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REVIEW

Gut Bacterial Microbiome and Hypertension: A Narrative Review of Mechanisms, Clinical Implications, and Therapeutic Perspectives

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Abstract: The gut bacterial microbiome (GBM) plays an emerging role in the pathophysiology of chronic diseases, including hypertension (HTN). Growing evidence suggests that gut dysbiosis, defined by an altered microbial composition and diversity, is involved in the onset and progression of HTN. Exploring the underlying mechanisms linking the GBM and HTN paves the way for novel targeted therapeutic strategies. This narrative review aims to synthesize current data on the interactions between the GBM and HTN, highlight the bidirectional nature of this relationship, and discuss the clinical implications of microbiome modulation in hypertension management. Gut dysbiosis leads to increased intestinal permeability, facilitating systemic translocation of lipopolysaccharides, which in turn activate inflammatory (TLR4, NF-κB) and sympathetic pathways, contributing to endothelial dysfunction and elevated blood pressure. Moreover, certain microbial metabolites, such as short-chain fatty acids (SCFAs), exhibit antihypertensive effects, whereas trimethylamine-N-oxide (TMAO) is associated with increased vascular stiffness and activation of the renin–angiotensin–aldosterone system. The relationship between the GBM and HTN is reciprocal: while dysbiosis can promote HTN, HTN itself may disrupt the gut microbial ecosystem. This bidirectional interaction suggests the existence of a pathological vicious cycle. Innovative strategies to modulate the GBM, including the use of probiotics, prebiotics, postbiotics, and specific dietary interventions such as the Dietary Approaches to Stop Hypertension diet, are currently under investigation. The emergence of pharmacological approaches targeting pathogenic microbial metabolites, such as TMAO, also represents a promising avenue toward precision medicine in hypertension.

Keywords: hypertension, gut bacterial microbiome, clinical implications, therapeutic perspectives

1 Introduction

The gut bacterial microbiome (GBM) refers to the diverse community of microorganisms, primarily bacteria, that stably colonize the human gastrointestinal tract. This complex microbial ecosystem, comprising tens of thousands of species and trillions of cells, maintains a mutualistic relationship with the host and fulfills a wide array of essential health-related functions. The GBM is involved in nutrient digestion, the synthesis of vitamins (notably K and B vitamins), bile acid metabolism, the production of microbial metabolites such as short-chain fatty acids (SCFAs), maintenance of intestinal barrier integrity, and modulation of both innate and adaptive immune responses [1, 2].

Over the past two decades, the advent of high-throughput sequencing and metagenomics has enabled a more precise characterization of the composition and functional capacity of the GBM. These technological advances have revealed its central role in the pathogenesis of an expanding spectrum of non-communicable chronic diseases, including metabolic disorders (such as obesity and type 2 diabetes), chronic inflammatory bowel diseases, neurodegenerative conditions, and more recently, cardiovascular diseases [3, 4]. In this context, bacterial diversity, species richness, and the dynamic balance among key phyla, particularly *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*, have emerged as critical determinants of intestinal and systemic homeostasis.

Hypertension (HTN) remains one of the leading cardiovascular risk factors, accounting for millions of deaths worldwide each year [5]. Despite considerable advances in the understanding of its underlying mechanisms and in the development of therapeutic strategies, a substantial proportion of cases are still classified as "essential hypertension," meaning they lack an identifiable etiology. Against this backdrop, the hypothesis that alterations in the GBM, commonly referred to as dysbiosis, may contribute to the pathophysiology of HTN has garnered increasing scientific interest [6]. This perspective opens new avenues for research aimed at understanding how host, microbiome interactions may influence blood pressure (BP) regulation and serve as potential therapeutic targets.

Dysbiosis is characterized by reduced microbial diversity, an overrepresentation of pathobionts, and disrupted microbial metabolic functions [7–9]. This imbalance may lead to increased intestinal permeability, or "leaky gut", facilitating the translocation of bacterial products such as lipopolysaccharides (LPS) into systemic circulation, where they trigger low-grade inflammatory responses. These inflammatory signals can in turn affect key physiological systems, including the gut–brain axis, the autonomic nervous system, the renin–angiotensin–aldosterone system (RAAS), and the vascular endothelium, ultimately contributing to elevated BP [10, 11].

The growing recognition of the GBM's role in BP regulation has led to the development of therapeutic strategies targeting the microbiome. Interventions under investigation include the administration of probiotics (beneficial live microorganisms), prebiotics (substrates promoting the growth of beneficial bacteria), synbiotics (a combination of probiotics and prebiotics), as well as dietary and pharmacological approaches with potential antihypertensive effects [12]. However, findings from experimental and clinical studies remain heterogeneous and sometimes contradictory, precluding the formulation of standardized therapeutic recommendations. Moreover, the precise mechanisms of action, interindividual variability in response, and long-term effects of such interventions are not yet fully understood [13].

In this context, a narrative review of the literature is warranted to synthesize current knowledge, identify areas of uncertainty, and guide future research. This review therefore aims to comprehensively examine the pathophysiological mechanisms through which the GBM may influence the development and progression of HTN. It focuses on relevant microbial metabolites, inflammation- and immunity-related processes associated with dysbiosis, and the bidirectional interactions between intestinal bacterial composition and BP parameters. Furthermore, it explores the clinical implications of these findings and discusses the therapeutic prospects of GBM modulation in the prevention and treatment of HTN.

2 Core biological mechanisms linking the gut microbiome and hypertension

2.1 Composition, diversity, and functions of the gut bacterial microbiome

The human GBM constitutes a dynamic, highly complex ecosystem comprising approximately 10^14 microorganisms, roughly tenfold more than the total number of human cells [4, 14]. Most of these microbes reside in the colon and are dominated by two phyla, *Firmicutes* and *Bacteroidetes*, although *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* also perform important functions [15, 16].

GBM diversity and composition are shaped by multiple factors, including mode of delivery at birth, diet, environment, antibiotic exposure, age, and underlying disease states. High microbial diversity is generally considered a hallmark of eubiosis and intestinal health [17].

Functionally, the GBM participates in the fermentation of indigestible dietary fibres, synthesis of vitamins (K, B_{12}, biotin), production of bioactive metabolites, most notably shortchain fatty acids (SCFAs), defence against pathogens, and finetuning of immune and neuroendocrine responses [18, 19]. Hence, the GBM behaves as a metabolic "organ" that exerts distal effects on numerous pathophysiological axes, including cardiovascular regulation.

2.2 Involvement of the gut microbiome in blood pressure regulation

A growing body of evidence indicates that the GBM influences BP through several interrelated pathways, three of which stand out.

2.2.1 Production of vasoactive metabolites

SCFAs such as butyrate, propionate, and acetate, generated by bacterial fermentation of dietary fibres, play pivotal roles in BP regulation. Their antihypertensive effects are mediated by activation of Gproteincoupled receptors (GPR41, GPR43, GPR109A) expressed on endothelial, immune, and neuronal cells [12, 20]. Butyrate, in particular, is antiinflammatory, enhances endothelial nitricoxide synthase (eNOS) activity, increases nitricoxide bioavailability, and promotes endothelialdependent vasodilatation [19].

By contrast, trimethylamineNoxide (TMAO), derived from hepatic oxidation of trimethylamine produced by gut bacteria from nutrients such as choline and Lcarnitine, is associated with heightened risk of hypertension, atherosclerosis, and endothelial dysfunction. TMAO promotes vascular inflammation, platelet aggregation, and arterial stiffness [21, 22].

The GBM also modulates the RAAS. SCFAs can inhibit angiotensin II synthesis, downregulate its AT_1 receptors, and suppress aldosterone secretion, collectively lowering BP [11, 12]. Severe dysbiosis, conversely, may activate the RAAS, leading to vasoconstriction, sodium retention, and chronic BP elevation.

2.2.2 Immunoinflammatory modulation

The GBM is a major regulator of host immunity, shaping cytokine production and other inflammatory mediators [23]. Excessive immune activation fosters lowgrade chronic inflammation, commonly seen in hypertension, characterised by arterial stiffness and endothelial dysfunction [24–26]. These vascular changes are recognised risk factors for BP elevation.

2.2.3 Interaction with the autonomic nervous system

GBM–autonomic nervous system crosstalk, particularly with sympathetic outflow, is integral to cardiovascular control [27, 28]. Through the gut–brain axis, microbial signals influence sympathetic tone via neurotransmitters such as γaminobutyric acid (GABA), serotonin, and tryptophan derivatives. GABA dampens sympathetic activity, while serotonin and its precursor tryptophan further modulate sympathetic responses, collectively affecting heart rate and BP.

2.3 Bidirectional relationship between the gut microbiome and hypertension

Gut dysbiosis (GD), a qualitative and/or quantitative disturbance of GBM composition, can be triggered by chronic stress, unbalanced diets, recurrent antibiotic use, or chronic diseases [29]. In hypertensive individuals, GD manifests as reduced bacterial diversity, particularly a loss of beneficial genera (*Lactobacillus*, *Bifidobacterium*, *Akkermansia*), and an overrepresentation of proinflammatory taxa within the *Firmicutes* (e.g., *Clostridium* spp.) and *Proteobacteria* phyla [6, 30]. The relationship is bidirectional: GD promotes inflammatory, neurovascular, and metabolic mechanisms that raise BP, while sustained hypertension itself perturbs the GBM, establishing a vicious cycle mediated by shared pathways (TLR4 RAAS, gut-brain axis) [13, 31].

2.3.1 Gut microbiome as a driver of hypertension

Murine studies show that fecal transplantation from hypertensive donors elevates BP in normotensive recipients, demonstrating a causal link between GD and hypertension [32]. GD is accompanied by heightened immune activation, with macrophage infiltration and overproduction of proinflammatory cytokines such as IL6 and TNFα, leading to vascular injury and endothelial dysfunction [10, 33].

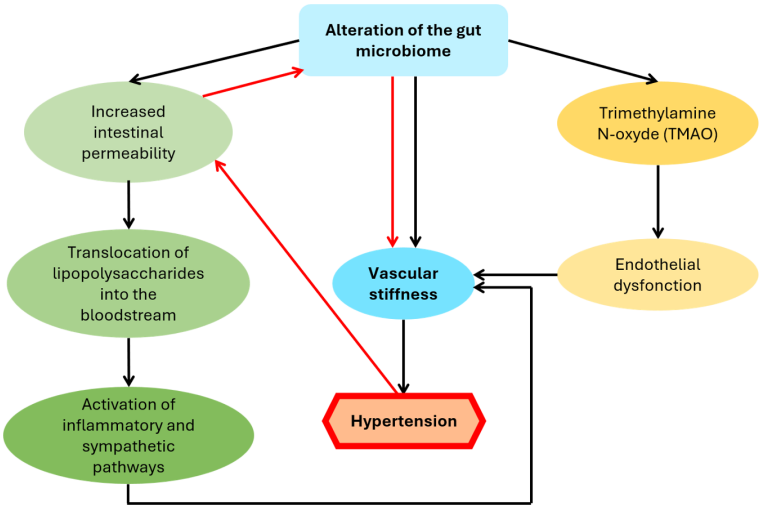
LPS from Gramnegative bacteria translocate across a compromised gut barrier and engage Tolllikereceptor4 (TLR4) on immune cells. This triggers the IKK–NFκB cascade, driving proinflammatory gene expression and chronic innate immune activation. The resulting inflammation fosters RAAS overactivity, vasoconstriction, and sodium retention. Concurrently, oxidative stress increases reactive oxygen species, depleting nitric oxide and exacerbating arterial stiffness [34].

2.3.2 Hypertension as a modulator of the gut microbiome

Persistent BP elevation alters the intestinal ecosystem [35–39]. Haemodynamic changes reduce mesenteric blood flow, disturbing the luminal milieu and disadvantaging strict anaerobes, thereby favouring dysbiosis [13]. HTN also disrupts epithelial tight junction proteins (claudin1, occludin, ZO1), increasing gut permeability (“leaky gut”). Translocated LPS activates TLR4 on immune cells, sustaining NFκBmediated cytokine release (IL6, TNFα, IL1β) that worsens vascular inflammation, remodelling, and BP elevation [10, 31, 40].

This chronic inflammatory state further impairs barrier integrity and diminishes beneficial metabolites such as butyrate, reinforcing the hypertensivedysbiosis loop. HTN should therefore be viewed not merely as a cardiovascular disorder but as a multifactorial condition with a critical microbial–digestive component. Recognising this bidirectionality opens therapeutic avenues centred on GBM modulation [13, 31].

Figure 1 illustrates these bidirectional pathophysiological mechanisms. GD heightens intestinal permeability, facilitating systemic LPS translocation. LPS activate inflammatory and sympathetic pathways that raise BP. GD also increases production of the proatherogenic metabolite TMAO, promoting endothelial dysfunction and vascular stiffness, key contributors to HTN. Red arrows highlight the twoway interactions: hypertensioninduced intestinal hypoperfusion and chronic inflammation exacerbate dysbiosis, perpetuating a pathogenic loop. This model positions the GBM as a pivotal regulator of cardiovascular homeostasis and underscores microbiometargeted interventions as promising therapeutic strategies for HTN management.



Note: The red arrows vividly depict the bidirectional nature of the interplay between hypertension and gut dysbiosis, highlighting mutual influences that can perpetuate a vicious cycle.

Figure 1 Bidirectional pathophysiological mechanisms linking gut dysbiosis and hypertension

3 Potential applications: Toward gut microbiome modulation for hypertension management

The burgeoning field of gutmicrobiome research has profoundly reshaped our understanding of HTN pathophysiology. Given the demonstrated role of GD in the initiation and maintenance of elevated BP, targeted microbiome modulation now represents an innovative, multidimensional therapeutic strategy. The overarching goal is to restore intestinal eubiosis and thereby interrupt the inflammatory, metabolic, and vascular feedback loops that sustain HTN.

3.1 Role of probiotics and prebiotics

Probiotics, defined as live microorganisms that confer a health benefit when administered in adequate amounts, are among the most extensively studied microbiome interventions. Several randomized trials report that specific *Lactobacillus* strains (*L. plantarum, L. casei, L. helveticus*) and *Bifidobacterium* spp. can significantly lower both systolic and diastolic blood pressure by reshaping microbial composition, enhancing barrier integrity, boosting SCFA production, and modulating host immune responses [41, 42].

Prebiotics including soluble fibres, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), selectively promote the growth of beneficial bacteria and augment antihypertensive metabolite production. They also reduce circulating LPS levels, key drivers of the lowgrade inflammation associated with HTN [43, 44].

3.1.1 Dietary approaches to shape the gut microbiome and blood pressure

Diet is a primary architect of the gut microbiome and, consequently, of BP regulation. Diets rich in fibre, fruits, vegetables, polyphenols, omega3 fatty acids, and fermented dairy

products are linked to higher microbial diversity, increased SCFA output, and tighter intestinal permeability, all factors that help lower BP [13, 34].

Nutritional patterns such as the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet exert robust antihypertensive effects through antiinflammatory, antioxidant, and microbiomemodulating actions. Their high content of soluble fibre, flavonoids, potassium, and magnesium benefits endothelial function and reduces arterial stiffness [45, 46].

3.2 Pharmacological perspectives: Toward molecularly targeted approaches

3.2.1 Postbiotics and modulation of key molecular pathways

Postbiotics, bioactive metabolites generated by gut bacteria, constitute a new therapeutic class capable of directly regulating molecular pathways implicated in HTN. SCFAs (acetate, propionate, butyrate) activate Gproteincoupled receptors (GPR41, GPR43) and elicit hypotensive effects through vasodilatation, oxidativestress reduction, and innateimmune modulation [47].

These metabolites also impinge on the RAAS by downregulating angiotensinconverting enzyme (ACE) expression, thereby limiting angiotensin II generation, a potent vasoconstrictor and proinflammatory agent [48]. Moreover, butyrate and related postbiotics inhibit M1macrophage activation and curb cytokine release (TNFα, IL6, IL1β), helping to prevent chronic vascular inflammation.

3.2.2 TrimethylamineNoxide inhibition: An Emerging metabolic target

TMAO, a prohypertensive metabolite derived from microbial metabolism of dietary choline and carnitine, has emerged as both biomarker and pathogenetic mediator in cardiovascular disease. TMAO promotes vascular stiffness, endothelial dysfunction, and RAAS activation, thereby worsening blood pressure control [40, 49]. Current therapeutic avenues include:

(1) FMO3 inhibition: Flavincontaining monooxygenase3 catalyses conversion of trimethylamine (TMA) to TMAO [50]. Pharmacological blockade of FMO3 reduces plasma TMAO and its deleterious effects [51, 52].

(2) Targeted microbiome modulation: Dietary strategies or selected probiotics can diminish TMAproducing bacteria, curtailing TMAO formation upstream [53, 54].

(3) Blocking TMAOinduced endothelial signalling: TMAO upregulates endothelin1, a potent vasoconstrictor [55]. Inhibiting this pathway could restore normal vascular function [56].

4 Conclusion and future perspectives

4.1 Summary of pathophysiological mechanisms

The interactions between the GBM and BP regulation reveal a complex bidirectional relationship, involving both pro-hypertensive and antihypertensive mediators. GD, characterized by qualitative and quantitative alterations in the microbial community, enhances intestinal barrier permeability, allowing systemic translocation of LPS. These microbial components activate Toll-like receptor 4 (TLR4), triggering an inflammatory cascade through the NF-κB signaling pathway, which leads to the production of pro-inflammatory cytokines (IL-6, TNF-α). The resulting vascular stiffness, endothelial dysfunction, and sympathetic overactivation are central drivers of HTN.

Conversely, some microbial metabolites, such as short-chain fatty acids (SCFAs), exert vasoprotective effects via the activation of G-protein-coupled receptors (GPR41, GPR43). These effects include favorable modulation of the RAAS, reduction of oxidative stress, and promotion of vasodilation. In contrast, TMAO, a metabolite derived from choline and carnitine metabolism, is associated with increased arterial stiffness and RAAS activation, reinforcing the pro-hypertensive profile of Western dietary patterns.

4.2 Methodological challenges and current gaps

Despite significant progress, several limitations hinder the clinical translation of current findings. First, the high interindividual variability of the GBM, shaped by genetic, dietary, environmental, and geographic factors, complicates the identification of universal microbial signatures associated with hypertension. Second, most available evidence arises from cross-sectional, observational, or preclinical studies, with a lack of longitudinal and randomized clinical trials necessary to establish robust causal relationships.

Moreover, microbiome-targeted interventions (probiotics, prebiotics, postbiotics, and dietary strategies) lack standardization in terms of dosage, duration, tolerability, and long-term outcomes, limiting their widespread clinical adoption.

4.3 Research outlook and clinical development

To overcome these challenges, an integrative approach leveraging multi-omics technologies, such as metagenomics, metabolomics, transcriptomics, and proteomics, is essential to better understand the dynamic host–microbiome interactions in the context of HTN. This strategy could facilitate the identification of robust microbial biomarkers for diagnostic, prognostic, or therapeutic purposes.

Personalized interventions tailored to individual microbial profiles pave the way for microbiome-based precision medicine. Nutritional or pharmacological therapies could thus be adapted to each patient's metabolic and immunological characteristics. For example, diets enriched in soluble fiber, polyphenols, or specific microbial substrates may serve as adjuncts or alternatives to conventional antihypertensive therapies.

4.4 Toward concrete translational applications

Gut microbiome modulation is emerging as an innovative, multidimensional, and promising approach for the prevention and management of HTN. By targeting multiple pathophysiological pathways, including systemic inflammation, oxidative stress, intestinal permeability, RAAS activation, and endothelial dysfunction, interventions involving probiotics, prebiotics, postbiotics, or specialized nutrition offer novel therapeutic prospects.

However, their implementation in clinical practice will require large-scale, randomized controlled trials to confirm their efficacy, safety, and long-term sustainability. Ultimately, the strategic combination of pharmacotherapy, functional nutrition, and microbiome modulation may transform the management of HTN, integrating it into a broader, more holistic and sustainable model of cardiovascular health.

Conflicts of interest

The authors declare that they have no conflict of interest.

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