Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Nutraceutical Interventions for Hypertension: A Comprehensive Review of Current Evidence

Yusra Ahmad[1], Hiba Parveen[1*], Arati Tamta[2], Yogita Tyagi[3], Pragati Bailwal[1], Nahid Parveen[1], Gauri Shankar[1], Chetan[4], Muhammad Murtaza[5]

[1*]Faculty of Pharmacy, Veer Madho Singh Bhandari Uttarakhand Technical University, Dehardun

[2]School of Health Sciences, Quantum University, Roorkee - Dehradun Highway, Mandawar, Roorkee, Uttarakhand

[3]Uttaranchal Institute of Pharmaceutical Sciences (UIPS), Uttaranchal University, Dehradun

[4]Nims Institute of Pharmacy, NIMS University Rajasthan Jaipur

[5]Glocal University Pharmacy College, Glocal University Saharanpur

Corresponding author

Hiba Parveen

Assistant Professor, Faculty of Pharmacy, Veer Madho Singh Bhandari Uttarakhand Technical University, Dehardun

Email ID: hibaparveen52@gmail.com

Cite this paper as: Yusra Ahmad, Hiba Parveen, Arati Tamta, Yogita Tyagi, Pragati Bailwal, Nahid Parveen, Gauri Shankar, Chetan, Muhammad Murtaza, (2025) Nutraceutical Interventions for Hypertension: A Comprehensive Review of Current Evidence. *Journal of Neonatal Surgery*, 14 (32s), 1378-1386.

1. INTRODUCTION

Hypertension, also known as high blood pressure, is a chronic medical condition in which the force of the blood against the walls of the arteries is consistently too high [1]. It is one of the major risk factors for cardiovascular diseases, including heart attacks, strokes, and kidney disease [2]. Hypertension is often referred to as a "silent killer" because many people with it do not experience symptoms, even when their blood pressure reaches dangerous levels. Blood pressure is measured in millimeters of mercury (mm Hg) and recorded as two numbers [3].

Hypertension, or high blood pressure, is a condition where the force of the blood against the artery walls is consistently too high [4]. It is measured using two numbers: systolic pressure, the top number, which indicates the pressure in the arteries when the heart beats, and diastolic pressure, the bottom number, which reflects the pressure in the arteries when the heart is at rest between beats [5]. A normal blood pressure reading is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Blood pressure is considered elevated when the systolic pressure is between 120–129 mm Hg and the diastolic remains under 80 mm Hg [6]. Hypertension Stage 1 is diagnosed when the systolic pressure ranges from 130–139 mm Hg or the diastolic pressure is between 80–89 mm Hg [7].

Although hypertension is often referred to as a "silent killer" due to its lack of symptoms, in some cases individuals may experience signs such as severe headaches, shortness of breath, nosebleeds, vision problems, chest pain, or dizziness [8]. These symptoms usually occur when blood pressure reaches dangerously high levels. Diagnosis is commonly made using a blood pressure monitor, and to confirm hypertension, multiple readings over time are typically required [9]. Additional tests may be conducted to identify any underlying conditions or damage caused by high blood pressure. These can include blood tests to detect issues like kidney disease, urine tests to check for kidney problems, and an electrocardiogram (ECG) to assess the heart's function. Early detection and management are essential to prevent serious complications such as heart disease, stroke, and kidney failure [10].

Nutraceuticals

The term "nutraceuticals" was introduced by Stephen defelice, founder and chairman of the Foundation for Innovation in Medicine, in 1989 [11]. A nutraceutical is defined as a "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease [12].

The definition encompasses medicinal products made from natural ingredients. Several classes of nutraceuticals have been proposed to have potential benefits in the treatment of CVD and the ones with the strongest evidence are briefly summarized below [13]

Sterols/stanols

Plant sterols/stanols are phytosterols, and have been identified in a range of plant products including various fruits and vegetables, cereals, seeds and nuts. Their biological activity results from their molecular structural similarity to cholesterol

[15].

Polyphenols

Polyphenols are phytochemicals with widespread distribution in foods of plant origin. They are found in fruits, vegetables, cereal and legumes. Additionally, they are found in beverages produced from plant products such as tea, coffee, wine and cocoa. Polyphenols are structurally diverse, and over 8,000 have been identified. These include flavonoids, phenolic acids, stilbenes and lignans [16].

Polyphenols found in grapes and grape derivatives, cocoa and tea are of interest in the prevention of CVD [17]. Phenolic compounds are found in grapes and these include anthocyanins, flavanols, flavonol, stilbenes and phenolic acids [18].

Resveratrol (3,5,4‟-trihydroxy-trans-stilbene) is the most extensively studied grape-derived stilbene contained mainly in grapes. However, resveratrol is common to a variety of species including cranberries, blueberries, peanuts, and Japanese knotweed [19].

Derivatives of cocoa beans (Theobroma cacao) are widely consumed in cocoa and chocolate. A variety of polyphenols have been identified in cocoa and its derivative. These include catechins, flavonol glycosides, anthocyanins and procyanidins. Cocoa-containing foods provide a higher content of flavonoids per serving than other beverages such as red wine and tea [20].

The very widespread and frequent consumption of tea makes investigation of its nutraceutical propertied essentials. Polyphenols found in tea include catechins, theaflavins, tannins, and flavonoids. The degree of fermentation of tea leaves influences the chemical composition. Green tea, which is minimally fermented, contains more catechins such as epigallocatechin gallate, epicatechin-3-gallate, epigallocatechin and epicatechin whereas the more extensively fermented black tea is rich in flavins and thearubigins [21, 22, 23].

Spirulina

Spirulina is a blue-green microalga (Cyanobacterium). Spirulina is a rich source of protein, vitamins, minerals, carotenoids, and phycocyanins and has a very long history of use as a human foodstuff with no apparent concerns over safety [24].

Dietary interventions such as reducing dietary sodium, dietary approaches to stop hypertension (DASH), and Mediterranean diet have been considered the mainstay treatment of BP, lipid levels and CV events (Dickinson et al., 2006a, Doménech et al., 2014, Estruch et al., 2013). Extensive body of literature has reported beneficial effects of functional foods and nutraceuticals as adjunctive therapies to pharmacotherapy for treating HTN (Fitzpatrick, 2004, Shaterzadeh-Yazdi et al., 2017) [25].

The concept of “nutraceutical” is the hybrid of „nutrition‟ and „pharmaceutical‟ which was coined by Dr. Stephen L. Defelice, MD, the founder and chairman of the Foundation for Innovation in Medicine (FIM), (Cranford, in 1989 for the first time) (Das, Bhaumik, Raychaudhuri, & Chakraborty, 2012). The term “nutraceuticals” evolved over the years and the terminology varies across countries. This term can be defined as “a food (or a part of food) that provides medical or health benefits, including the prevention andor treatment of a disease” (Dillard and German, 2000, Olas, 2018) [26].

“[A food] consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions” (Chumphukam et al., 2019). In general, nutraceuticals as natural functional/medical foods or bioactive phytochemicals are substances derived from foods and used in the medicinal forms of pills, capsules, potions and liquids, which provide physiological benefits or protect against chronic disease (Kailasapathy, 2009). According to a recent cross-sectional study, 82.5% of CV patients used nutraceuticals as a health promoting activity (Aykan & Aykan, 2018) [27].

Categories of Nutraceuticals:

Categories of nutraceuticals and their role in hypertension

The mechanism of action and chemical nature of nutraceuticals can be considered for their classification. The BP lowering nutraceuticals can be categorized as foods (i.e., tea and cocoa), nutrients (i.e., magnesium, calcium, vitamin C, omega 3 polyunsaturated fatty acids (pufas), soluble fibers) and non-nutrient nutraceuticals (i.e., coenzyme Q10, lycopene, prebiotics) [28].

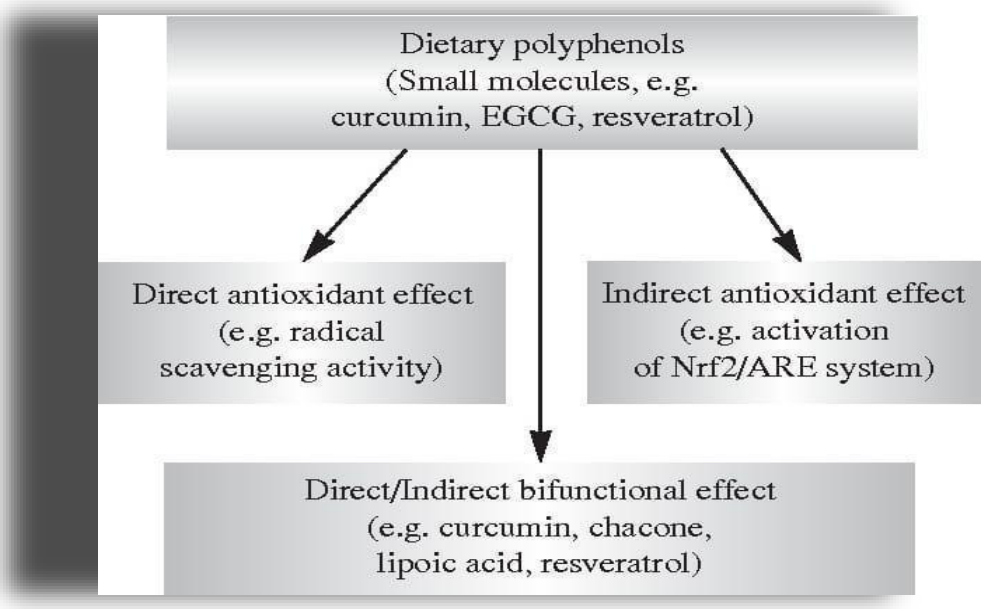

FIGURE: Mechanism of Action of Polyphenols

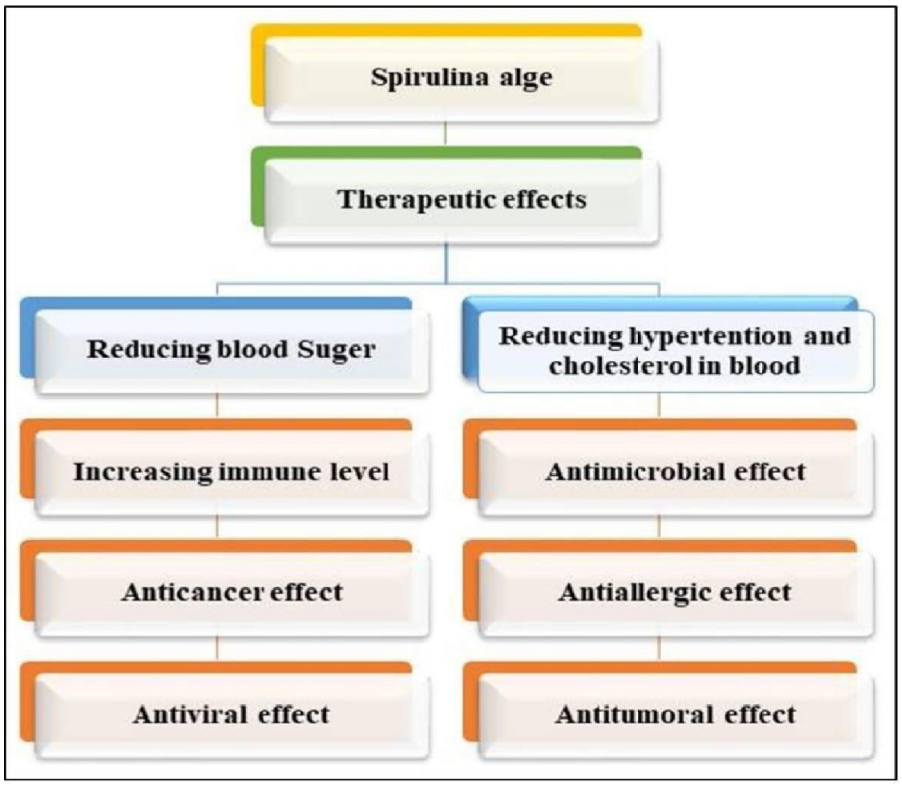

Fig. 1.2: Mechanism of Spirulina

Various relevant studies

Grosso G et al (2018) states that tested the association between total and individual classes of dietary polyphenols and incidence of hypertension in the Polish arm of the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study. The highest quartile of total polyphenol intake was associated with 31% decreased risk of hypertension compared with the lowest intake (OR 0.69, 95% CI 0.48, 0.98) in women. There was no significant association in men. Among main classes of polyphenols, flavonoids and phenolic acids were independent contributors to this association [29].

Dan liao et al. (2018) states that Spirulina is generally used as a nutraceutical food supplement dueto its nutrientprofile, lack of toxicity, and therapeutic effects. Clinical trials have investigated the influenceof spirulina on metabolic-related risk factors but have yielded conflicting results in humans [30].

M. Suzulinska et al. (2017) states that Spirulina maxima consumption is known to be associated with enhanced cardiovascular and metabolic health. Human studies on this topic have recently been described in a few papers; however, Spirulina supplementation consider-ably improved total antioxidant status (TAS; $p = 0.001$) and insulin sensitivity ratio (M; $p < 0.001$) in Spirulina group compared to placebo-treated individuals.

Afjal Shamsi et al. (2017) states that Hypertension affects many aspects of the patients‟ life. Factors such as attitudes, beliefs and experiences, and social and cultural conditions of patients have effective roles in hypertension treatment process. The aim of this research was to explore perspectives and experiences of patients with hypertension while living with this disease [31].

Miranda AM et al (2016) states that evaluated the association between the intake of polyphenols and hypertension in a general population of Sao Paulo. Polyphenol intake was calculated by matching food consumption data from the 24HR with the Phenol-Explorer database. The associations between the hypertension and tertiles of the total and classes of polyphenols intake were tested by multivariate logistic regression analysis. After multivariate adjustment for potentialconfounding factors the findings showed an inverse and linearly association between the hypertension and highest tertiles of tyrosols (OR = 0.33; 95%CI 0.18, 0.64), alkylphenols (OR = 0.45; 95%CI 0.23, 0.87), lignans (OR = 0.49; 95%CI 0.25, 0.98), as well as stilbenes (OR = 0.60; 95%CI 0.36, 0.98), and other polyphenols (OR = 0.33; 95%CI 0.14, 0.74). However, total polyphenol intake, and phenolic acids were significantly associated only in the middle tertile with hypertension and flavonoids were not significant associated.

Tjelle TE et al (2015) states that tested whether consumption of two polyphenol-rich juices could lower BP. They found out that the variation in the BP measurements was significantly reduced in the pooled juice group compared with the placebo group (1•4 and 1•7 mmhg; P= 0•03). Feindings suggesdt that polyphenol-rich berry juice may contribute to a BP- and BP variability lowering effect, being more pronounced in hypertensive than in normotensive subjects.

Domnico Fotino et al. (2013) states that Coenzyme Q10 (CoQ10; also called ubiquinone) is an antioxidant that has been postulated to improve functional status in congestive heart failure (CHF). Several randomized controlled trials have examined the effects of CoQ10 on CHF with inconclusive results.

Young JM et al (2012) states that examined the effects of adjunctive coenzyme Q10 therapy on 24-h ambulatory blood pressure (BP) in subjects with the metabolic syndrome and inadequate BP control. They found that when compared with placebo, treatment with coenzyme Q10 was not associated with statistically significant reductions in systolic (P = 0.60) or diastolic 24-h ambulatoryBP (P = 0.12) or heart rate (P = 0.10), although daytime diastolic BP loads, were significantly lowerduring coenzyme Q10 administration with thresholds set at >90 mm Hg (P = 0.007) and ≥85 mm Hg(P = 0.03).

A .Selen Gurkan et al (2005) states that coenzyme Q10 (CoQ10) is an essential cofactor of the electron transport chain which plays a pivotal role to supply energy for chemical reactions in the body, and a lipophilic antioxidant component of the lipid membranes that surround all cells and thevarious organelles such as microsomes and mitochondria. Even though the antioxidants are produced by the body, their blood level is reduced by aging.

James M. Roberts et al. (2003) states that Hypertension in Pregnancy was recently convened by the National Heart, lungs and Blood Institute to determine the state of knowledge in this area and suggest appropriate directions for research. Hypertensive disorders in pregnancy, especially preeclampsia, are a leading cause of maternal death worldwide

The inflammation

Both cross-sectional and longitudinal investigations have proposed a connection between inflammation and hypertension [32]. In hypertension and hypertensive-related TOD, such as elevated carotid IMT, there are increases in high sensitivity C-reactive protein (HS-CRP) and other inflammatory cytokines such interleukin-1B (IL-1B), IL-6, tumor necrosis alpha (TNF-α), and chronic leukocytosis [33]. Future CV occurrences are predicted by HS-CRP [32, 33]. For hypertension and CVD, elevated HS-CRP is a risk factor as well as a risk marker [34, 35]. Blood pressure may rise in a few of days in direct proportion to an increase in HS-CRP of more than 3 µg/mL [34, 35]. HS-CRP inhibits nitric oxide and eNOS [34, 35]. HS-CRP down-regulates the AT2R, which typically balances the AT1R [34, 35]. Vasoconstriction results from angiotensin II's (A-II) activation of nuclear factor Kappa B (NF-κB), which upregulates several cytokines, including IL-6, CAMs, and chemokines. These occurrences raise blood pressure, as do increases in endothelin-1 and oxidative stress [32].

Immune system dysfunction

Cytokine generation, central nervous system stimulation, and kidney damage are the three main ways that innate and adaptive immune responses are connected to hypertension and hypertension-induced CVD. This comprises chronic leukocytosis with elevated neutrophils and decreased lymphocytes, dysregulation of CD4+ and CD8+ lymphocytes, and salt-sensitive

hypertension with elevated renal inflammation due to T cell imbalance [36–38]. Blacks' blood pressure rises by 6/2 mmHg in the highest tertile compared to the lowest due to leukocytosis, particularly elevated neutrophils and reduced lymphocyte count [38]. Numerous T-cell subtypes and macrophages control blood pressure, penetrate artery walls, trigger TLRs, and cause autoimmune vascular injury [38, 39]. T cells, macrophages, and dendritic cells are among the immune cells that are activated by angiotensin II, which also encourages cell infiltration into target organs [39]. CD4+ T lymphocytes express AT1R and PPAR gamma receptors, and release TNF-α, interferon and interleukins within the vascular wall when activated[39] (Figure 5). T cell-produced IL-17 may be essential to the development of angiotensin II-induced hypertension [39]. TLR 4 mRNA in monocytes is noticeably greater in hypertensive patients than in healthy individuals [40]. The TLR 4 is lowered more when blood pressure is drastically reduced to systolic blood pressure (SBP) of less than 130 mmHg as opposed to SBP of just 140 mmHg [40]. TLR expression is activated by A-II, which causes inflammation and innate immune system activation. TLR 4 activation results in vascular remodeling, collagen buildup in the artery, LVH, cardiac fibrosis, migration, downstream macrophage activation, and an increase in metalloproteinase 9 [40]. Inflammation and immunological dysfunction may be either increased or decreased by the autonomic nervous system [41]. The spleen, nicotinic acetylcholine receptor subunits, and immune cells that produce cytokines are innervated by efferent cholinergic anti-inflammatory pathways via the vagal nerve, which affect vasoconstriction and blood pressure [41]. Vascular inflammation and hypertension may be mediated by local CNS ischemia or inflammation [39].

Over thirty inflammatory genes are modulated by aldosterone, which is linked to enhanced adaptive immunity and autoimmune responses, CD4+ T cell activation, and Th 17 polarization with elevated IL 17, TGF-β, and TNF-α [42, 43]. Through both non-hemodynamic effects and elevated blood pressure, elevated serum aldosterone is a risk factor for CVD and CHD on its own [42, 43]. Even when hypertension persists, CV risk is decreased by blocking mineralocorticoid receptors in the heart, brain, blood vessels, and immune cells [42, 43].

Table 1: Natural Antihypertensive Compounds by Class

Antihypertensive Class	Natural Compound	Source	Key Reference (APA Format)
ACE Inhibitors	Peptides from garlic	*Allium sativum*	Ried et al. (2013). *BMC Cardiovasc Disord.* 13, 13.
Calcium Channel Blockers	Resveratrol	Grapes, berries	Magyar et al. (2012). *Oxid Med Cell Longev.* 2012, 646282.
Diuretics	Hibiscus tea polyphenols	*Hibiscus sabdariffa*	McKay et al. (2010). *J Nutr.* 140(2), 298–303.
Beta-Blockers	Omega-3 fatty acids	Fish oil, flaxseed	Miller et al. (2014). *Am J Hypertens.* 27(7), 885–896.
Vasodilators	Nitrates (beetroot juice)	*Beta vulgaris*	Kapil et al. (2015). *Hypertension.* 65(2), 320–327.
Angiotensin II Antagonists	Quercetin	Apples, onions	Larson et al. (2012). *J Med Food.* 15(1), 71–77

Dietary Strategies to Prevent Hypertension

In individuals with borderline and stage I hypertension, the Dietary Approaches to Stop Hypertension (DASH) I and II diets clearly showed a substantial decrease in blood pressure [44, 45]. Untreated hypertension patients with SBP < 160 mmHg and DBP 80-95 mmHg were assigned to one of three diets for four weeks while participating in DASH I: the control diet, the fruit and vegetable diet (F + V), or a combination diet that included F + V and low-fat dairy [44]. In each group, DASH II introduced increasing sodium restriction [45]. The control diet had a sodium/potassium ratio of 1.7, fiber at 9 g/d, macronutrients at 4 servings daily, potassium, magnesium, and calcium at 25% of the US average, and sodium at 3 g/d. With a sodium-to-potassium ratio of 0.7, 31 g of fiber, 8.5 servings of fruits and vegetables per day, potassium, magnesium, and calcium levels rose to 75%, and macronutrients were higher than the US average thanks to the F + V diet. With the addition of low-fat dairy, the combined diet resembled the F + V diet. At two weeks, the hypertensive individuals in DASH I saw a drop in blood pressure of 10.7/5.2 mmHg, whereas those in DASH II experienced a decrease of 11.5/6.8 mmHg. As long as the patients followed the diet, these decreases continued. In reaction to the drops in blood pressure, the DASH diet raises serum aldosterone levels and plasma renin activity (PRA) [46, 47]. The average daily rise in PRA was 37 ng/mL [47]. The beta 2 adrenergic receptor's G46A polymorphism was linked to a response. G46A's A allele suppressed PRA and aldosterone

and reduced blood pressure more. The GG genotype did not respond, but the arachidonic acid (AA) genotype did. By blocking the rise in PRA, adding an ARB, ACEI, or DRI enhanced the GG group's blood pressure response to the DASH diet. In salt-sensitive individuals, a low-sodium DASH diet improves vascular function (augmentation index), lowers blood pressure, and reduces oxidative stress (urine F2-isoprostanes) [48]. Furthermore, after week two of the DASH diet, pulse wave velocity dropped and plasma nitrite rose [49].

Na+ (sodium) decrease

The US consumes 5000 mg of salt per day on average, with other regions eating 15000–20,000 mg [50]. Nonetheless, 500 mg/d of salt is most likely the least need [50]. Increased salt consumption is linked to higher blood pressure, as well as an increased risk of cardiovascular disease, cerebrovascular accidents, LVH, CHD, MI, renal insufficiency, proteinuria, and excessive SNS activity, according to epidemiologic, observational, and controlled clinical studies [1,50]. In hypertensive patients, particularly those who are salt sensitive, cutting down on sodium consumption will dramatically drop blood pressure by 4-6/2-3 mmHg, which is proportionate to the extent of sodium restriction. In high-risk individuals, it may also prevent or postpone hypertension and lessen the risk of future cardiovascular events [51–53].

Synergistic Effects of Nutraceuticals and Antihypertensive Therapies

Strategic combinations of specific nutrients with antihypertensive medications have demonstrated enhanced blood pressure control compared to pharmacotherapy alone. Clinically validated pairings include: (1) sesame with β-blockers, diuretics, or nifedipine; (2) Pycnogenol® with ACE inhibitors or calcium channel blockers; (3) lycopene with ACE inhibitors, calcium antagonists, or diuretics; (4) alpha-lipoic acid with ACE inhibitors or acetyl-L-carnitine; (5) vitamin C with calcium channel blockers; (6) N-acetylcysteine with arginine; (7) garlic with ACE inhibitors, diuretics, or β-blockers; (8) coenzyme Q10 with ACE inhibitors or calcium channel blockers; (9) taurine with magnesium; and (10-11) potassium or magnesium with all antihypertensive classes.

However, many antihypertensive agents may induce nutrient deficiencies that can compromise therapeutic efficacy or cause adverse metabolic effects. Diuretics, for instance, deplete potassium, magnesium, phosphorus, zinc, and coenzyme Q10 while potentially elevating glucose and homocysteine levels. Similarly, β-blockers reduce coenzyme Q10, and ACE inhibitors/ARBs decrease zinc availability.

The vascular endothelium and vascular smooth muscle cells play pivotal roles in hypertension pathogenesis and related cardiovascular disorders. Nutrigenomic interactions and epigenetic modifications significantly influence cardiovascular health, with dietary components exerting protective effects through multiple vascular mechanisms. Oxidative stress, inflammation, and immune dysregulation contribute substantially to hypertension development. Evidence supports the targeted use of specific nutraceuticals - including vitamins, antioxidants, and minerals - as adjuncts to conventional therapy, provided they complement balanced nutrition and lifestyle modifications.

A comprehensive clinical approach should integrate evidence-based nutrition, regular physical activity, weight management, smoking cessation, and moderation of alcohol/caffeine intake alongside pharmacological interventions for optimal hypertension management. This multimodal strategy can be effectively implemented in routine clinical practice to improve patient outcomes

2. CONCLUSION

Nutraceuticals interventions show promising potential as adjuncts to conventional antihypertensive therapy, enhancing blood pressure control through multiple mechanisms, including oxidative stress reduction, improved endothelial function, and nutrient replenishment. Key compounds like garlic, omega-3 fatty acids, coenzyme Q10, and potassium demonstrate clinically relevant effects. However, variability in study designs and patient responses necessitates further high-quality trials to standardize dosing and efficacy. A personalized approach—integrating evidence-based nutraceuticals with lifestyle modifications and pharmacotherapy—may optimize hypertension management. Clinicians should consider potential drug-nutrient interactions while tailoring treatments to individual patient needs for improved cardiovascular outcomes.

Acknowledgement

I would share my gratitude to my co-authors for their timely contribution.

Conflict of interest

No Conflict of interest

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