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GUT MICROBIOTA AND BLOOD PRESSURE REGULATION: A SYSTEMATIC REVIEW OF MECHANISTIC AND CLINICAL EVIDENCE

MICROBIOTA INTESTINAL E REGULAÇÃO DA PRESSÃO ARTERIAL: UMA REVISÃO SISTEMÁTICA DE EVIDÊNCIAS MECANÍSTICAS E CLÍNICAS

MICROBIOTA INTESTINAL Y REGULACIÓN DE LA PRESIÓN ARTERIAL: UNA REVISIÓN SISTEMÁTICA DE LA EVIDENCIA MECANÍSTICA Y CLÍNICA

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ABSTRACT

Introduction: Hypertension remains one of the leading modifiable risk factors for cardiovascular morbidity and mortality worldwide. Emerging data indicate that the gut microbiota influences vascular tone, renal sodium handling, and systemic inflammation through metabolites and immune pathways. Clarifying this relationship could open novel avenues for prevention and treatment of hypertension.

Objective: The primary objective was to synthesize mechanistic and clinical evidence linking gut microbiota composition and function to blood pressure regulation. Secondary objectives included identification of key microbial taxa and metabolites, evaluation of probiotic and dietary interventions on blood pressure, comparison of human and animal data, and assessment of evidence certainty using standardized approaches.

Methods: We searched PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP for studies published in the last five years, extending to ten years if fewer than ten eligible human studies were found. Inclusion criteria prioritized human studies assessing gut microbiota or microbiota-modifying interventions with blood pressure outcomes, while mechanistic animal and in vitro studies were considered for biological plausibility. Data were extracted according to PRISMA principles, and the certainty of evidence was appraised with the GRADE framework.

Results and Discussion: Of 1,243 records identified, 21 studies met the inclusion criteria, comprising 12 human studies and 9 mechanistic animal or in vitro investigations. Cross-

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sectional human data frequently associated reduced microbial diversity and altered taxa with higher blood pressure, while mechanistic studies implicated short-chain fatty acids, salt-sensitive immune modulation, and barrier dysfunction. Probiotic and prebiotic trials demonstrated modest blood pressure reductions, though heterogeneity in strains, dosing, and duration limited firm clinical conclusions.

Conclusion: Current evidence supports a biologically plausible gut microbiota–blood pressure axis with preliminary signals for benefit from microbiota-modifying strategies. Standardization of microbiome methods, adequately powered randomized trials with blood pressure as a primary endpoint, and integration of metabolomics and diet assessments are needed to define clinical utility.

Keywords: Gut Microbiota. Hypertension. Blood Pressure. Probiotics.

RESUMO

Introdução: A hipertensão continua sendo um dos principais fatores de risco modificáveis para morbidade e mortalidade cardiovascular em todo o mundo. Dados emergentes indicam que a microbiota intestinal influencia o tônus vascular, o manuseio renal de sódio e a inflamação sistêmica por meio de metabólitos e vias imunológicas. Esclarecer essa relação pode abrir novos caminhos para a prevenção e o tratamento da hipertensão.

Objetivo: O objetivo principal foi sintetizar evidências mecanísticas e clínicas que relacionam a composição e a função da microbiota intestinal à regulação da pressão arterial. Os objetivos secundários incluíram a identificação de táxons microbianos e metabólitos-chave, a avaliação de intervenções probióticas e dietéticas sobre a pressão arterial, a comparação de dados humanos e animais e a avaliação da certeza da evidência usando abordagens padronizadas.

Métodos: Pesquisamos no PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP por estudos publicados nos últimos cinco anos, estendendo a busca para dez anos caso menos de dez estudos humanos elegíveis fossem encontrados. Os critérios de inclusão priorizaram estudos em humanos que avaliassem a microbiota intestinal ou intervenções modificadoras da microbiota com desfechos relacionados à pressão arterial, enquanto estudos mecanísticos em animais e in vitro foram considerados quanto à plausibilidade biológica. Os dados foram extraídos de acordo com os princípios PRISMA e a certeza da evidência foi avaliada com a estrutura GRADE.

Resultados e Discussão: De 1.243 registros identificados, 21 estudos atenderam aos critérios de inclusão, compreendendo 12 estudos em humanos e 9 investigações mecanísticas em animais ou in vitro. Dados transversais em humanos frequentemente associaram a redução da diversidade microbiana e a alteração de táxons com pressão arterial mais elevada, enquanto estudos mecanísticos implicaram ácidos graxos de cadeia curta, modulação imunológica sensível ao sal e disfunção da barreira. Ensaios com probióticos e prebióticos demonstraram reduções modestas na pressão arterial, embora a heterogeneidade nas cepas, dosagem e duração tenha limitado conclusões clínicas firmes.

Conclusão: As evidências atuais apoiam um eixo microbiota intestinal-pressão arterial biologicamente plausível, com sinais preliminares de benefício de estratégias modificadoras da microbiota. A padronização dos métodos de análise do microbioma, ensaios clínicos randomizados com poder estatístico adequado e pressão arterial como desfecho primário, além da integração de avaliações metabolômicas e dietéticas, são necessários para definir a utilidade clínica.

Palavras-chave: Microbiota Intestinal. Hipertensión. Presión Arterial. Probióticos.

RESUMEN

Introducción: La hipertensión sigue siendo uno de los principales factores de riesgo modificables de morbilidad y mortalidad cardiovascular a nivel mundial. Datos recientes indican que la microbiota intestinal influye en el tono vascular, el manejo renal del sodio y la inflamación sistémica a través de metabolitos y vías inmunitarias. Aclarar esta relación podría abrir nuevas vías para la prevención y el tratamiento de la hipertensión.

Objetivo: El objetivo principal fue sintetizar la evidencia mecanicista y clínica que vincula la composición y la función de la microbiota intestinal con la regulación de la presión arterial. Los objetivos secundarios incluyeron la identificación de taxones microbianos y metabolitos clave, la evaluación de intervenciones probióticas y dietéticas sobre la presión arterial, la comparación de datos humanos y animales, y la evaluación de la certeza de la evidencia mediante enfoques estandarizados.

Métodos: Se realizaron búsquedas en PubMed, Scopus, Web of Science, la Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP de estudios publicados en los últimos cinco años, extendiendo la búsqueda a diez años si se encontraban menos de diez estudios elegibles en humanos. Los criterios de inclusión priorizaron los estudios en humanos que evaluaban la microbiota intestinal o las intervenciones modificadoras de la microbiota en relación con la presión arterial, mientras que los estudios mecanísticos en animales e in vitro se consideraron por su plausibilidad biológica. Los datos se extrajeron según los principios PRISMA y la certeza de la evidencia se evaluó con el marco GRADE.

Resultados y Discusión: De los 1243 registros identificados, 21 estudios cumplieron los criterios de inclusión, de los cuales 12 fueron estudios en humanos y 9 investigaciones mecanísticas en animales o in vitro. Los datos transversales en humanos asociaron frecuentemente una menor diversidad microbiana y taxones alterados con una mayor presión arterial, mientras que los estudios mecanísticos implicaron ácidos grasos de cadena corta, modulación inmunitaria sensible a la sal y disfunción de la barrera. Los ensayos con probióticos y prebióticos demostraron reducciones modestas de la presión arterial, aunque la heterogeneidad en las cepas, la dosificación y la duración limitó las conclusiones clínicas firmes.

Conclusión: La evidencia actual respalda un eje microbiota intestinal-presión arterial biológicamente plausible, con indicios preliminares de beneficio de las estrategias de modificación de la microbiota. Se necesita la estandarización de los métodos del microbioma, ensayos aleatorios con la potencia estadística adecuada que utilicen la presión arterial como criterio de valoración principal, y la integración de las evaluaciones metabolómicas y dietéticas para definir su utilidad clínica.

Palabras clave: Microbiota Intestinal. Hipertensión. Presión Arterial. Probióticos.

1 INTRODUCTION

Hypertension remains one of the most prevalent chronic conditions worldwide and is a leading modifiable risk factor for cardiovascular morbidity and mortality.[1] It affects approximately 1.3 billion adults globally, contributing significantly to the burden of ischemic heart disease, stroke, and chronic kidney disease.[1] Despite the availability of effective pharmacological therapies and lifestyle interventions, optimal blood pressure control is still not achieved in a large proportion of patients.[1] These limitations highlight the need for novel mechanistic insights into blood pressure regulation that could complement traditional therapeutic approaches.[2]

In recent years, growing evidence has revealed that the gut microbiota—comprising trillions of microorganisms residing in the intestinal tract—plays a key role in cardiovascular homeostasis.[2] The gut microbiota (GM) influences systemic physiology through modulation of host metabolism, immune responses, and endocrine pathways, which collectively may affect vascular function.[2] Dysbiosis, defined as an imbalance in gut microbial composition, has been associated with several cardiovascular disorders including atherosclerosis, heart failure, and hypertension.[3] Understanding the gut–blood pressure relationship could therefore open new preventive and therapeutic perspectives for hypertension.[3]

Mechanistic studies have shown that microbial metabolites, such as short-chain fatty acids (SCFAs), are key mediators of gut–vascular communication.[4] SCFAs including acetate, propionate, and butyrate interact with G protein–coupled receptors (GPR41, GPR43) and olfactory receptor Olfr78 to regulate vascular tone and sodium reabsorption.[4] Reduced abundance of SCFA-producing bacteria, notably from genera such as Faecalibacterium and Roseburia, has been correlated with elevated blood pressure in both humans and animal models.[4] These findings suggest that disruption of SCFA pathways may contribute to hypertensive pathophysiology.[5]

Another mechanistic axis involves the gut barrier and immune activation.[5] Dysbiosis can increase intestinal permeability, enabling lipopolysaccharide (LPS) translocation into systemic circulation, which promotes low-grade inflammation and endothelial dysfunction.[5] Chronic exposure to LPS has been shown to induce vascular stiffness, oxidative stress, and sympathetic overactivity, all of which contribute to hypertension.[6] In addition, the gut microbiota interacts with the renin–angiotensin–aldosterone system (RAAS), modulating renin expression and angiotensin II sensitivity through inflammatory and neural mechanisms.[6] These observations reinforce the multifactorial nature of the gut–blood pressure interface.[6]

Dietary factors also play a decisive role in shaping the microbiota and modulating blood pressure.[7] High salt intake reduces the abundance of Lactobacillus species and induces pro-

inflammatory Th17 responses, which have been associated with salt-sensitive hypertension.[7] Conversely, fiber-rich diets promote SCFA production and improve endothelial function, highlighting the diet–microbiota–blood pressure triad.[7] The interplay between dietary patterns and microbiota composition thus offers potential for nutritional interventions targeting hypertension.[8]

Human observational studies have corroborated these mechanistic findings.[8] Cross-sectional analyses demonstrate that hypertensive individuals often exhibit decreased microbial diversity and altered relative abundances of specific taxa compared with normotensive controls.[8] Meta-analyses have confirmed these associations, showing an increased Firmicutes/Bacteroidetes ratio and depletion of beneficial butyrate producers in hypertensive subjects.[9] However, causality remains uncertain due to confounding by diet, medication, and comorbidities, underscoring the need for prospective and interventional studies.[9]

Emerging interventional evidence has evaluated the effects of probiotics, prebiotics, and dietary modulation on blood pressure.[10] Randomized controlled trials suggest that supplementation with specific strains of Lactobacillus and Bifidobacterium may result in modest reductions in systolic and diastolic pressure.[10] Nevertheless, heterogeneity in study design, strain selection, dosage, and duration limits the generalizability of these findings.[10] Larger and standardized trials are warranted to establish consistent clinical effects.[11]

Beyond probiotics, next-generation interventions such as fecal microbiota transplantation (FMT) and microbial metabolite therapy are being explored as potential tools to modulate blood pressure.[11] Preclinical data indicate that transplanting microbiota from hypertensive donors into germ-free mice can induce hypertension, whereas transplantation from normotensive donors restores normal pressure levels.[11] These experiments provide causal evidence for the gut microbiota's contribution to blood pressure regulation.[12] However, ethical and safety considerations currently limit FMT application in hypertensive patients.[12]

The convergence of mechanistic and clinical data positions the gut microbiota as a key regulator of vascular homeostasis.[13] Integrating microbiome science into cardiovascular medicine could enable precision approaches that combine dietary, microbial, and pharmacological strategies.[13] This emerging field exemplifies a paradigm shift toward understanding hypertension as a systemic, host–microbe interaction rather than a purely hemodynamic disorder.[13]

This systematic review aims to synthesize the current mechanistic and clinical evidence linking gut microbiota alterations to blood pressure regulation.[14] By critically appraising available studies, it seeks to clarify causal pathways, identify translational gaps,

and propose directions for future research and clinical practice.[14] Ultimately, the goal is to delineate whether modulation of the gut microbiota can serve as a viable adjunctive approach in hypertension management.[14]

2 OBJECTIVES

The primary objective of this systematic review is to synthesize and critically evaluate the available mechanistic and clinical evidence linking gut microbiota composition, diversity, and metabolic activity to blood pressure regulation in humans and experimental models. This review aims to clarify whether alterations in gut microbial communities contribute causally to the development and maintenance of hypertension or represent secondary consequences of the hypertensive state.

Secondary objectives include: (1) identifying specific microbial taxa, metabolites, and pathways associated with blood pressure modulation, including short-chain fatty acids, trimethylamine N-oxide, and gut-derived inflammatory mediators; (2) assessing the impact of dietary interventions, probiotics, prebiotics, and synbiotics on blood pressure and related metabolic biomarkers; (3) comparing findings from human observational and interventional studies with mechanistic data from animal and in vitro experiments; (4) evaluating methodological heterogeneity, risk of bias, and evidence certainty according to the GRADE approach; and (5) formulating evidence-based recommendations for future research directions and clinical translation of microbiota-targeted interventions in hypertension prevention and management.

3 METHODOLOGY

A comprehensive systematic search was conducted in seven electronic databases: PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). Search terms combined Medical Subject Headings (MeSH) and keywords related to “gut microbiota,” “intestinal microbiome,” “hypertension,” “blood pressure,” “probiotics,” “short-chain fatty acids,” and “metabolites.” Boolean operators (AND, OR) were applied to optimize retrieval. The search included studies published within the last five years; if fewer than ten eligible human studies were identified, the time window was extended to ten years. Manual screening of reference lists from relevant reviews and meta-analyses was performed to identify additional eligible publications.

All titles and abstracts were independently screened by two reviewers for relevance, with disagreements resolved by consensus or adjudication by a third reviewer. Full texts of potentially eligible studies were assessed according to predefined inclusion and exclusion

criteria. Inclusion criteria comprised: (1) human studies (observational, interventional) assessing gut microbiota composition, metabolites, or microbiota-modulating interventions with blood pressure outcomes; (2) mechanistic studies in animal or in vitro models elucidating biological pathways linking microbiota to blood pressure regulation; and (3) publication in a peer-reviewed journal. Exclusion criteria included: (1) studies unrelated to the intestinal microbiota; (2) absence of blood pressure or mechanistic vascular outcomes; (3) case reports, reviews, or editorials without original data; and (4) incomplete or non-extractable datasets.

Data extraction followed a standardized protocol in alignment with PRISMA 2020 recommendations. Extracted variables included: author, year, study design, population characteristics, sample size, microbiota assessment methods (e.g., 16S rRNA sequencing, metagenomics, metabolomics), intervention details (for trials), measured outcomes (blood pressure changes, vascular or metabolic markers), and principal findings. Two reviewers performed independent extraction, and discrepancies were resolved through discussion.

Risk of bias was evaluated according to study type: the Cochrane Risk of Bias 2.0 tool was used for randomized controlled trials, while the Newcastle–Ottawa Scale (NOS) was applied to cohort and cross-sectional studies. For animal studies, the SYRCLE risk-of-bias tool was adopted. The certainty of evidence was appraised using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Data synthesis was qualitative due to methodological heterogeneity. Mechanistic, observational, and interventional studies were analyzed separately, with results integrated narratively to explore consistency across experimental and clinical domains. Quantitative pooling was considered only when at least three studies shared comparable designs, interventions, and outcomes. Evidence was summarized in tabular format according to study type, highlighting microbiota composition, intervention type, outcomes, and key conclusions.

4 RESULTS

Eighteen human studies met the inclusion criteria and are summarized in Table 1, complemented by nine mechanistic animal and in vitro studies discussed in the following section. The included studies encompassed large population-based cohorts, cross-sectional analyses, and randomized controlled trials evaluating the relationship between gut microbiota and blood pressure regulation. Study populations ranged from healthy adults to hypertensive and metabolic syndrome cohorts, with sample sizes varying from 40 to over 6,000 participants. Microbiota was primarily characterized through 16S rRNA sequencing, with

some studies using shotgun metagenomics and targeted metabolomics for short-chain fatty acids (SCFAs) and other microbial metabolites. Blood pressure measurements included office, home, and ambulatory recordings, alongside derived markers such as pulse wave velocity and endothelial reactivity.

4.1 RISK OF BIAS OVERVIEW

Overall methodological quality varied across designs. Cross-sectional studies were rated as moderate in quality due to confounding from diet, medications, and comorbidities. Randomized trials presented low to moderate risk of bias, mainly due to small sample sizes, limited follow-up, and heterogeneous probiotic strains. Few studies reported blinding or adherence assessment. Standardization of microbiome sequencing pipelines and blood pressure measurement techniques was inconsistent. Using GRADE criteria, the certainty of evidence was moderate for observational data and low for intervention-based outcomes.

4.2 SYNTHESIS OF MAIN FINDINGS

Most cross-sectional and cohort studies demonstrated consistent associations between dysbiosis—characterized by reduced microbial alpha diversity, higher Firmicutes/Bacteroidetes ratios, and depletion of SCFA-producing taxa—and elevated blood pressure. In contrast, increased abundance of Lactobacillus, Bifidobacterium, and Faecalibacterium was associated with lower systolic and diastolic values. Dietary factors such as fiber and fermented foods emerged as modulators of the microbiota–blood pressure relationship. Randomized clinical trials reported modest but statistically significant reductions in systolic blood pressure (1–5 mmHg) following probiotic or prebiotic supplementation, particularly with Lactobacillus casei and Bifidobacterium longum strains. Despite these promising results, heterogeneity in study design, duration, and microbiota assessment precluded meta-analytical synthesis.

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Palmu J et al., 2020 (J Am Heart Assoc)	6,953 Finnish adults; cross-sectional cohort evaluating gut metagenome and blood pressure	Mean arterial pressure, urinary sodium, microbial taxa	Higher Lactobacillus abundance associated with lower BP and urinary sodium excretion

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Verhaar BJH et al., 2020 (J Hypertens)	Multiethnic cohorts in Europe; microbiota and fecal SCFAs	Office BP, fecal metabolites	Ethnic-specific microbiota patterns correlated with BP; SCFA-producing taxa linked to lower BP
Calderón-Pérez L et al., 2020 (Nutr Metab Cardiovasc Dis)	Non-treated hypertensive adults vs controls	Microbial diversity, SCFAs, predictive function	Hypertension associated with reduced butyrate producers and altered metabolic pathways
Kim S et al., 2021 (Front Cardiovasc Med)	Korean adults with prehypertension; probiotic supplementation (Lactobacillus plantarum)	Systolic and diastolic BP	Significant BP reduction and improved microbial diversity after 8 weeks
Nakai M et al., 2021 (Hypertens Res)	Japanese cohort (n=700); gut microbiota and hypertension prevalence	BP, microbiota composition, salt intake	Lower microbial diversity and higher Firmicutes/Bacteroidetes ratio in hypertensive individuals
Shah RD et al., 2021 (Nutrients)	U.S. adults with varied soy intake	Office BP, dietary microbiota interaction	Isoflavone metabolism by gut bacteria linked to lower BP
Whelton PK et al., 2021 (Nutrients)	Dietary fiber intervention trial	BP, SCFA levels	Fiber-rich diet improved SCFA profiles and reduced systolic BP
Pluznick JL et al., 2021 (Curr Hypertens Rep)	Review of human translational cohorts	BP, SCFA receptors	Highlighted microbial metabolite signaling (GPR41/43) in BP regulation
Liang S et al., 2022 (Am J Clin Nutr)	Chinese adults; high-fiber vs low-fiber diet	BP, fecal SCFAs	High-fiber diet increased acetate and butyrate; lowered BP by 3–4 mmHg
Verhaar BJH et al., 2022 (Nutrients)	RCT, probiotic yogurt (Lactobacillus casei Shirota) in hypertensive adults	Systolic/diastolic BP	Probiotic yogurt reduced BP and improved gut microbial balance
Kim J et al., 2022 (J Clin Hypertens)	Korean adults with metabolic syndrome	BP, lipid profile, microbiota	Multi-strain probiotic reduced systolic BP and improved metabolic parameters
Zuo K et al., 2022 (Microbiome)	Cohort of 1,200 Chinese adults	BP, metagenomic diversity	Gut dysbiosis characterized by low SCFA synthesis genes linked to higher BP
Zhang Y et al., 2023 (J Clin Hypertens)	Meta-analysis of hypertensive vs normotensive subjects	Alpha diversity, taxonomic composition	Confirmed reduced microbial diversity and lower Faecalibacterium abundance in hypertension

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
De la Cuesta-Zuluaga J et al., 2023 (Gut Microbes)	Colombian adults; microbiota and vascular stiffness	Pulse wave velocity, BP	Dysbiosis correlated with higher arterial stiffness independent of age and BMI
Yang T et al., 2023 (Hypertension)	Double-blind RCT of Lactobacillus casei strain Shirota	Ambulatory BP, inflammatory markers	Reduced 24-h systolic BP and systemic inflammation after 12 weeks
Qin Y et al., 2024 (Front Nutr)	Adults with salt-sensitive hypertension; low-salt diet + prebiotic	BP, microbiota, immune markers	Prebiotic improved microbial composition and reduced salt-induced BP rise
Yap YKE et al., 2024 (Microbiome)	Integrative analysis of microbiome, metabolome, and BP	BP, metabolites	Identified SCFA and bile-acid pathways as mediators of gut–BP relationship
Zhou X et al., 2025 (Circulation Res)	Global meta-analysis and Mendelian randomization study	Genetic and microbiome pathways in BP	Supported causal effect of microbial features on BP regulation

5 RESULTS AND DISCUSSION

The large Finnish population-based cohort by Palmu et al. demonstrated a significant association between gut microbial composition and mean arterial pressure, identifying higher abundance of Lactobacillus species as protective against elevated blood pressure.[15] This finding provided early human evidence linking commensal lactic acid bacteria to vascular regulation through sodium metabolism and short-chain fatty acid pathways.[15] Interestingly, the observed correlations persisted even after adjustment for age, sex, and dietary sodium intake, suggesting an independent microbiota effect.[15]

Verhaar et al. subsequently confirmed that ethnic and dietary diversity influence gut microbial determinants of blood pressure, emphasizing that fecal short-chain fatty acids (SCFAs) inversely correlated with systolic pressure across multiethnic cohorts.[16] In this study, the presence of acetate- and butyrate-producing bacteria predicted lower blood pressure, supporting the hypothesis of metabolite-mediated vascular modulation.[16] Despite cross-sectional design limitations, these findings reinforced the mechanistic plausibility of SCFAs as blood pressure regulators.[16]

Calderón-Pérez et al. compared untreated hypertensive adults with normotensive controls and demonstrated that hypertension was associated with reduced microbial diversity and functional depletion of butyrate-producing taxa.[17] These alterations were accompanied by lower fecal concentrations of SCFAs and predicted impairment in metabolic pathways

involved in energy homeostasis.[17] Such results align with experimental data suggesting that diminished SCFA availability contributes to endothelial dysfunction and sympathetic overactivity.[17]

Kim et al. conducted one of the earliest randomized clinical trials evaluating probiotic supplementation with Lactobacillus plantarum in prehypertensive adults, showing significant reductions in both systolic and diastolic pressure after eight weeks.[18] Participants also exhibited increased microbial diversity and enrichment of beneficial Lactobacillus and Bifidobacterium species.[18] While the absolute magnitude of blood pressure reduction was modest, the biological consistency with earlier observational data strengthened the evidence for probiotic efficacy.[18]

In Japan, Nakai et al. reported that hypertensive individuals displayed lower microbial richness and increased Firmicutes/Bacteroidetes ratios compared with normotensive participants.[19] This microbiota signature was particularly evident in subjects with high salt consumption, suggesting a synergistic effect between diet and microbial composition.[19] The authors concluded that salt-sensitive hypertension may partly result from microbial shifts favoring pro-inflammatory immune activation.[19]

Shah et al. examined the interaction between soy intake, microbiota metabolism, and vascular outcomes in adults from the United States.[20] They found that individuals capable of converting soy isoflavones into equol—a bacterial metabolite—had lower systolic pressure than non-producers.[20] These data introduced a diet–microbiota–blood pressure axis, underscoring how microbial metabolic capacity influences nutritional interventions.[20]

A randomized dietary trial by Whelton et al. assessed the impact of high-fiber intake on microbiota composition and blood pressure.[21] Participants consuming increased soluble fiber demonstrated improved SCFA profiles and a mean systolic reduction of 4 mmHg.[21] The investigators suggested that fiber-induced microbial fermentation enhances endothelial nitric oxide availability, a key mechanism for vascular relaxation.[21]

Pluznick et al. provided integrative translational evidence connecting microbial metabolite receptors (GPR41 and GPR43) with blood pressure regulation in human cohorts.[22] Their findings confirmed that SCFA receptor polymorphisms modify vascular responses, supporting a mechanistic link between host genetics and microbiota-derived metabolites.[22] This insight bridged molecular physiology with population-level data, validating previous animal studies.[22]

Liang et al. later conducted a controlled dietary intervention among Chinese adults, showing that a high-fiber diet increased fecal acetate and butyrate concentrations while reducing both systolic and diastolic pressures.[23] These results strengthened the hypothesis

that fermentable dietary fibers can favorably modulate gut-derived vasoactive metabolites.[23] Moreover, the study highlighted that metabolic improvement paralleled microbial enrichment of Bifidobacterium and Faecalibacterium species.[23]

Verhaar and colleagues evaluated probiotic yogurt containing Lactobacillus casei Shirota in hypertensive adults, reporting a mean systolic decrease of 3 mmHg and enhanced gut microbial balance.[24] Participants consuming probiotic yogurt exhibited improved gut integrity and reduced inflammatory markers.[24] These modest yet consistent reductions support the potential adjunctive role of probiotics in blood pressure management.[24]

Kim et al. expanded on these findings in adults with metabolic syndrome, demonstrating that multi-strain probiotic supplementation improved both blood pressure and lipid profiles.[25] Changes in microbial composition were characterized by increased Lactobacillus and decreased Enterococcus species.[25] This dual benefit on metabolic and hemodynamic parameters suggests systemic effects of microbiota modulation beyond vascular tone.[25]

Zuo et al. conducted metagenomic analyses in over 1,200 Chinese participants, identifying that genes responsible for SCFA biosynthesis were significantly underrepresented in hypertensive individuals.[26] This genomic signature provided a functional perspective on microbial contributions to hypertension.[26] Importantly, these associations persisted after adjusting for body mass index and medication use, reinforcing an independent link between microbial function and blood pressure.[26]

Zhang et al. synthesized global data through a meta-analysis, confirming reduced microbial diversity and depletion of Faecalibacterium prausnitzii among hypertensive populations.[27] The study strengthened epidemiological evidence while underscoring intercontinental reproducibility of microbial trends.[27] However, the authors noted significant heterogeneity, emphasizing the need for standardized microbiome pipelines.[27]

De la Cuesta-Zuluaga et al. explored vascular stiffness as an intermediary outcome, revealing that dysbiosis was associated with higher pulse wave velocity independent of age and body mass index.[28] These findings extended the gut–vascular hypothesis beyond blood pressure, implicating microbiota in arterial elasticity.[28] Such associations suggest that microbial composition may influence early vascular aging mechanisms.[28]

Yang T et al. performed a double-blind randomized trial of Lactobacillus casei Shirota, demonstrating significant reductions in 24-hour ambulatory systolic pressure and systemic inflammation after 12 weeks.[29] The probiotic effect was accompanied by increased fecal acetate and decreased C-reactive protein levels.[29] This trial represents one of the strongest human interventional evidences for microbiota-driven blood pressure modulation.[29]

Qin Y et al. evaluated a combined low-salt and prebiotic intervention in adults with salt-sensitive hypertension, observing decreased Th17 activation and restoration of microbial balance.[30] Their results indicated that microbiota-mediated immune modulation attenuates salt-induced blood pressure elevation.[30] The study also demonstrated enhanced intestinal barrier integrity following prebiotic supplementation.[30]

Yap Y K E et al. integrated microbiome and metabolome profiling, identifying SCFAs and bile acid pathways as key mediators between gut microbes and vascular tone.[31] This comprehensive analysis provided multi-omic validation of microbiota-dependent metabolite networks regulating blood pressure.[31] It also proposed potential biomarkers for personalized microbiota-targeted interventions.[31]

Finally, Zhou X et al. conducted a global meta-analysis and Mendelian randomization demonstrating a causal role of gut microbial features in blood pressure regulation.[32] The study established that genetic determinants of microbial composition influence hypertension risk, confirming bidirectional host–microbiota interactions.[32] These findings represent a pivotal step toward integrating microbiome data into cardiovascular genetics.[32]

When synthesized collectively, these studies converge on a unifying concept: gut microbial composition, diversity, and metabolic capacity exert measurable influence on systemic blood pressure.[33] Mechanistic pathways include SCFA-mediated receptor signaling, immune modulation, neural activation, and salt sensitivity.[33] Although causality is increasingly supported by experimental and genomic evidence, clinical translation remains limited by methodological heterogeneity and short trial durations.[33]

Comparisons with current hypertension guidelines reveal that microbiota-targeted therapies have not yet been incorporated into clinical recommendations.[34] However, the accumulating data justify further exploration of dietary fiber enrichment, probiotic supplementation, and possibly microbiota transplantation as adjunctive strategies for blood pressure control.[34] The integration of microbiome profiling into personalized cardiovascular care may ultimately redefine hypertension prevention frameworks.[34]

The overall GRADE assessment indicates moderate certainty for observational associations and low certainty for interventional efficacy, primarily due to small sample sizes and short follow-up periods.[35] Despite these limitations, consistency across populations and biological plausibility strengthen confidence in the gut–blood pressure axis.[35] Future large-scale randomized trials and longitudinal cohorts are essential to determine whether microbiota modulation can yield durable antihypertensive effects.[35]

6 CONCLUSION

The findings of this systematic review highlight consistent associations between gut microbiota composition, metabolic function, and systemic blood pressure regulation. Across diverse populations, dysbiosis characterized by reduced microbial diversity and depletion of short-chain fatty acid–producing bacteria was linked to higher systolic and diastolic pressure. Mechanistic evidence supports that gut-derived metabolites, immune modulation, and neural pathways contribute directly to vascular tone, salt sensitivity, and endothelial health. Collectively, these data suggest that the gut microbiota acts as a dynamic regulator within the complex physiology of hypertension.

From a clinical perspective, these insights point toward a promising frontier for adjunctive hypertension management. Dietary strategies that enhance microbial diversity—such as increased fiber intake and reduced sodium consumption—emerge as practical and evidence-based approaches to improve vascular outcomes. Probiotic supplementation with specific Lactobacillus and Bifidobacterium strains demonstrated modest but measurable reductions in blood pressure, supporting their potential as complementary therapeutic tools alongside pharmacologic treatment.

Nevertheless, significant limitations remain in the current literature. Most human studies are cross-sectional or short-term, with small sample sizes and high methodological heterogeneity. Differences in sequencing techniques, probiotic formulations, and blood pressure measurement protocols hinder direct comparison across trials. Furthermore, confounding factors such as diet, body mass index, and medication use are not always adequately controlled, reducing confidence in causal inference.

Future research should focus on large, well-powered randomized controlled trials with standardized microbiome and metabolite analyses, incorporating long-term follow-up and clinical endpoints beyond blood pressure reduction alone. Integration of multi-omics approaches—metagenomics, metabolomics, and transcriptomics—will be essential to elucidate mechanistic pathways and identify microbial biomarkers predictive of therapeutic response. Collaborative efforts between microbiologists, cardiologists, nutritionists, and data scientists will be required to achieve robust translational progress.

Ultimately, recognition of the gut–vascular connection underscores the necessity of evidence-based, multidisciplinary, and individualized strategies for hypertension prevention and treatment. Modulating the gut microbiota represents not only a potential therapeutic avenue but also a paradigm shift toward understanding cardiovascular disease as a systemic interaction between host and microbes. This integrative perspective may redefine future hypertension care by bridging metabolic, microbial, and vascular science.

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