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REVIEW

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A review of gut microbial metabolites and therapeutic approaches in hypertension

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Abstract

Background Hypertension is a prevalent and complex disease that is increasingly recognized to be influenced by the gut microbiome and its metabolites. Understanding the relationship between gut microbial metabolites and blood pressure regulation could provide new therapeutic avenues.

Main body This review examines the role of key microbial metabolites—short-chain fatty acids, trimethylamine N-oxide, tryptophan derivatives, polyamines, bile acids, and phenylacetylglutamine—in blood pressure regulation. Short-chain fatty acids, produced through dietary fiber fermentation, can lower blood pressure by modulating immune responses and reducing inflammation. Elevated trimethylamine N-oxide levels are associated with increased cardiovascular risk and hypertension, influencing cholesterol metabolism and promoting atherosclerosis. Tryptophan derivatives interact with vascular and renal functions to modulate blood pressure. Polyamines affect blood pressure regulation through their impact on nitric oxide synthesis and vascular tone. Bile acids influence blood pressure via gut microbiota modulation and activation of metabolic receptors. Phenylacetylglutamine has been linked to hypertension through its effects on platelet hyperactivity and thrombosis. Therapeutic approaches targeting these metabolites, including probiotics, prebiotics, fecal microbiota transplantation, dietary interventions, and polyphenols, have shown varying degrees of success. Probiotics and prebiotics promote the growth of beneficial gut bacteria and may lower blood pressure. Dietary interventions, such as the Mediterranean diet, positively affect blood pressure and cardiovascular health by modulating the gut microbiota. Polyphenols, known for their antioxidant properties, are associated with blood pressure reductions and improved vascular function. Fecal microbiota transplantation shows promise in restoring gut microbial balance and improving metabolic health, potentially influencing blood pressure regulation.

Conclusion The review highlights the significant role of gut microbial metabolites in regulating blood pressure, offering new avenues for hypertension management. Key metabolites, including short-chain fatty acids, trimethylamine N-oxide, and bile acids, play critical roles in blood pressure modulation. Therapeutic strategies targeting these metabolites, such as probiotics, prebiotics, and dietary interventions, hold promise, though further research is needed to fully understand their mechanisms and optimize their use. Advancing microbiota-based interventions through large-scale studies and exploring personalized therapies will be essential for developing effective treatments in hypertension management.

Keywords Gut microbial metabolites, Hypertension, Probiotics, Prebiotics, Diet, Polyphenols, Fecal microbiota transplantation

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Background

Hypertension, or high blood pressure, is a major public health concern globally. It is a significant risk factor for cardiovascular diseases and a leading cause of mortality and morbidity. The World Health Organization reports that approximately 1.28 billion people worldwide suffer from hypertension, with a significant number residing in low- and middle-income countries where awareness, treatment, and control are suboptimal (Available from 2023). Despite the availability of numerous antihypertensive drugs, many patients remain inadequately controlled, highlighting the need for novel therapeutic approaches (Ghatage et al. 2021). Recent research has illuminated the potential role of the gut microbiome in influencing blood pressure (BP) regulation.

There is a lot of data regarding the functions microorganisms play in human health and disease. Certain bacteria form symbiotic relationships with their human hosts that aid in physiological maintenance, whereas other bacteria are harmful and have a role in the development and pathogenesis of diseases (Fan and Pedersen 2021). The gut microbiota, comprising trillions of microorganisms, produces metabolites that can modulate host physiology (Fan and Pedersen 2021). These metabolites, including short-chain fatty acids (SCFAs) like acetate and butyrate, have been shown to exert BP-lowering effects through mechanisms such as vasodilation and anti-inflammatory actions (Wu et al. 2021; Xu and Marques 2022; Olalekan et al. 2024). Trimethylamine-N-oxide (TMAO), derived from dietary choline and carnitine, has been linked to increased cardiovascular risk, while tryptophan derivatives and polyamines have roles in modulating vascular function and inflammation. Bile acids and Phenylacetylglutamine (PAGln) also influence BP through their metabolic effects and interactions with host physiology.

Hypertension, characterized by elevated BP, remains a leading cause of mortality worldwide, with a significant portion of patients failing to achieve adequate control despite available therapeutic interventions. In this context, exploring novel interventions, such as targeting gut microbial metabolites, holds promise for advancing hypertension management (Xu and Marques 2022; Jama and Marques 2023). Studies have demonstrated the BP-lowering effects of certain gut microbial metabolites, such as acetate and butyrate, yet their full therapeutic potential remains underexplored (Jama and Marques 2023). Hence, this review aims to delve into the intricate relationships between these metabolites and hypertension, examining how they contribute to BP regulation and evaluating various therapeutic approaches. By doing so, the review seeks to highlight potential new strategies for enhancing hypertension management and improving patient outcomes, ultimately advancing our understanding of the gut microbiome's role in cardiovascular health.

Gut microbiota composition and dysbiosis in hypertension

The human gut houses a diverse array of microorganisms, collectively known as the gut microbiota, which actively participate in various physiological processes. These microorganisms metabolize the host's dietary intake, yielding an array of metabolic byproducts such as TMAO, tryptophan catabolites, and short-chain fatty acids (SCFAs) (Rahman et al. 2023). Alongside their influence on the development of the host immune system, gut microbiota profoundly impacts host metabolism by facilitating the breakdown of complex carbohydrates, providing protection against pathogenic bacteria, and contributing to the synthesis of vital compounds like vitamins, SCFAs, and bile acids (Turroni et al. 2020). This intricate interplay between gut microbial metabolism and host health underscores the significant role of the gut microbiota in shaping overall host physiology and metabolism, highlighting how arterial hypertension, a prevalent chronic disease, is closely intertwined with metabolites secreted by intestinal bacteria, particularly SCFAs, TMAO, Tryptophan and Indole Derivatives, Polyamines, Bile Acids and Phenylacetylglutamine as detailed in Table 1 (Agus et al. 2021; Liu et al. 2020; Suta et al. 2023; Tokarek et al. 2023).

Notably, dysbiosis, characterized by an imbalance in microbial composition, has emerged as a critical factor in various disease states (Brüssow 2020). The colonization of gut microbiota commences shortly after birth, with Actinobacteria, Proteobacteria, and Firmicutes being the primary phyla observed during early childhood (Caballero-Flores et al. 2023). Alterations in gut microbiota composition, or dysbiosis, have been implicated in hypertension, with changes in microbial metabolite production being a notable consequence (Avery et al. 2021). Studies have demonstrated that hypertension is associated with dysregulation of gut microbiota, particularly under conditions of high salt diet-induced hypertension (Zheng et al. 2023). Furthermore, differences in the structure and composition of gut microbiota have been observed in hypertensive individuals, with specific microbial profiles correlating with the severity of hypertension (Muralitharan et al. 2020; Xu et al. 2021).

In individuals with hypertension, elevated levels of bacteria such as Eubacteriumxylanophilum, Eisenbergiella, and LachnospiraceaeUCG001 have been observed, contrasting with a decrease in beneficial bacteria like Alistipes, Phascolarctobacterium, Bilophila, and Butyricimonas, which are more abundant in normotensive individuals (Li et al. 2023). Certain bacterial taxa were linked

Table 1 Role of gut microbial metabolites in blood pressure regulation

Metabolite	Role in blood pressure regulation	Mechanisms in BP regulation	Important considerations/ limitations	References
Short-Chain Fatty Acids (SCFAs)—Butyrate, Acetate, Propionate	Essential for BP management and cardiovascular health	Vasodilation via GPR41 and GPR43 activation, anti-inflammatory effects, support gut barrier integrity, reduce cardiac hypertrophy, fibrosis, and vascular dysfunction	Inefficient SCFA absorption in hypertensive individuals may reduce benefits	Amiri et al. (2022), Bartolomaeus et al. (2019), Cookson (2021), Lin et al. (2022), Onyszkiewicz et al. (2019), Poll et al. (2020), Xia et al. (2023)
Trimethylamine N-Oxide (TMAO)	Promotes hypertension pathogenesis and adverse cardiovascular outcomes	Induces endothelial dysfunction via inflammation and oxidative stress, activates CaMKII, promotes vasoconstriction	Elevated TMAO levels are associated with increased hypertension risk	Han et al. (2024), Jiang et al. (2021), Mohan and George (2021), Mutengo et al. (2023), Shanmugham et al. (2023), Zhen et al. (2023)
Tryptophan and Indole Derivatives—3-IAld, IPA	Influence vascular function and immune responses, potential therapeutic targets	3-IAld inhibits VSMC phenotype transition, reduces extracellular matrix degradation and inflammatory cytokine expression; IPA prevents oxidative stress injury and inhibits proinflammatory cytokine synthesis	IPA may reduce nitric oxide production, complicating its role in hypertension management	Geddo et al. (2024), Huang et al. (2023), Konopelski and Mogilnicka (2022)
Polyamines—Spermidine, Spermine	Regulate oxidative balance, cell proliferation, and apoptosis	Induce autophagy, improve endothelial function, enhance gut barrier function, reduce cardiovascular disease risk, improves lipid metabolism in obesity	Disruption in polyamine metabolism leads to physiological disturbances, unclear mechanisms in hypertension regulation	Ma et al. (2020a), Matsumoto et al. (2019), Yoon et al. (2023), Zahedi et al. (2022)
Bile Acids—Taurine-conjugated bile acids	Impact cardiovascular health, modulate vasomotor function	Activate FXR and TGR5 receptors, increase NO production, regulate calcium influx, and reduce ADMA levels	Specific therapeutic approaches targeting bile acids and their signaling pathways are still being researched	Guizoni et al. (2020), Ishimwe et al. (2022) and Li et al. (2020)
Phenylacetylglutamine (PAGln)	Associated with heart failure severity and coronary artery disease progression	Enhances ROS and pro-inflammatory cytokine production, induces vascular inflammation and endothelial dysfunction	Elevated PAGln levels are linked to cardiovascular diseases and hypertension	Fang et al. (2022); Fu et al. (2024), Romano et al. 2023 and Zhu et al. (2023)

to various aspects of BP regulation. Alistipes finegoldii and Lactobacillus spp. were only present in individuals with normal BP variability, mean BP surges (MBPS), and nighttime dipping. Conversely, Prevotella spp. and Clostridium spp. were associated with extreme dipping and individuals in the highest quartiles of BP standard deviation and MBPS (Dinakis et al. 2022). Metabolic disorders linked to dysbiosis frequently involve changes in gut microbiota composition and function. Specific microbiota-derived metabolites, such as bile acids, SCFAs, TMAO, and tryptophan derivatives, play a role in their development (Agus et al. 2021).

The pathogenesis of hypertension involves multifaceted factors encompassing genetics, environment, hormones, hemodynamics, and inflammation. Emerging evidence underscores the significant role of the gut microbiome in hypertension development and pathogenesis. Interventions targeting the gut microbiota, such as the use of probiotics, hold promise as adjunctive therapies in managing hypertension, underscoring the potential for leveraging gut microbial modulation in the management of cardiovascular diseases.

Microbiota-derived short-chain fatty acids (SCFAs) in hypertension

Microbiota-derived short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, are essential metabolites produced in the gastrointestinal tract. They result from the bacterial fermentation of dietary fiber by microbes like Enterococcus, Bacteroidetes, Acidaminococcus, and Salmonella (Wu et al. 2021; Kaye et al. 2020). These SCFAs serve not only as energy sources for host cells but also as signaling molecules between the gut microbiota and extra-intestinal organs. They exert specific effects on cardiovascular health.

Butyrate, a short-chain fatty acid (SCFA) synthesized by gut bacteria such as Clostridium, Eubacterium, and Roseburia, is crucial in regulating blood pressure (BP) through various mechanisms. Butyrate induces vasodilation by activating G-protein-coupled receptors (GPR41 and GPR43) on vascular endothelial cells, which reduces vascular resistance and lowers BP (Onyszkiewicz et al. 2019). Additionally, butyrate exerts significant anti-inflammatory effects, mitigating systemic inflammation and oxidative stress—key contributors to hypertension development (Amiri et al. 2022). It also supports gut barrier integrity, preventing the translocation of pro-inflammatory substances into systemic circulation that could elevate BP (Xia et al. 2023). Furthermore, butyrate's effects are modulated by its influence on serotonin (5-HT) release from enteroendocrine cells (EECs). Elevated 5-HT levels in the gut can enhance the gut-brain axis signaling, which may contribute to its BP-regulating effects by altering central nervous system responses (Cookson 2021).

Gut-derived acetate, produced by the fermentation of dietary fibers by specific gut bacteria such as Faecalibacterium and Roseburia, also plays a significant role in BP regulation. Acetate not only serves as a substrate for butyrate-producing bacteria, thereby indirectly influencing BP through butyrate production, but it also has direct effects on BP. Acetate can induce vasodilation and reduce vascular resistance, contributing to lower BP levels (Cookson 2021; Poll et al. 2020). Additionally, acetate increases the release of serotonin (5-HT) from EECs in the gut. This elevated 5-HT can further influence central BP regulation by modulating gut-brain axis signaling, which complements butyrate's actions on BP (Cookson 2021). Acetate's role in reducing mean arterial pressure (MAP) and heart rate (HR) is also significant; it directly decreases cardiac contractility and modulates the autonomic nervous system. This modulation is evidenced by the attenuation of HR reduction when β-1 adrenergic receptor antagonists and sympathomimetics are used, reflecting its influence on sympathetic tone (Poll et al. 2020). Overall, a balanced gut microbiota that produces both butyrate and acetate is essential for effective BP management and cardiovascular health.

Propionate, produced by bacteria including Veillonellaceae and Prevotella, exhibits anti-inflammatory effects and protects against cardiovascular diseases. It reverses the imbalance between regulatory and effector T cells caused by hypertension, promoting positive effects on cardiac remodeling (Bartolomaeus et al. 2019). Propionate, supplemented along with acetate has been show to play a vital role in regulating BP and cardiovascular health. It reduces cardiac hypertrophy, fibrosis, vascular dysfunction, and hypertension by lowering systemic inflammation and decreasing immune cell infiltration in the heart (Lin et al. 2022). Propionate activates G-protein-coupled receptors (GPR41 and GPR43) on cardiac fibroblasts, inhibiting myofibroblast formation and collagen production, thus preventing fibrosis and extracellular matrix disarray. Additionally, acetate also contributes to these beneficial effects, further improving heart function under pressure-overload stress (Lin et al. 2022).

SCFAs levels in circulation may be a critical determinant of their antihypertensive potency. In a cross-sectional study, hypertensive (HT) individuals had higher levels of short-chain fatty acids (SCFAs) in their feces but lower levels in their plasma compared to normotensive (NT) individuals (Calderón-Pérez et al. 2020). This suggests less efficient SCFA absorption in HT individuals, which may reduce the beneficial effects of SCFAs on BP regulation, such as vasodilation and anti-inflammatory properties. Inefficient SCFA absorption could thus

contribute to higher BP in HT individuals, highlighting the role of SCFAs in maintaining cardiovascular health.

Microbiota-derived trimethylamine N-oxide (TMAO) in hypertension

SCFAs have garnered attention for their potential role in both the pathogenesis and treatment of hypertension. Additionally, TMAO has been recognized for its impact on hypertension. TMAO is a metabolite produced in the liver from trimethylamine (TMA), which is derived from gut bacterial metabolism of dietary substances such as choline, betaine, and L-carnitine (Yu et al. 2020). Emerging evidence suggests a close association between TMAO levels and hypertension pathogenesis (Mutengo et al. 2023; Zhen et al. 2023).

Elevated TMAO levels are implicated in several adverse cardiovascular outcomes, including endothelial dysfunction, atherosclerosis, and thrombosis. TMAO's role in endothelial dysfunction is particularly significant, as it promotes inflammation, oxidative stress, and impaired vascular reactivity, all of which are critical factors in hypertension development (Mohan and George 2021; Shanmugham et al. 2023). Studies have shown that TMAO induces endothelial dysfunction through inflammation and oxidative stress, characterized by increased reactive oxygen species (ROS) production and upregulation of cytokines and adhesion molecules (Shanmugham et al. 2023). Excessive reactive oxygen species (ROS) activates calmodulin-dependent protein kinase II (CaMKII), increasing vasoconstriction, but the CaMKII inhibitor KN-93 prevents trimethylamine N-oxide (TMAO)-induced enhancement of this response and angiotensin II (Ang II)'s pressor effect (Jiang et al. 2021).

Further studies have elucidated the relationship between TMAO and hypertensive disorders during pregnancy. Higher plasma levels of betaine and an inverse relationship between the betaine/choline ratio and hypertensive disorders of pregnancy suggest that early pregnancy plasma betaine and choline levels can serve as predictive markers for these conditions (Xu et al. 2024). A meta-analysis has confirmed a dose-dependent association between circulating TMAO concentrations and hypertension risk in patients with pre-existing cardiovascular diseases, reinforcing the role of TMAO in increasing hypertension risk (Han et al. 2024).

Targeting TMAO holds promise for managing hypertension. Studies have indicated that reducing TMAO levels can improve endothelial function and reduce vascular reactivity. For example, therapeutic strategies such as the use of 3,3-dimethyl-1-butanol (DMB) to reduce TMAO levels have demonstrated significant reductions in right ventricle systolic pressure and pulmonary vascular muscularization in rat models of pulmonary hypertension (Huang et al. 2022). Additionally, Mendelian Randomization (MR) studies have provided causal evidence linking elevated TMAO levels with increased systolic BP, further suggesting that targeting TMAO production could be beneficial for BP reduction (Wang et al. 2022). Inhibition of TMAO generation in high salt diet-induced hypertension models has also shown potential by reducing neuroinflammation and oxidative stress in the hypothalamic paraventricular nucleus (Liu et al. 2022). Furthermore, other dietary factors such as high choline intake from supplements or certain foods, like egg yolks, have been shown to elevate TMAO levels, suggesting that dietary modifications could also influence TMAO-related hypertension management (Böckmann et al. 2022).

The significant role of TMAO in the pathogenesis of hypertension underscores its potential as a therapeutic target. While TMAO is associated with increased hypertension risk, therapeutic interventions targeting TMAO production, or its downstream effects could offer novel strategies for managing hypertension and associated cardiovascular diseases. Continued research is essential to fully elucidate the mechanisms underlying TMAO-induced hypertension and to develop effective preventive and therapeutic approaches.

Tryptophan and indole derivatives in hypertension

The role of tryptophan and its indole derivatives in the pathogenesis and treatment of hypertension is becoming increasingly intriguing, owing to their substantial impact on diverse biological processes and cardiovascular health. Tryptophan, an essential dietary amino acid, is metabolized into various compounds within the gut microbiota and tissue cells, affecting numerous physiological functions. Tryptophan metabolism produces several bioactive compounds, including Indole-3-aldehyde (3-IAId) and indole-3-propionic acid (IPA), which have shown significant cardiovascular effects.

In a study by Huang et al., 3-IAId demonstrated a protective role against aortic dissection (AD) in a murine model (Huang et al. 2023). The application of 3-IAId resulted in a significant decrease in aortic dissection and rupture rates, as well as mortality rates. This protective effect is attributed to its ability to inhibit the phenotype transition of vascular smooth muscle cells (VSMCs), reduce extracellular matrix degradation, decrease macrophage infiltration, and suppress inflammatory cytokine expression. These findings indicate that 3-IAId holds promise as an intervention strategy for preventing thoracic aortic dissection and potentially other vascular diseases, such as hypertension.

Gut microbiota-derived metabolites of tryptophan, such as indole-3-propionic acid (IPA), play a crucial role in cardiovascular health. Konopelski and Mogilnicka

highlighted that IPA shares biological effects similar to its precursor tryptophan, including impacts on the cardiovascular system (Konopelski and Mogilnicka 2022). Indole-3-propionic acid (IPA) prevents oxidative stress injury, lipoperoxidation, and inhibits the synthesis of proinflammatory cytokines. It also impacts the energetic balance and cardiovascular health, although its synthesis may be influenced by atherosclerosis risk factors. Protective measures, like adopting a Mediterranean diet, have been shown to elevate plasma IPA concentrations, indicating that dietary interventions could improve cardiovascular health and potentially alleviate hypertension. However, Geddo et al. explored IPA's effects on endothelial function and found that physiological concentrations of IPA reduced nitric oxide (NO) production in bovine aortic endothelial cells (Geddo et al. 2024). This reduction in NO, a crucial vasodilator, suggests that IPA could negatively affect vascular tone regulation, complicating its role in hypertension management. The contrasting results from these studies highlight its potential inhibitory effect on NO production which may reflect a dose-dependent response. Therefore, further investigation is needed to understand how varying IPA concentrations influence its cardiovascular effects and reconcile these findings with its overall role in hypertension management.

In conclusion, tryptophan and its indole derivatives play a multifaceted role in the pathogenesis and treatment of hypertension. Their influence on vascular function, immune and inflammatory responses, and interaction with gut microbiota highlight their potential as therapeutic targets. Further research into their specific mechanisms and effects will enhance our understanding and development of novel strategies for managing hypertension.

Gut-derived polyamines in hypertension

Polyamines, specifically spermidine and spermine, are positively charged aliphatic molecules essential for various cellular processes, including nucleic acid regulation, protein synthesis, oxidative balance, and cell proliferation. These molecules play a significant role in maintaining physiological homeostasis and mediating tissue injury. Disturbances in polyamine metabolism have been associated with several maladaptive changes, highlighting their importance in health and disease.

Polyamines are integral to several physiological functions due to their ability to regulate nucleic acids and proteins. They are involved in protein synthesis, nucleic acid interactions, oxidative stress management, and cell proliferation. Cellular levels of polyamines are meticulously controlled through mechanisms of import, export, de novo synthesis, and catabolism, with specific enzymes and enzymatic cascades dedicated to polyamine metabolism. The disruption of these pathways, whether through spontaneous mutations, genetic engineering, or experimentally induced injuries, leads to significant physiological disturbances. Studies have demonstrated the adverse effects of altered polyamine metabolism in both in vitro and in vivo models, emphasizing the critical role of polyamines in maintaining physiological balance and mediating injury responses (Zahedi et al. 2022).

Matsumoto et al. investigated the impact of inducing microbial polyamine production in the gut, particularly spermidine, on endothelial function crucial in hypertension and cardiovascular disease (Matsumoto et al. 2019). They found that consuming yogurt with Bifidobacterium animalis subsp. lactis (Bifal) and arginine (Arg) increased putrescine production, a spermidine precursor. Spermidine induces autophagy, reducing cardiovascular disease risk. The study showed that the Bifal + Arg yogurt group had improved endothelial function, suggesting potential in preventing or reducing atherosclerosis risk through enhanced microbial polyamine production and spermidine synthesis (Matsumoto et al. 2019).

Polyamines, crucial in hypertension, are primarily produced in the intestine by gut microbiota, involving complex biosynthetic pathways and specific transport systems. Notable bacteria like Enterococcus faecalis and Campylobacter jejuni are involved, synthesizing polyamines via various pathways. Studies show the synergistic effect of Bifidobacterium spp., E. faecalis, and Escherichia coli, with arginine supplementation enhancing polyamine production. B. animalis subsp. lactis supplementation increases intestinal polyamine levels (Yoon et al. 2023). Changes in polyamine levels, such as increased spermidine, can affect the composition and function of the gut microbiome in obese mice, resulting in reduced obesity rates. Spermidine exhibits a microbiota-dependent anti-obesity effect by promoting the expansion of Lachnospiraceae NK4A136, thereby enhancing gut barrier function (Ma et al. 2020b).

Spermine, a key polyamine, has garnered interest for its potential implications in hypertension and related conditions. While much research has focused on spermidine, recent studies have begun to highlight spermine's role in hypertension. Liang et al. identified a significant reduction in spermine levels, alongside spermidine/spermine N1-acetyltransferase-1 (SAT1), in endothelial cells under ferroptosis-induced hypertension. This suggests a complex interplay between spermine levels and hypertension-related endothelial dysfunction (Liang et al. 2023). Spermine's direct role in hypertension remains less established compared to spermidine. Wei et al. explored spermine's regulatory effects on immune and signal transduction pathways in diabetic cardiomyopathy,

yet did not find a direct connection to hypertension (Wei et al. 2022). Additionally, Sieckmann et al. observed that reduced spermine levels in kidney injury models, including hypertension, reflect broader impacts on kidney function rather than specific hypertensive effects (Sieckmann et al. 2023). Collectively, while spermine's influence in hypertension is emerging, further research is needed to delineate its precise role and therapeutic potential.

Polyamines play a multifaceted role in the pathogenesis and treatment of hypertension. Their involvement in regulating oxidative balance, cell proliferation, and apoptosis underscores their importance in maintaining vascular health. Disruptions in polyamine metabolism contribute to vascular remodeling and oxidative stress, key factors in hypertension development. Targeting polyamine metabolic pathways offers a promising avenue for therapeutic intervention, potentially leading to novel treatments for hypertension and related vascular diseases. Further research is needed to fully elucidate the mechanisms by which polyamines influence hypertension and to develop effective polyamine-based therapies.

Gut-derived bile acids in hypertension

Bile acids play a crucial role in cardiovascular health, with levels increasing under pathological conditions. They impact cardiovascular health by activating various receptors, including the farnesoid X receptor (FXR), pregnane X receptor, vitamin D receptor, and G protein-coupled receptor Gpbar1 (TGR5) (Ishimwe et al. 2022; Li et al. 2020). Specifically, FXR, highly expressed in vascular smooth muscle cells and endothelial cells, modulates vasomotor function and vascular disease progression. Bile acids induce vasorelaxation, increase NO production, and regulate calcium influx in the vasculature. Moreover, FXR activation has implications in kidney health, influencing renal tubular cell survival and function. In salt-sensitive hypertension, bile acids may regulate BP through the epithelial Na + channel (ENaC) and BASIC (bile acid-sensitive ion channel). Activation of FXR leads to the upregulation of the angiotensin II type 2 receptor, which may contribute to the mitigation of salt-sensitive hypertension. Furthermore, bile acids are involved in regulating inflammation, which can impact hypertension. Activation of FXR and TGR5 by endogenous ligands and pharmacological agents presents potential therapeutic targets for addressing salt-sensitive hypertension (Ishimwe et al. 2022).

Taurine-conjugated bile acids, a subtype of bile acids, significantly impact cardiovascular health by enhancing vascular relaxation. They boost NO production and availability, essential for vascular health, through the upregulation of endothelial nitric oxide synthase (eNOS) expression and phosphorylation, improved NO bioavailability, and enhanced antioxidative defenses (Guizoni et al. 2020). Additionally, activation of FXR and TGR5 by taurine-conjugated bile acids promotes NO production by reducing asymmetric dimethylarginine (ADMA), an inhibitor of NO synthase, and mobilizing calcium ions.

Targeting bile acid metabolism and signaling pathways offers promising therapeutic strategies for managing hypertension. Modulating receptors like FXR and TGR5 to enhance NO production and improve vascular function could be effective. Therapies aimed at restoring healthy gut microbiota and bile acid profiles could alleviate salt-sensitive hypertension and improve overall cardiovascular health. Additionally, dietary interventions that promote a healthy gut microbiota and bile acid profile, such as a Mediterranean diet, could enhance cardiovascular health and mitigate hypertension (Guizoni et al. 2020).

Gut-derived phenylacetylglutamine in hypertension

Phenylacetylglutamine (PAGln), a gut-derived metabolite, has gained attention due to its association with heart failure (HF) severity and the progression of coronary artery disease (CAD). PAGln is formed through the conjugation of phenylacetic acid (PAA), a metabolite produced by gut bacteria from the amino acid phenylalanine, with glutamine (Krishnamoorthy et al. 2024). This conjugation typically occurs in the liver and kidneys. Genetic modification of certain microbes and studies with gnotobiotic mice revealed two pathways for PAA synthesis: phenylpyruvate oxidoreductase (PPFOR) and phenylpyruvate decarboxylase (PPDC). These enzymes are essential for bacterial PAA production via oxidative and non-oxidative decarboxylation of phenylpyruvate. Metagenomic analysis shows these pathways are more prevalent in gut microbiomes (Zhu et al. 2023).

PAGln influences cardiovascular health through several mechanisms. Elevated levels of PAGln have been associated with increased oxidative stress and inflammation in cardiovascular tissues. Specifically, PAGln can enhance the production of reactive oxygen species (ROS) and pro-inflammatory cytokines, which contribute to endothelial dysfunction and vascular inflammation (Fang et al. 2022). These mechanisms can contribute to the advancement of atherosclerosis and CAD by fostering the development of plaques and vascular lesions, which are also associated with hypertension. Elevated plasma PAGln levels have been linked to atrial fibrillation (AF) in HF by inducing thoracic aortic coarctation in mice. PAGln worsened ROS accumulation and increased levels of phosphorylated Phospholamban and CAMK II, indicating its involvement in promoting atrial fibrillation in heart failure mice through the activation of the CAMK II

Table 2 Studies investigating probiotics in blood pressure regulation

Study design	Intervention	Endpoint (s)	Mechanism of action	Positive contribution to BP regulation	Negative contribution/ limitations	Reference
Randomized, parallel, double-blind, placebo-controlled trial	*Bifidobacterium animalis* subsp. *lactis* CECT 8145 (live and heat-killed)	Diastolic BP, waist circumference, body mass index	Increase in Akkermansia spp., reduction in waist circumference and visceral fat area	Decrease in diastolic BP after heat-killed form	BP outcomes only noted for diastolic BP; gender-specific results not generalized	Pedret et al. (2019)
Randomized clinical trial	Orange juice enriched with probiotics (*Lacticaseibacillus casei* Shirota, *Lacticaseibacillus rhamnosus* GG)	Blood pressure, body weight, insulin resistance	Probiotic-enriched orange juice resulted in metabolic improvements including BP	Reduced peripheral blood pressure, body weight, and improved insulin resistance	No significant changes in central blood pressure or triglycerides; short intervention period	Papakonstantinou et al. (2024)
Randomized, double-blind, placebo-controlled trial assessing multi-strain probiotic effects	Multi-strain probiotics (*Limosilactobacillus* fermentum, *Lactobacillus rhamnosus*, etc.)	Sleep quality, subjective measures, and BP	Improved subjective sleep quality but no significant BP changes	No change in systolic or diastolic BP with multi-strain probiotics	No observed effect on BP; focus primarily on sleep quality	Kerksick et al. 2024)

signaling pathway (Fu et al. 2024). A study demonstrated that PAGln directly influenced HF-related phenotypes, suggesting its potential as a therapeutic target for HF modulation (Romano et al. 2023).

Phenylacetylglutamine is a significant gut-derived metabolite that influences cardiovascular health through mechanisms involving oxidative stress, inflammation, and vascular remodeling. Dysbiosis plays a crucial role in altering PAGln levels, thereby affecting the pathogenesis of cardiovascular diseases. Ongoing research is essential to fully understand the mechanisms by which PAGln influences cardiovascular health and to develop effective treatments targeting this metabolite.

Studies on treatments targeting gut microbiome in the regulation of blood pressure

Conventional antihypertensive medications, such as ACE inhibitors, beta-blockers, and diuretics, are widely used to manage hypertension. Although these drugs are effective, they are often accompanied by side effects like dizziness, fatigue, and electrolyte imbalances (Karunarathna et al. 2024). As a result, there is growing interest in alternative treatments, including dietary supplements, herbal products, functional foods, and lifestyle modifications, which have shown promise in managing hypertension and other health conditions (Adeyanju et al. 2022; Oduyemi et al. 2023; Osonuga et al. 2022a, b, 2024). Among these alternatives, gut microbiota-based interventions are gaining attention due to their potential to offer fewer side effects and additional health benefits.

Microbiota-based interventions, such as probiotics, prebiotics, fecal microbiota transplantation (FMT), dietary modifications, and polyphenols, have been extensively studied for their potential in blood pressure regulation. Probiotics and prebiotics have shown promising yet diverse outcomes, along with tailored dietary interventions. Polyphenols and FMT have also been explored for their effects on BP.

Probiotics

Recent research on probiotics and blood pressure (BP) regulation, as summarized in Table 2, reveals mixed outcomes. One study reported that Bifidobacterium animalis subsp. lactis CECT 8145, particularly in its heat-killed form, led to a significant decrease in diastolic BP and improvements in waist circumference, although the results were specific to diastolic BP and not generalized by gender (Pedret et al. 2019). Another study found that probiotic-enriched orange juice improved peripheral BP and other metabolic markers but showed no significant changes in central BP (Papakonstantinou et al. 2024). In contrast, a study on multi-strain probiotics found improvements in subjective sleep quality but no significant impact on BP (Kerksick et al. 2024). These studies highlight the variable effects of probiotics on BP and underscore the need for further investigation.

Prebiotics

Prebiotics are non-digestible food components that promote the growth and activity of beneficial gut bacteria. A controlled open-label trial demonstrated that a specially designed diet combined with fecal microbiota transplantation improved blood glucose and BP levels by increasing beneficial bacteria like Bifidobacterium, although it had a limited duration and lacked long-term follow-up (Su et al. 2022). Another study comparing native inulin with maltodextrin found that prebiotic treatment led to significant reductions in diastolic BP and facilitated weight loss, though its effectiveness was reduced when used alongside metformin (Hiel et al. 2020). Additionally, a randomized controlled trial showed that oat bran supplementation resulted in significant reductions in both office and ambulatory BP, alongside decreased use of antihypertensive medications, by modulating gut microbiota (Xue et al. 2021). These findings, detailed in Table 3, underscore the potential of prebiotics in BP regulation and highlight the variability in their effectiveness.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) involves transferring fecal microbiota from a healthy donor to a recipient's gut to restore microbial balance. Clinical trials investigating FMT in blood pressure (BP) regulation have shown mixed results. One controlled open-label trial examined the effects of a specially designed diet and diet plus FMT on blood glucose and BP levels, revealing that both treatments increased beneficial bacteria like Bifidobacterium, which are associated with lower BP, and decreased harmful sulfate-reducing bacteria, suggesting improved BP regulation. However, the lack of a placebo control group was a significant limitation of this study (Su et al. 2022). Another randomized, double-masked placebo-controlled study investigated the impact of oral encapsulated fecal microbiome from healthy lean donors versus a saline placebo on BMI standard deviation scores over six weeks. This study suggested potential indirect benefits of FMT on BP regulation through reductions in abdominal adiposity and overall improvements in metabolic health, despite not finding a significant effect on weight loss (Leong et al. 2020).

Dietary intervention

Dietary interventions have demonstrated considerable potential in influencing blood pressure (BP) regulation and enhancing overall cardiovascular health. Table 4

Table 3 Studies investigating prebiotics in blood pressure regulation

Study design	Intervention	Endpoint (s)	Mechanism of action	Positive contribution to BP regulation	Negative contribution/ limitations	Reference
Controlled open-label trial	Specially designed diet and diet combined with fecal microbiota transplantation	Control of blood glucose and BP levels	Beneficial bacteria like *Bifidobacterium* showed a consistent increase	Improvement in blood glucose levels and BP	Limited duration of the trial and lack of long-term follow-up	Su et al. (2022)
Randomized, single-blinded, multicentric, placebo-controlled trial	Native inulin versus maltodextrin coupled with dietary advice for 3 months	Improvement in anthropometry and metabolic parameters	Influence on gut microbiota characteristic with a large increase in *Bifidobacterium*	Facilitation of weight loss and more significant reduction in diastolic BP in comparison to the placebo	The effectiveness of the prebiotic treatment was reduced when administered alongside metformin	Hiel et al. 2020)
Randomized controlled trial	Oat bran supplement (30 g/d containing 8.9 g of dietary fiber)	Office Systolic BP and Diastolic BP, 24 h ambulatory BP	Increased intake of oat bran supplement significantly reduced office and ambulatory BP compared to the control group. Modulated the gut microbiota	Reduction in office Systolic BP and Diastolic BP, as well as 24 h ambulatory BP, greater than control group. Reduction in use of antihypertensive drugs in the oat bran group		Xue et al. 2021)

Table 4 studies investigating dietary interventions in blood pressure regulation

Study design	Intervention	Endpoint (s)	Mechanism of action	Positive contribution to BP regulation	Negative contribution/ limitations	References
Double-blinded, parallel-design, randomized controlled trial	Adaptation of a Mediterranean-like diet tailored for Asians, enriched with fiber and unsaturated fatty acids, with or without C15:0 supplementation	Reduction in weight, liver proton density fat fraction (PDFF), total cholesterol, gamma-glutamyl transferase, and triglyceride concentrations	The Mediterranean-like diet tailored for Asians induces mild weight loss, which brings about multiple health benefits in females with NAFLD. Additionally, C15:0 supplementation reduces LDL-cholesterol and may lead to favorable shifts in the gut microbiome	There were significantly greater reductions in body weight, liver PDFF, total cholesterol, gamma-glutamyl transferase, and triglyceride concentrations compared to the control group. Additionally, reductions in fat mass, visceral adipose tissue, subcutaneous abdominal adipose tissue, insulin, glycated hemoglobin, and BP were observed in all groups, in parallel with weight loss	No significant limitations	Chooi et al. (2024)
10-week, randomized, controlled, multifaceted lifestyle intervention	High-quality dietary pattern intervention incorporating nutrition and physical activity education, produce harvesting, cooking demonstrations, nutrition counseling, and kinetic activities	Dietary patterns, cardiovascular risk factors, gut microbiome composition	The lifestyle intervention improved total diet quality, increased whole grain intake, decreased energy intake, and enhanced fecal elimination of microbe-derived metabolites. Furthermore, there were shared microbiota-BP relationships observed between caregiver-child dyads	Improvement in dietary patterns and cardiovascular risk factors following lifestyle intervention. Shared microbiota-BP relationships between caregiver-child dyads	Study focused on the impact of lifestyle intervention on diet quality, gut microbiome, and cardiovascular risk factors without specific dietary supplements	Hill et al. (2022)
Randomized controlled cross-over study	Mediterranean diet with 3–4 daily serves of dairy foods versus low-fat control diet	Changes in gut microbiome composition; clinical, anthropometric, and cognitive outcomes	Modulation of gut microbiota and increase in Butyricicoccus and decrease in Collinsella and Veillonella in the group following the Mediterranean diet supplemented with dairy foods (MedDairy)	Increase in Butyricicoccus correlated with lower systolic BP; positive correlation with changes in fasting glucose levels	No significant change in overall fecal microbial structure or composition; limited sample size (34 adults)	Choo et al. (2023)
Randomized controlled trial	Phytosterols-enriched low-fat milk versus control milk	Serum LDL-cholesterol levels	Reduction in LDL-cholesterol levels and diastolic BP through modulation of gut microbiota	Significant reduction in serum LDL-cholesterol levels, total cholesterol and diastolic BP	Limited by short intervention duration	Cheung et al. (2017)

Table 5 Studies investigating polyphenols in blood pressure regulation

Study design	Intervention	Endpoint (s)	Mechanism of action	Positive contribution to BP regulation	Negative contribution/ limitations	References
Randomized controlled trial	Polyphenol-rich diet versus control diet	Serum zonulin levels and BP	Reduction in serum zonulin levels and an increase in fiber-fermenting and butyrate-producing bacteria	Reduction in diastolic and systolic BP, increase in beneficial gut bacteria (Ruminococcaceae and members of the genus *Faecalibacterium*)	No significant limitations	Bo et al. (2021)
Randomized controlled trial	Wild blueberry powder versus placebo	Vascular function, cognitive performance, BP	Increase in flow-mediated dilation, reduction in systolic BP	Improvement in vascular and cognitive function, decrease in 24 h ambulatory Systolic BP	No changes in the cerebral blood flow or gut microbiota composition were found	Wood et al. (2023)
Randomized controlled trial	Aronia berry extract versus placebo	Arterial function, gut microbiome	Improvement in arterial indices, increase in butyrate-producing bacteria (*Lawsonibacter asaccharolyticus* and *Intestinimonas butyriciproducens* species)	No significant changes in BP, endothelial function, or blood lipids	No significant limitations	Sayec et al. (2022)
Randomized controlled trial	Aronia berry extract/whole fruit powder versus placebo	Vascular function, gut microbiota composition	Increase in flow-mediated dilation, modulation of gut microbiota composition	Improvement in endothelial function, modulation of gut microbiota composition	No significant limitations	Istas et al. (2019)

outlines recent studies investigating various dietary approaches to BP management.

Polyphenols

Polyphenols are bioactive compounds found in plant-based foods, known for their antioxidant properties. Clinical trials investigating polyphenols in BP regulation by modulating gut microbiome have shown promising results as highlighted in Table 5. Specifically, these studies demonstrate that polyphenol-rich interventions can positively influence BP through mechanisms such as increasing beneficial gut bacteria, enhancing vascular function, and improving endothelial health.

Microbiota-based interventions offer various approaches for blood pressure regulation and improving cardiovascular health. While probiotics, prebiotics, and dietary modifications have shown promising results, polyphenols and FMT have produced mixed outcomes. Future research should focus on elucidating the mechanisms of these interventions and exploring their long-term effects to provide more definitive recommendations for clinical practice.

Conclusions

Hypertension is a complex, multifactorial disease influenced by genetic, environmental, and lifestyle factors. Recent research has highlighted the significant role of the gut microbiome and its metabolites in regulating BP. Key microbial metabolites, including short-chain fatty acids, trimethylamine N-oxide, tryptophan derivatives, polyamines, bile acids, and phenylacetylglutamine, have been identified as crucial players in BP regulation. Therapeutic approaches targeting these metabolites and their pathways offer promising avenues for hypertension management. Probiotics, prebiotics, dietary interventions, polyphenols, and fecal microbiota transplantation have shown varying degrees of success in modulating gut microbiota and influencing BP.

Despite the progress made in understanding the role of gut microbial metabolites in hypertension, several gaps in knowledge and areas for further research remain. Future research should focus on elucidating the precise mechanisms through which gut microbial metabolites influence BP. Understanding these pathways will help identify potential therapeutic targets. Large-scale, randomized controlled trials are needed to validate the efficacy of microbiota-based interventions in BP management. These studies should aim to determine the optimal strains and dosages of probiotics, prebiotics, and polyphenols for BP reduction. Among the identified metabolites, SCFAs and TMAO appear to have significant potential for therapeutic development. Future studies should prioritize these metabolites to explore their role in BP regulation and potential as therapeutic agents.

Research should investigate the potential for personalized gut microbiome interventions based on individual microbiota compositions. Personalized approaches could enhance the effectiveness of treatments and minimize adverse effects. Long-term studies are necessary to assess the sustainability of microbiota-based interventions and their impact on BP and overall cardiovascular health over time. Exploring the synergistic effects of combining different microbiota-based interventions, such as probiotics with dietary modifications, could provide more effective strategies for BP management. Establishing clear regulatory guidelines for the use of microbiota-based therapies in clinical practice will be crucial for their safe and effective implementation.

Abbreviations

BP	Blood pressure
SCFA	Short-chain fatty acid
TMAO	Trimethylamine N-oxide
TMA	Trimethylamine
3-IAld	Indole-3-Aldehyde
IPA	Indole-3-Propionic Acid
NO	Nitric Oxide
MAP	Mean arterial pressure
HR	Heart rate
ROS	Reactive oxygen species
CaMKII	Calmodulin-dependent protein kinase II
Ang II	Angiotensin II
MR	Mendelian randomization
VSMCs	Vascular smooth muscle cells
FXR	Farnesoid X receptor
TGR5	G protein-coupled receptor Gpbar1
ENaC	Epithelial Na + channel
ADMA	Asymmetric dimethylarginine
HF	Heart failure
CAD	Coronary artery disease
PAGln	Phenylacetylglutamine
PAA	Phenylacetic acid
PPFOR	Phenylpyruvate oxidoreductase
PPDC	Phenylpyruvate decarboxylase
AF	Atrial fibrillation
FMT	Fecal microbiota transplantation
LDL	Low-density lipoprotein
MedDairy	Mediterranean diet supplemented with dairy foods
NAFLD	Non-alcoholic fatty liver disease
PDFF	Proton density fat fraction
BMI	Body mass index

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Author contributions

SOO conceived and designed the study. SOO wrote the initial version of the manuscript. OOB, ASP, PGO reviewed the initial version of the manuscript. SOO, OOB, ASP, PGO wrote the final draft of the manuscript. All authors have read and approved the final version of the manuscript.

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Declarations

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