood pressure with changes to either component alone.[21]
- **Zinc Intake**: Hypertension and coronary heart disease are linked to low blood zinc levels. By means of metallothionein, zinc is delivered to cardiac and vascular muscle as well as other tissues. Intramuscular zinc deficiency combined with metallothionein genetic deficiencies may result in abnormal cardiac remodelling, elevated oxidative stress, mitochondrial dysfunction, cardiomyocyte dysfunction, and apoptosis, which can then cause myocardial fibrosis, heart failure, or hypertension.[22]
- **DASH Diet**: Dietary Approaches to Stop Hypertension (DASH) eating plans plays an important role in maintaining and treating blood pressure.[23] More precisely, eating plenty of fruits, vegetables, whole grains, legumes, nuts, lean protein, and low-fat dairy products is encouraged by the DASH diet. It also emphasizes consuming minimal amounts of added sugar, salt, and saturated fat. Numerous research has examined the potential impact of adult population adherence to the DASH diet on the risk of hypertension, however the findings have been conflicting.[24][25]

Table 1: The Chart of DASH diet (Dietary Approaches to Stop Hypertension).

Food Group	Recommended Servings
Vegetables	4-5 servings per day
Fruits	4-5 servings per day
Grains	6-8 servings per day
Lean meats, poultry, fish	2 or fewer servings per day
Nuts, seeds, legumes	4-5 servings per week
Fat-free or low-fat dairy products	2-3 servings per day
Fats and oils	2-3 servings per day
Sweets	Limited, 5 servings or less per week

ANTIHYPERTENSIVE NUTRACEUTICALS

- **Garlic:** Garlic (Allium sativum) has long been valued for both its culinary and medicinal properties. Garlic is largely made up of water (65%) and carbohydrates such as fructose, sulfur compounds, proteins, and free amino acids.[26] Garlic's nutritional and therapeutic properties are attributed to the sulfur compounds it contains or produces. It has recently been proven that some of the cardiovascular advantages of garlic are attributable to the presence of allicin, also known as diallyl thiosulfinate and s-allyl cysteine.[27] Garlic is believed to lower blood pressure and oxidative stress since its components have been proven to suppress the transcription factors NF-κB and angiotensin converting enzyme while increasing the synthesis of the vasodilatory molecule nitric oxide and hydrogen sulfide. Studied conducted in the rats showed that garlic consumption in 2K1C rats was linked to decreased ACE activity in serum and other tissues, indicating that garlic's ability to lower blood pressure is partially mediated by its inhibition of ACE.[28] Third, in rat isolated pulmonary arteries, garlic and its active metabolite allicin have been demonstrated to cause a NO-dependent relaxation; this reaction was most likely mediated by garlic's promotion of NO formation.[29]
- **Omega-3 Fatty Acids:** In clinical experiments, omega-3 polyunsaturated fatty acids dramatically reduced blood pressure.[30] Compared to eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) is more efficient in lowering blood pressure and heart rate.[31] Fish oil and omega-3 fatty acids can boost NO production, decrease adrenal AT1R density and affinity (suppression of RAAS), change the salt transport system, lower aldosterone levels, and improve vasodilation by changing prostaglandins E1 and G1 Additionally, decrease blood viscosity (hypolipidemic activity), strengthen insulin sensitivity (because of its strong antioxidant, anti-inflammatory, and immunomodulatory qualities), and lessen arterial stiffness and resistance.[32] Fish oil supplementation (3.7 grams/day of EPA and DHA) decreased systolic blood pressure by 2.1 mm Hg and diastolic blood pressure by 1.6 mm Hg, according to the findings of meta-analyses of 36 randomized clinical studies. A meta-analysis of 70 randomized controlled studies showing a decrease in blood pressure, 4.51 mmHg systolic and 3.05 mmHg diastolic, and resistance was conducted using EPA at a mean dose of 3.9 grams per day.[33]
- **Coenzyme Q10:** Co-enzyme Q-10, also known as ubiquinone, is a powerful antioxidant in the lipid phase, a free radical scavenger, an oxidative stress reducer, a regenerator of other vitamins and antioxidants, a cofactor and coenzyme in mitochondrial oxidative

phosphorylation, which lowers blood pressure.[34] Because of its strong anti-inflammatory and powerful capacity to scavenge free radicals, Co Q10 is a naturally occurring lipid phase antioxidant that also increases NO availability, which enhances endothelial function. Moreover, it suppresses renal SNS, increases Na+ and H2O excretion, and modifies RAAS by lowering catecholamine synthesis. Furthermore, it enhances the heart's ability to produce ATP, which lessens the effects of cardiac overload.[35] According to a meta-analysis by Rosenfeldt and colleagues, supplementing with Co Q10 may help hypertension patients' SBP drop by up to 17 mmHg and their DBP drop by up to 10 mmHg. The study included 12 clinical trials with 362 participants.[36]

- **Green Tea:** Green tea has a high concentration of catechins, particularly epigallocatechin-3-gallate (EGCG), which has been linked to a number of health benefits, including the ability to prevent diabetes, fight obesity, fight infection, fight cancer, and lower blood pressure.[37] It has been demonstrated that it increases the expression of eNOS, leading to increased NO generation. It also modifies the synthesis of PGE1, which enhances endothelial function. In addition to its strong ACE inhibitory effects, green tea raises GABA and modifies SNS to regulate blood pressure. In addition, it has potent anti-inflammatory and antioxidant (inhibit NADPH oxidase activity) qualities to improve vascular function. Peng et al. did a meta-analysis which revealed that consuming green tea on a regular basis might significantly lower average SBP (-1.98 mmHg) and DBP (-1.92 mmHg) in comparison to the control group.[38]
- **Beetroot juice:** Beetroot's active compounds, betaine and betalain (betacyanins), are in charge of the plant's numerous biological characteristics.[39] One of the greatest natural sources of nitrate, or nitric oxide, beetroot improves performance and lowers blood pressure. After being broken down from inorganic nitrate (NO3), active nitrite (NO2) is produced. This NO2 circulates in the circulation, transforms into functional nitric oxide (NO), and lowers HT by protecting vascular endothelium from ROS-dependent damage. Beetroot juice, which is high in nitrate, directly promotes vasodilation by increasing endothelium's availability of NO. Furthermore, because NO is a strong antioxidant, it might lessen inflammatory responses and endothelial oxidative stress, which will enhance endothelium and vascular function.[40]
- **L-Arginine:** Among the well-liked anti-hypertensive supplements, L-arginine was frequently utilized in the DASH diet or in conjunction with conventional anti-hypertensive medications to treat hypertension and its associated problems. This amino

acid functions as a precursor to nitric oxide.[41] Numerous clinical investigations have demonstrated that administering L-arginine intravenously or orally to normal and hypertensive people lowers homocysteine levels, improves endothelial function, and leads in a slight drop in blood pressure.[42] L-arginine has also been linked to increased immunity, growth hormone release, and decreased atherosclerosis. Human consumption of L-arginine is thought to be between 3 and 6 grams per day, with 20 grams per day as safe limit. Since L-arginine is a substrate for NO synthesis, it is theoretically possible to increase the production of NO, enhance blood vessel function, and decrease blood pressure by taking supplements of L-arginine.[43] In contrast to a placebo, Dong and colleagues found that oral L-arginine therapy administered for 2–12 weeks at a dosage of 4–24 g/day may significantly reduce the mean levels of SBP (-5.39 mmHg) and DBP (-2.66 mmHg).[44]

- **Vitamin B6:** hypertension is linked to low blood levels of vitamin B6, or pyridoxine. For four weeks, those receiving 5 mg/kg/day of vitamin B6 had an 8.4% reduction in blood pressure. In addition to increasing the synthesis of glutathione to neutralize aldehydes, blocking calcium channels, improving insulin resistance, lowering central sympathetic tone, and lessening end organ sensitivity to glucocorticoids and mineralocorticoids, Thus, vitamin B6 functions similarly to CCBs, diuretics, and central a-agonists. The suggested dosage is 200 mg taken orally as a supplement each day.[45]
- **Grape and its related products:** For blood pressure regulation, resveratrol and grape seed polyphenols (GSP) are strongly advised. Anthocyanins, flavanols, and phenolic acids are components of GSP, which have been shown to have cardioprotective effect by enhancing NO bioavailability, hypolipidemic activity, antiplatelet activity, and improved insulin sensitivity.[46] The meta-analysis, which included 247 participants from 8 clinical studies, found that those who took a high dose of resveratrol (>300 mg) saw a substantial drop in their SBP levels (-11.90 mmHg) but not their DBP.[47]
- **Onion:** Allium cepa (onion) nutraceutical formulations are recommended for the treatment of a number of acute and chronic illnesses.[48] The effects of a quercetin-rich onion skin extract on 24-hour ambulatory blood pressure and endothelial function in overweight-to-obese patients with pre-hypertension were assessed in a 12-week treatment period followed by a 6-week washout period. The trial included sixty-eight subjects (thirty-four males and thirty-four females) and was double-blinded, placebo-controlled, and cross-over. The results of this study indicate that quercetin (162 mg/day) from onion

skin extract supplements decreases ambulatory blood pressure in hypertension patients, indicating quercetin's potential cardioprotective impact.[49]

- **Soyabean:** One of the most often consumed leguminous foods is soybean (Fabaceae family), which has a number of biological benefits, most notably an anti-hypertensive effect. It contains isoflavones, peptides and phytoestrogens.[50] Numerous studies have demonstrated the considerable anti-hypertensive effect of soybean food items (milk peptide, isoflavones), which also significantly control RAAS (GABA), enhance vascular width (vasodilator), and increase NO generation.[51] In a meta-analysis study comprising 14 RCTs, Taku et al. found that daily use of soy isoflavones (25-375 mg) for 24 weeks significantly decreased SBP (-1.92 mmHg) in normal and prehypertensive subjects without affecting DBP when compared with placebo.[52]

Table 2: Nutraceuticals with their mechanism of action.

Nutraceutical	Mechanism of Action in Hypertension
Omega-3 fatty acids (e.g., fish oil)	Increasing the synthesis of nitric oxide causes vasodilation. anti-inflammatory properties, alteration in the blood lipid composition
Coenzyme Q10	characteristics of antioxidants, augmentation of endothelial function Potential reduction in blood pressure
Garlic extract	Increased nitric oxide leads to vasodilation; antioxidant and anti-inflammatory properties; and possible ACE inhibitor-like activity
Magnesium	Smooth muscle relaxation-induced vasodilation, calcium influx modulation, enhanced endothelial performance
Potassium	Control of the sodium-potassium balance and vasodilation through the encouragement of relaxed smooth muscle
Green tea extract	Benefits of antioxidants and anti-inflammatory agents, A possible ACE inhibitor-like effect on the modulation of endothelial function
Resveratrol (found in grapes)	Effects of antioxidants and anti-inflammation Vasodilation via the generation of nitric oxide

FORMULATION AND CHALLENGES INVOLVED

Nutraceuticals can be challenging to formulate due to their high melting point, low water solubility, and chemical instability of the active ingredients. For instance, although they are poorly soluble, curcumin, oil-soluble vitamins and omega-3 fatty acids have great nutritional significance. Therefore, developing them as innovative delivery methods is one feasible strategy. They are expensive due to these unique distribution methods. Therefore, efforts are required to reduce the cost of these formulations.[53] Numerous difficulties arise in creating a high-quality nutraceutical formulation that is safe, safe enough, technically feasible, and economically affordable. Botanicals are complex components having various chemical elements; often, a single product contains several classes of chemicals, in contrast to

medication molecules, which are well-defined chemical entities. The majority of these plants can tolerate high humidity, heat, light, oxygen, and an alkaline pH. These often have a fluctuating particle size distribution, low bulk density, and poor flow. Therefore, understanding the fundamentals of the physicochemical properties of the various ingredient types, using suitable manufacturing techniques, choosing the appropriate excipients, and adding appropriate manufacturing overages based on critical stability studies are all necessary for the successful development of nutraceutical formulation.[54]

CONCLUSION

In conclusion, nutraceuticals show promise in the management and prevention of hypertension. Research is mounting to support the idea that certain of the bioactive substances included in nutraceuticals may help control blood pressure and improve cardiovascular health in general. Although they shouldn't take the place of traditional medical care, nutraceuticals can enhance current therapy and offer new advantages.

Several studies have shown that nutraceuticals, including garlic extract, Coenzyme Q10, omega-3 fatty acids, and other polyphenols, can lower blood pressure. These substances have anti-inflammatory, antioxidant, and vasodilatory qualities that improve vascular health and support normal blood pressure.

Moreover, lowering the risk of hypertension can be achieved by include nutraceuticals and a balanced diet high in whole foods. Nutraceutical intake is closely aligned with the Dietary Approaches to Stop Hypertension (DASH) diet, which places an emphasis on fruits, vegetables, lean meats, whole grains, and low-fat dairy. This dietary plan can be a part of a holistic approach to avoid hypertension, combined with the prudent use of nutraceutical supplements. Still, there are issues with dosage calculation, quality assurance, and standardization for nutraceuticals. It is necessary to create rules and regulations to guarantee the effectiveness and security of these items. Furthermore, individual reactions to nutraceuticals might differ, which emphasizes the importance of customized treatment plans.

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