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REVIEW

Regulatory effect of gut microbes on blood pressure

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Abstract

Hypertension is an important global public health issue because of its high morbidity as well as the increased risk of other diseases. Recent studies have indicated that the development of hypertension is related to the dysbiosis of the gut microbiota in both animals and humans. In this review, we outline the interaction between gut microbiota and hypertension, including gut microbial changes in hypertension, the effect of microbial dysbiosis on blood pressure (BP), indicators of gut microbial dysbiosis in hypertension, and the microbial genera that affect BP at the taxonomic level. For example, increases in *Lactobacillus*, *Roseburia*, *Coprococcus*, *Akkermansia*, and *Bifidobacterium* are associated with reduced BP, while increases in *Streptococcus*, *Blautia*, and *Prevotella* are associated with elevated BP. Furthermore, we describe the potential mechanisms involved in the regulation between gut microbiota and hypertension. Finally, we summarize the commonly used treatments of hypertension that are based on gut microbes, including fecal microbiota transfer, probiotics and prebiotics, antibiotics, and dietary supplements. This review aims to find novel potential genera for improving hypertension and give a direction for future studies on gut microbiota in hypertension.

KEYWORDS
blood pressure, diversity, gut microbe, hypertension, probiotic

1 | INTRODUCTION

Hypertension, the major risk factor for cardiovascular disease, is a major health issue that affects people worldwide. In 2015, 1.13 billion people suffered from hypertension,[1] predicted to reach 1.56 billion by 2025.[2] From 1990 to 2015, the number of deaths from cardiovascular and cerebrovascular disease has dramatically increased, following the trend of hypertension prevalence.[3–5] The pathogenesis of hypertension is complex, with many factors.[6] Numerous single-gene variants associated with hypertension were discovered in previous

study, although they explained only a small fraction of the variation in blood pressure (BP) between individuals (<5%).[7]

Emerging evidence suggests that gut microbes can regulate BP.[8–10] Gut microbial dysbiosis may be attributed to lifetime patterns of cardiovascular disease from childhood to adulthood.[11] The effect of antibiotic therapy on hypertension in rats provides first evidence that the gut microbiota are involved in the etiology of hypertension.[12] Gut microbes may contribute directly to the pathogenesis of hypertension through cellular targets downstream.[8,13] There are some reviews focusing on the relationships between gut microbiota and hypertension.[14–17] However, there are no reviews summarizing the potential microbes regulating BP at the taxonomic level and the variety of probiotics for improving hypertension.

We present a summary of the current developments in understanding the regulatory effects of gut microbes on BP. Specifically, we discuss the interaction observed between gut microbiota and hypertension, categorize the microbial genera that affect BP, and outline how to regulate BP on the basis of gut microbes or probiotics.

2 | THE INTERACTION BETWEEN GUT MICROBIOTA AND HYPERTENSION

2.1 | Changes to gut microbial community in hypertension

Previous studies have suggested the occurrence of gut microbial dysbiosis in animal models and patients with hypertension (Table 1), including decreased microbial diversity as well as disordered structures and functions within the microbial community. Animal models of hypertension, including spontaneously hypertensive rats (SHRs),[8,18–20] angiotensin II (Ang II)-induced rats,[8] Dahl salt-sensitive rats,[9,19] and NG-nitro-L-arginine methyl ester (L-NAME)/salt-induced mice,[21] were found to have altered structure of gut microbiota compared with their respective normotensive strains. Dysbiosis of gut microbiota was also observed in studies on patients with hypertension, conducted mainly in Chinese,[6,22,23] American,[24] and Brazilian,[25] populations. In a population of 41 healthy people, 56 patients with prehypertension, and 99 patients with primary hypertension in northern China, Li et al. revealed dramatically decreased microbial diversity and dysbiosis of microbial function in patients with prehypertension and those with hypertension.[6] In another Chinese population, Xie et al. further analyzed the relationship between gut microbiota and BP, finding that the dysbiosis of gut microbiota differed among patients with hypertension, isolated diastolic hypertension, and systolic hypertension.[22] Differences in gut microbiota between White and Black individuals were observed in an American population. They reported that Black individuals with hypertension had higher BP, higher prevalence of treatment-resistant hypertension, stronger pro-inflammatory ability of gut microbiota, and more oxidative stress markers than White individuals with hypertension.[26] However, a longitudinal 26-patient cohort with a follow-up of 5 years suggested that no significant change was observed in gut microbial composition, whereas the fecal metabolome was linked to 24-h BP levels and elevated levels of short-chain fatty acid (SCFA) in the feces of patients with hypertension. The function of gut microbiota seemed to be more modified over time than the composition of the gut microbiota in patients with altered BP level.[27]

Furthermore, dysbiosis of gut microbiota was observed in patients suffering from hypertension combined with other diseases (Table 2). Two recent investigations have revealed that gut microbiota and hypertension were linked to neurogenic variables. Wang et al. revealed that hypertension with stress could destroy the domino effect between gut microbiota and homeostasis.[28] Stevens et al. suggested that the endotype of patients with depressive hypertension differed from that of patients with depression or hypertension alone.[29] Wedgwood et al. found that postnatal growth restriction in a rat model caused pulmonary hypertension and disturbed the microbiota of the distal small intestine and cecum.[30] Recently, coronavirus disease 2019 (COVID-19), which is caused by coronavirus and leads to severe acute respiratory syndrome, became a pandemic in 2020 and 2021. Patients with COVID-19 who had higher BP displayed more than 3-fold higher mortality rates than patients with normotension.[31] In a review, Magalhães et al. proposed that dysbiosis of gut microbiota was responsible for the poor results of COVID-19 in patients with hypertension.[32] In a cohort of 48 subjects, the activation of TLR4 through lipopolysaccharide (LPS) from the gut microbiota of patients with hypertension may be associated with the severity of COVID-19.[33] Moreover, gastrointestinal regulation of butyrate may be key to the increased comorbidity observed in patients with hypertension in COVID-19.[34]

2.2 | Dysbiosis of gut microbiota contributes to hypertension

A typical strategy for confirming the links between gut microbiota and disease is to use germ-free animals. Ang-II-induced increase in BP was lower in germ-free mice than conventional mice,[35] which suggested that gut microbiota promoted the development of hypertension. Joe et al. found that germ-free rats have relative hypotension compared with their conventional rats, suggesting an obligatory role of gut microbiota in BP homeostasis.[36] Using cross-fostering method, in spontaneously hypertensive stroke-prone rats (SHRSPs), an SHRSP-like microbiota not only enhanced inflammation and elevated BP, but also caused harm to the blood–brain barrier compared with a WKY-like microbiome.[37] Fecal microbiota transfer (FMT) from hypertensive controls[6,20,38–42] to normotensive control elevated BP, while FMT from normotensive to hypertensive controls reduced BP,[38,43] which confirmed a causal relationship between dysbiosis of gut microbiota and hypertension.

TABLE 1 Studies on the changes of gut microbiota in hypertensive animals and patients

Study	Year	Source	Method	Main results
Mell et al.[9]	2015	Dahl salt-sensitive and salt-resistant rats	16S rDNA V1-V3 using 454 Jr. platform	Dahl salt-sensitive and salt-resistant rats differ in their composition
Yang et al.[8]	2016	SHR, angiotensin II infusion rats	16S rDNA V4-V5 using Illumina Miseq	Significantly decreased diversity, increased F/B ratio, decrease of acetate- and butyrate-producing bacteria in SHRs
Santisteban et al.[19]	2017	Spontaneously hypertensive rats, chronic angiotensin II infusion rats	16S rDNA V4-V5 using Illumina Miseq	Increased BP with increased intestinal permeability, decreased tight junction proteins, and altered microbial communities in SHRs
Adnan et al.[20]	2017	Spontaneously hypertensive stroke-prone rats	16S rDNA V4 using Illumina Miseq	Significantly increased F/B ratio
Wilck et al.[21]	2017	L-NAME/salt-induced mice	16S rDNA V4 using Illumina Miseq	High salt intake affects the gut microbiota by depleting *Lactobacillus murinus*, and *Lactobacillus murinus* treatment prevents salt-sensitive hypertension by modulating TH17 cells
Li et al.[6]	2017	41 healthy controls, 56 subjects with prehypertension, 99 individuals with primary hypertension in northern China	Metagenomic sequencing using Illumina Miseq	Decreased diversity, *Prevotella*-dominated enterotype, distinct metagenomic composition with decreased bacteria associated with healthy status and overgrowth of bacteria such as *Prevotella* and *Klebsiella*, and microbial function associated with diseases in patients with prehypertension and those with and hypertension
Yan et al.[48]	2017	60 healthy controls and 60 patients with hypertension	Metagenomic sequencing using Illumina Miseq	Opportunistic pathogenic taxa were more abundant in hypertensive patients, while the short-chain-fatty-acid-producing bacteria were higher in controls. Higher membrane transport, lipopolysaccharide biosynthesis, and steroid degradation were observed in patients with hypertension, while higher metabolism of amino acid, cofactors, and vitamins was found in controls
Walejko et al.[26]	2018	Patients were either Black with normal BP (10 for metagenomic sequencing, 5 for metabolomics) and high BP or White with normal BP (20 and 13) and high BP (12 and 8) in the United States	Metagenomic sequencing using Illumina HiSeq4000, metabolomics	Distinct gut microbiota among 4 groups; higher sulfacetaldehyde, quinolinic acid, 5-aminolevulinic acid, leucine, and phenylalanine and lower 4-oxoproline and L-anserine in Black patients with high BP
Xie et al.[22]	2019	62 cases with normal BP and 67 cases with high BP in northern China	16S rDNA V3-V4 using Illumina HiSeq 2500	Gut microbiota dysbiosis differed among hypertension, isolated diastolic hypertension, and systolic hypertension patients
Li et al.[23]	2019	63 hypertensive patients with treatment-naive hypertension, 104 hypertensive patients with anti-hypertensive treatment, 26 subjects with normal BP but with hyperlipidemia, and 42 healthy subjects with normal diastolic BP, systolic BP, fasting blood glucose, cholesterol, and triglyceride levels in a rural area of northern China	16S rDNA V3-V4 using Ion S5™ XL platform	*Lactococcus*, *Alistipes*, or *Subdoligranulum* abundances were positively correlated with systolic or diastolic BP in hypertensive patients with treatment-naive hypertension
Sun et al.	2019	5115 participants aged 18–30 years from 4 US urban centers	16S rDNA V3-V4 using Illumina Miseq	Hypertension and systolic BP were inversely associated with diversity index. Several specific genera were significantly associated with hypertension and systolic BP, though results were attenuated with adjustment for body mass index

(Continues)

TABLE 1 (Continued)

Study	Year	Source	Method	Main results
Silveira-Nunes et al.[25]	2020	48 hypertensive and 32 normotensive Brazilian individuals aged >25 years from Southeast Brazil	16S rDNA V3-V4 using Illumina Miseq	Reduced biodiversity and distinct bacterial signatures, an inflamed immune profile with an increase in TNF/IFN-g ratio, and in TNF and IL-6 production in individuals with hypertension
Calderón-Pérez et al.[76]	2020	29 nontreated hypertensive and 32 normotensive subjects	16S rDNA V3-V4 and metagenomic sequencing using Illumina Miseq	No significant differences in the overall bacterial composition and diversity of bacterial community between the 2 groups, a positive correlation between the hypertension-associated species and systolic and diastolic blood pressure
Kim et al.[50]	2020	18 patients with PAH and 13 controls	Metagenomic sequencing Illumina HiSeq4000	Significant taxonomic and functional changes of microbial communities between 2 groups, increased synthesis of arginine, proline, and ornithine pathways in the patients with PAH
Huart et al.[27]	2021	6 men and 1 woman were categorized as patients with hypertension, while the remaining 10 men and 9 women were normotensive	16S rDNA V1-V3 using Illumina Miseq	No significant change in composition of gut microbial community, while the fecal metabolome is associated with 24-h BP levels, with higher SCFA levels in the feces of patients with hypertension
Vemuri et al.[58]	2022	8 hypertensive and 8 normotensive primates (*Mscaca mulatta*)	16S rDNA V3-V4 using Illumina Miseq	Hypertension contributes to microbial translocation in the gut and eventually unhealthy shifts in the gut microbiome

2.3 | Indicators of gut microbial dysbiosis in hypertension

2.3.1 | Diversity

In most diseases, lower microbial diversity is considered as an indicator of gut microbial dysbiosis,[44] which may make individuals vulnerable to potential risks such as hypertension.[45] Decreased diversity of gut microbiota was observed in various hypertensive animal models, such as SHRs,[8] Ang-II-induced rats,[8,46] hypertensive obstructive sleep apnea rats,[39] high-fructose-induced hypertensive rats,[47] and Dahl rats.[9] The same results were confirmed in patients with hypertension, such as a cohort of 56 prehypertensive cases, 99 hypertensive cases, and 41 controls in China[6]; a cohort of 60 cases and 60 controls patients in China[48]; a small cohort of 7 cases and 10 controls in the United States[8]; a cohort of 57 hypertensive women cases and 391 controls from TwinsUK[49]; a cohort of the biracial (Black and White) population in the United States (186 cases, 343 controls)[24]; a recent study of 80 Brazilian adults (48 cases and 32 controls)[25]; a cohort of patients with pulmonary arterial hypertension (PAH) in Brazil (16 cases, 12 controls).[50] Another cohort study with employees of the Kailuan Group Corporation in China suggested that patients with isolated diastolic hypertension had lower gene numbers and bacterial richness than control and patients with isolated systolic hypertension.[51] However, some studies have come to a contrary conclusion. Callejo et al. showed that no difference in diversity was observed in a rat model of PAH.[52] In a cohort of 50 patients with grade 3 hypertension and 30 healthy controls, the gut microbiota of the individuals with hypertension was more diverse than healthy controls.[53]

2.3.2 | Firmicutes/Bacteroidetes (F/B) ratio

Increased F/B ratio is often used as an indicator of gut microbial dysbiosis.[54] An increased F/B ratio has been reported in hypertensive animal models such as SHRs,[8] Ang-II-induced rats,[8] PAH rats,[52] hypoxia-induced pulmonary hypertensive mice,[55] Dahl salt-sensitive hypertensive heart failure rats,[56] stroke-prone spontaneously hypertensive rats,[20] high-fat-diet L-NAME-induced rats,[57] hypertensive monkeys,[58] and patients with hypertension,[8] while a decrease of F/B ratio was observed in high-fructose-induced salt-sensitive hypertensive rats.[47] The F/B ratio in these studies has been described in details in Table 3. The increase of Firmicutes in hypertension may be due to Firmicutes being the main phylum to produce TMA,[59,60] which is harm to hypertension. Besides, Firmicutes members produce butyrate, while Bacteroidetes produce acetate and propionate.[61] Olfactory receptor 78 (Olfr78) can bind acetate and propionate, which induces an increased BP response. In contrast, G-protein-coupled receptor 41 (GPR41) induces a decrease of BP response to butyrate.[62]

TABLE 2 Recent studies on the changes of gut microbiota in hypertension associated with other disease

Study	Year	Source	Method	Main results
Wedgwood et al.[30]	2020	Sprague–Dawley rats combining postnatal growth restriction and hyperoxia	16S rDNA V4 using Illumina Miseq	Postnatal growth restriction with or without hyperoxia (but not hyperoxia alone) altered the microbiota of the distal small bowel and cecum
Wang et al.[28]	2021	Restraint stress in hypertensive rats	16S rDNA V3-V4 using Illumina Miseq	There was a remarkable significant increase of stress-related hormones and pro-inflammatory factor IL-6 along with a decrease in the diversity of gut microbiota and an imbalance in the F/B ratio
Okamura et al.[18]	2021	SHR, stroke-prone SHRs	Terminal-restriction fragment length polymorphism	Increased expression of acyl-CoA oxidase 2 in the kidney along with increased phytanic acid in plasma and the changed gut microbiota
Stevens et al.[29]	2021	18 diagnosed with hypertension only, 7 depression only, 8 depression plus hypertension, and 21 reference subjects with neither hypertension nor depression	Metagenome shotgun sequencing	Gut bacterial community ecology was defined by co-occurrence of *Eubacterium siraeum*, *Alistipes obesi*, *Holdemania filiformis*, and *Lacnospiraceae bacterium* 1.1.57FAA with *Streptococcus salivariu* in depression plus hypertension. The corresponding microbial functional genomics of depressive hypertension engaged pathways degrading GABA and beneficial short chain fatty acids, and are associated with enhanced sodium absorption and inflammasome induction
Wang et al.[190]	2021	9 nonsmokers without hypertension, 9 smokers without HTN, 18 nonsmokers with hypertension, and 23 smokers with hypertension in China	Metagenomic sequencing using Illumina platform	The gut microbiota in smoker with hypertension was disordered, with lower microbial diversity. The microbial enterotype in smoker with hypertension was inclined to *Prevotella*-dominant type. Dramatic changes in the intestinal genera and species composition and intestinal function were observed in smoker with hypertension
Lakshmanan et al.[112]	2021	29 pediatric subjects and divided them into 3 groups: 5 healthy controls, 17 T1DM with normal BP, and 7 T1DM with elevated BP	16S rDNA V3-V4 using Illumina Miseq	Distinct gut microbial composition, reduced diversity, a significant reduction of *Bifidobacterium* levels, and unique gut-microbial metabolic pathways, such as elevated lipopolysaccharide synthesis and glutathione metabolism in T1DM with elevated BP

2.4 | Potential taxa to regulate BP

Many studies have identified a few possible microbes involved in the regulation of BP. To determine the potential taxa for regulating the BP, we summarize the potential genera, sorting by classification level (Table 4). The details are listed in Supporting File S1.

To further uncover the potential genera for regulating BP, we construct a phylogenetic tree based on bacterial 16S-rRNA sequences using neighbor-joining methods (Figure 1). *Lactobacillus* (11 studies), *Roseburia* (8 studies), *Akkermansia* (8 studies), *Coprococcus* (7 studies), and *Bifidobacterium* (7 studies) were enriched in healthy or treated groups with lower BP (Figure 1, Table 4), suggesting that they have the potential to reduce BP. *Streptococcus* (3 studies), *Blautia* (3 studies), and *Prevotella* (3 studies) were enriched in hypertensive groups, which suggests that they are potentially harmful for hypertension (Figure 1, Table 4). However, the roles of some microbes in hypertension are debated. For example, 4 studies suggest that *Bacteroides* may be beneficial in reducing BP, while 5 studies suggest that it may be harmful to hypertension. These results could be due to microbial differences (most studies were based on amplicon sequencing, for which it is hard to obtain accurate results at the species level or strain level) and host differences (including age, gender, disease type, immunity, etc.), which need to be further studied.

3 | THE POTENTIAL MECHANISMS INVOLVED IN THE REGULATION BETWEEN GUT MICROBIOTA AND HYPERTENSION

Evidence shows that gut dysbiosis induces high levels of BP through SCFAs, trimethylamine *N*-oxide (TMAO), hormonal regulation including gaseous signal molecule, gut bacteria-derived bioactive peptides, serotonin, steroid hormones, and immunity response such as inflammation[63–65] (Figure 2).

3.1 | SCFAs

SCFAs (mainly including acetate, propionate, and butyrate) are the main metabolites produced by gut bacteria in the gut. Animal studies have demonstrated a direct correlation between fecal SCFAs and BP.[62,66,67] A reduction in SCFA-producing bacteria seems to be involved in the increase of BP found in SHRs, Ang-II-induced mice, and patients with hypertension.[8,66] Administration of SCFAs lowered BP in mice and rats,[68–72] while in humans, evidence of the relationship between fecal SCFA levels and BP are conflicting. Both higher and lower fecal SCFAs have been associated with higher BP,[27,48,73–78] which may be due to gut permeability and absorption. Potential mechanisms of SCFAs on the regulation of BP have been suggested, including specific receptors, anti-inflammatory effects, nervous system, metabolic regulation, and gut epithelial integrity.[17,79,80]

TABLE 3 The average F/B ratio in the study considering F/B ratio as indicator of gut dysbiosis

Hypertensive group	Normal group	Treatment group	Source	Study	Year
25.4	4.4	–	SHRs	Yang et al.[8]	2015
37.22	6.6	2.57	Chronic Ang-II-induced rats	Yang et al.[8]	2015
0.63	–	0.15, 0.19	DOCA-salt mice	Marques et al.[70]	2017
3.61	1.88	2.89	Spontaneously hypertensive stroke prone rats	Adnan et al.[20]	2017
72.7	25.5	–	PAH rats	Callejo et al.[52]	2018
3.33	1.44	1.62	High-fat-diet L-NAME-induced hypertensive rats	Chen et al.[57]	2019
16.67	5.5	5.37	SHRs	Han et al.[184]	2019
4.31	2.59	3.31	SHRs	Yu et al.[185]	2019
0.38	0.46		High-fructose-induced salt-sensitive hypertensive rats	Chen et al.[47]	2020
0.35	0.27	0.31	Hypoxia-induced pulmonary hypertension mice	Luo et al.[55]	2021
3	1.67	–	Hypertensive heart failure rats	Li et al.[56]	2021
2.42	–	1.35	SHRs	Han et al.[170]	2021
55.56	17.46	14.29	SHRs	Robles-Vera et al.[191]	2021
10	5.75	–	Hypertensive monkeys	Vemuri et al.[58]	2022

3.2 | TMAO

TMAO is a circulating metabolite produced from choline, phosphatidylcholine, and carnitine by hepatic enzymes or gut microbes.[81] TMA-producing bacteria are widely distributed in Actinobacteria and Proteobacteria and more abundant in Firmicutes. At the genus level, *Clostridium*, *Shigella*, *Proteus*, and *Aerobacter* are the main TMA-producing bacteria.[59,60] In addition, some pathogens, such as *Aeromonas*, *Burkholderia*, *Salmonella*, *Shigella*, *Campylobacter*, and *Vibrio*, can produce TMA.[59] In recent years, animal[82–84] and cohort[81,85,86] studies have indicated a significant positive dose-dependent association between circulating TMAO and BP.

3.3 | Hormonal regulation

3.3.1 | Gaseous signal molecule

NO and H_2S can be produced by gut bacteria and are important vasodilators. They are reported to relax various blood vessels, such as thoracic aorta, portal vein, and peripheral resistance vessels.[87–89] H_2S can restore NO bioavailability and reduce oxidative stress with alterations of gut microbiota.[10,62,90] Dietary nitrate reduced BP in healthy volunteers and patients with hypertension, indicating the antihypertensive role of NO through gut microbiota.[91] Administration of *Enterococcus faecalis* decreased the production of NO in the renal medulla and increased BP through upregulation of lysophospholipase A1 and phospholipase A2 group 4 A.[92] Daliri et al. reported that soy protein decreased BP, possibly by increasing the colonization of H_2S-producing bacteria in hypertensive rats.[93]

3.3.2 | Gut bacteria-derived bioactive peptides

In some cases, commensal gut bacteria-derived bioactive peptides have anti-inflammatory effects and can modulate host hypertensive hormones, such as angiotensin-converting enzyme and renin.[94] Gao et al. indicated that the novel angiotensin-converting enzyme (ACE)-inhibitory peptides could regulate the renal renin-angiotensin system, reduce BP, and rebalance gut microbial dysbiosis.[95] Edwards et al. suggested that *N*-formyl peptides lead to severe hypertension.[96] Some probiotics can improve hypertension via bioactive peptides. For example, recombinant *Lactobacillus plantarum* NC8, which expresses ACE-inhibitory peptides, can significantly reduce BP in SHRs.[97] A randomized, placebo-controlled study indicated that *Lactobacillus helveticus* LBK-16H fermented milk, which contains bioactive peptides, has an antihypertensive effect in patients with hypertension.[98]

3.3.3 | Serotonin

Serotonin is a neurotransmitter with diverse functions that can cause hypertension by increasing arterial contractility and smooth muscle growth.[15] The synthesis and secretion of serotonin can be influenced by gut microbiota. Previous studies have suggested that germ-free mice with human gut microbiota increase the levels of serotonin in serum, colon, and feces.[99,100] Spore-forming bacteria can promote serotonin biosynthesis through elevation of metabolites such as α-tocopherol, deoxycholate, and tyramine.[101] Commensal bacteria can promote the production of serotonin. For example, *Escherichia coli* K12 in the gut can produce serotonin.[102] *Clostridium ramosum* can promote

TABLE 4 Potentially beneficial and harmful gut microbes for hypertension

Taxa	Genus	Potentially beneficial	Potentially harmful
Firmicutes; Bacilli; Lactobacillales; Lactobacillaceae	*Lactobacillus*	Mouse,[21,192] rat,[160,169,172,182,184,193–195] human[21,196]	Human[25]
Firmicutes; Bacilli; Lactobacillales; Streptococcaceae	*Lactococcus*		Human[23]
Firmicutes; Bacilli; Lactobacillales; Streptococcaceae	*Streptococcus*	Rat[197]	Human[29,48,198]
Firmicutes; Bacilli; Lactobacillales; Enterococcaceae	*Enterococcus*		Rat[92]
Firmicutes; Bacilli; Bacillales; Staphylococcaceae	*Staphylococcus*		Rat[56,169]
Firmicutes; Bacilli; Bacillales; Paenibacillaceae	*Paenibacillus*	Human[199]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Sporobacter*	Human[49]	
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Robinsoniella*		Human[49]
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Oribacterium*		Human[198]
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Roseburia*	Human,[6,25,29,48,76] rat[183,197,200]	
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Butyrivibrio*	human[6,50]	
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Coprococcus*	Human,[6,25,50,201] mouse,[55] rat[8,202]	
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Marvinbryantia*	Human[199]	
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Blautia*	Rat[43,197]	Human,[203] mouse[46]
Firmicutes; Clostridia; Eubacteriales; Lachnospiraceae	*Anaerostipes*	Rat[204]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Faecalibacterium*	Human[6,48,76,165,201]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Oscillibacter*	Human[6]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Anaerotruncus*	Mouse[55]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Ruminiclostridium*	Human[49,199]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Butyricicoccus*		Rat[56]
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Ruminococcus*	Mouse,[46] rat[183]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Pseudoflavonifractor*	Human[199]	
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Subdoligranulum*	Human,[199] mouse[192]	Human[23]
Firmicutes; Clostridia; Eubacteriales; Oscillospiraceae	*Oscillospira*	Rat[205]	Mouse[46]
Firmicutes; Clostridia; Eubacteriales; Eubacteriaceae	*Eubacterium*	Human,[50,77,201] rat[56]	Human[29]
Firmicutes; Clostridia; Eubacteriales; Christensenellaceae	*Christensenella*		Mouse,[55] human[49]
Firmicutes; Clostridia; Eubacteriales; Peptococcaceae	*Peptococcus*		Rat[56]
Firmicutes; Clostridia; Eubacteriales Eubacteriales Family XIII	*Anaerovorax*	Human[49]	
Firmicutes; Clostridia; Eubacteriales; Peptostreptococcaceae	*Romboutsia*	Rat[206]	
Firmicutes; Clostridia; Eubacteriales; Clostridiaceae	*Clostridium*	Human[51]	Rat,[137] human[198]
Firmicutes; Erysipelotrichia; Erysipelotrichales; Erysipelotrichaceae	*Allobaculum*	Rat[178,183,205,207]	Rat[56]
Firmicutes; Erysipelotrichia; Erysipelotrichales; Erysipelotrichaceae	*Dubosiella*	Mouse[171]	
Firmicutes; Erysipelotrichia; Erysipelotrichales; Erysipelotrichaceae	*Faecalibaculum*		Rat[56]
Firmicutes; Erysipelotrichia; Erysipelotrichales; Erysipelotrichaceae	*Holdemania*		Human[29]
Firmicutes; Erysipelotrichia; Erysipelotrichales; Turicibacteraceae	*Turicibacter*	Rat[178]	
Firmicutes; Negativicutes; Selenomonadales; Selenomonadaceae	*Quinella*		Rat[56]
Firmicutes; Negativicutes; Selenomonadales; Selenomonadaceae	*Megamonas*		Human[23]

(Continues)

TABLE 4 (Continued)

Taxa	Genus	Potentially beneficial	Potentially harmful
Firmicutes; Negativicutes; Selenomonadales; Selenomonadaceae	*Anaerovibrio*	Mouse[41]	
Firmicutes; Negativicutes; Veillonellales; Veillonellaceae	*Megasphaera*		Human[23]
Bacteroidetes; Bacteroidia; Bacteroidales; Prevotellaceae	*Prevotella*	Human[196]	Human,[6,208] rat[170]
Bacteroidetes; Bacteroidia; Bacteroidales; Prevotellaceae	*Alloprevotella*	Mouse,[192] rat[197]	
Bacteroidetes; Bacteroidia; Bacteroidales; Bacteroidaceae	*Bacteroides*	Rat,[105] human[6,50,77]	Rat,[137,173,197] mouse,[42,70] human[76,196,208,209]
Bacteroidetes; Bacteroidia; Bacteroidales; Porphyromonadaceae	*Parabacteroides*	Rat[40,207,210]	Mouse,[46] human[48]
Bacteroidetes; Bacteroidia; Bacteroidales; Odoribacteraceae	*Odoribacter*	Human,[78] rat[43]	
Bacteroidetes; Bacteroidia; Bacteroidales; Odoribacteraceae	*Butyricimonas*		Rat[205]
Bacteroidetes; Bacteroidia; Bacteroidales; Rikenellaceae	*Alistipes*		Mouse,[192,211] human[23,29]
Bacteroidetes; Sphingobacteriia; Sphingobacteriales; Sphingobacteriaceae	*Pedobacter*	Rat[195]	
Actinobacteria; Actinomycetia; Corynebacteriales; Corynebacteriaceae	*Corynebacterium*		Rat[182]
Actinobacteria; Actinomycetia; Micrococcales; Micrococcaceae	*Rothia*		Human[51]
Actinobacteria; Actinomycetia; Bifidobacteriales; Bifidobacteriaceae	*Bifidobacterium*	Mouse,[192] rat,[172,174,183] human[6,29,112]	Human[50,162]
Actinobacteria; Actinomycetia; Actinomycetales; Actinomycetaceae	*Actinomyces*		Human[6]
Actinobacteria; Coriobacteriia; Eggerthellales; Eggerthellaceae	*Adlercreutzia*		Rat[56]
Actinobacteria; Coriobacteriia; Eggerthellales; Eggerthellaceae	*Gordonibacter*		Rat[56]
Proteobacteria; Gammaproteobacteria; Enterobacterales; Erwiniaceae	*Erwinia*		Rat[204]
Proteobacteria; Gammaproteobacteria; Enterobacterales; Enterobacteriaceae	*Klebsiella*		Human[48]
Proteobacteria; Betaproteobacteria; Burkholderiales; Sutterellaceae	*Sutterella*	Mouse[41,205]	
Proteobacteria; Betaproteobacteria; Nitrosomonadales; Spirillaceae	*Spirillum*	Human[162]	
Verrucomicrobia; Verrucomicrobiae; Verrucomicrobiales; Akkermansiaceae	*Akkermansia*	Rat,[57,183,184,195] Human[24,50,165,212]	
Desulfobacterota; Desulfovibrionia; Desulfovibrionales; Desulfovibrionaceae	*Desulfovibrio*		Human[6]
Deferribacteres; Deferribacteres; Deferribacterales; Deferribacteraceae	*Mucispirillum*	Rat[207]	
Spirochaetes; Spirochaetia; Spirochaetales; Treponemataceae	*Treponema*	Rat[56]	

the secretion of serotonin from enterochromaffin cells.[100] In addition, metabolites of gut microbiota such as SCFAs and bile acids (BAs) can induce enterochromaffin cells to secrete serotonin.[99,101]

3.3.4 | Steroid hormones

There is a possible relation between hypertension and gut-associated steroid metabolism. Through oxidation and reduction

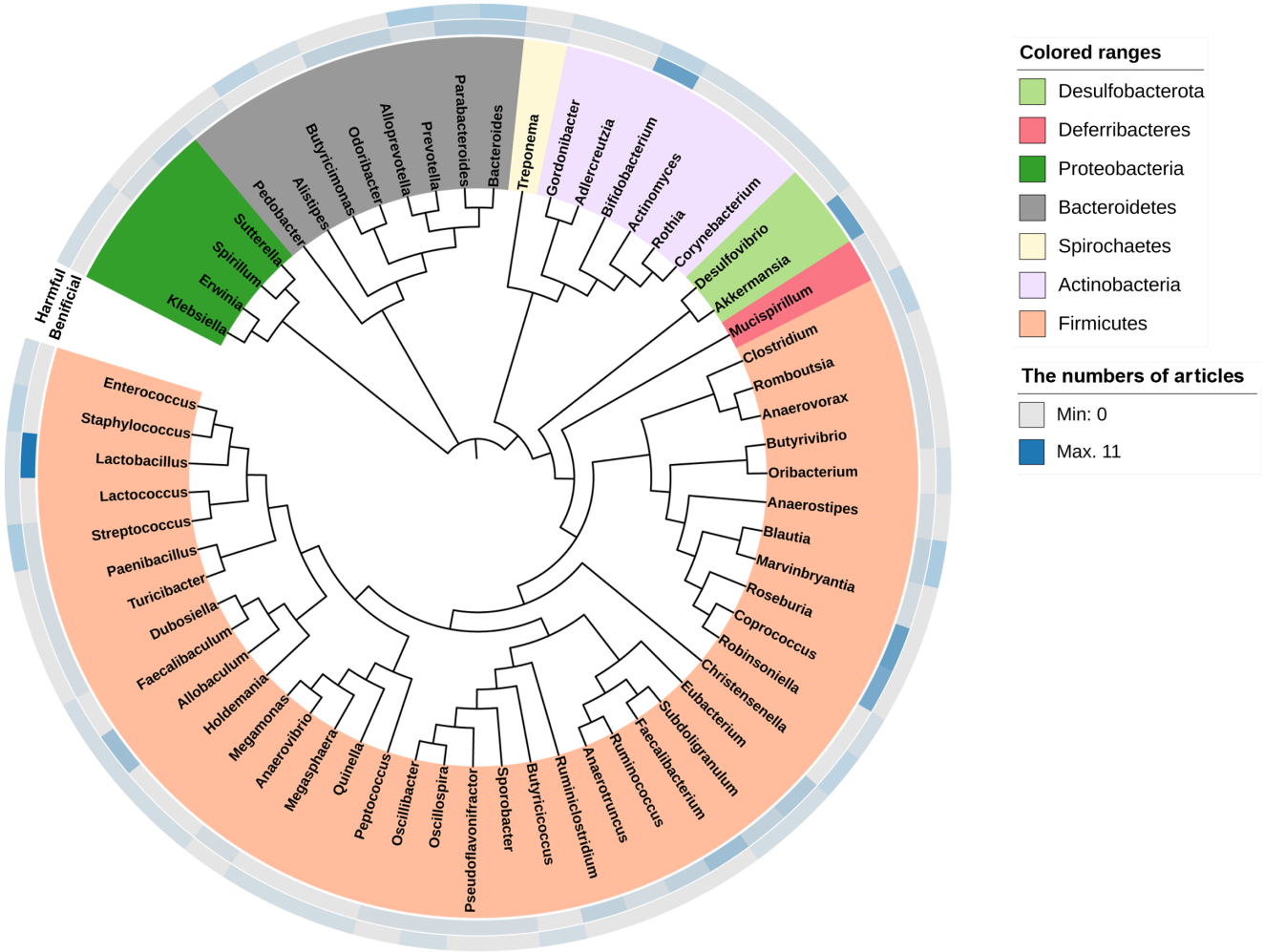

FIGURE 1 Phylogenetic tree of potential genera for regulating hypertension. The representative sequence of each genus was downloaded from a web-based tool at EzTaxon (https://www.ezbiocloud.net/),[186] which is listed in Table S1. The sequences were aligned using the default settings of MAFFT online.[187] The evolutionary trees were constructed using MEGA software version 11 on the basis of the neighbor-joining method[188] and visualized using Interactive Tree of Life (https://itol.embl.de/)[189].

reactions, gut microbiota can regulate the levels of androgens and glucocorticoids.[103] Besides, studies have suggested a relation between sex steroid hormones and hypertension. Estrogen level was decreased in hypertensive males, while estradiol was higher in hypertensive males and females.[104] In addition, gut microbiota-derived arachidonic acid reduces corticosterone,[105] which can be converted into aldosterone and increase salt and water retention to elevate BP.

3.4 | Immunity response

Indoles are aromatic, heterocyclic, organic compounds that can be produced through gut microbiota. Gut microbes can express indole-3-glycerol phosphate synthase, indole-3-glucerol phosphate lyase, and indole synthase, which may promote the production of indole.[106] Indole has been reported to be associated with hypertension. Administration of indole increased BP dose-dependently in rats.[107] However, infusion of indole in the brain reduces BP, indicating that peripherally indoles may be prohypertensive, while indoles in the brain may be antihypertensive.[108] Another study showed that probiotic *Lactobacillus* inhibited Th17 cells and ameliorated hypertension by restoring indole-3 lactic acid levels.[21] Regarding the inflammation in hypertension, indoles can inhibit TH17 cells and suppress the release of IL-17A.[109] In addition, indoles can bind to aryl hydrocarbon receptor precursor to regulate T cells, which inhibit the TH17 responses by releasing anti-inflammatory cytokine IL-10.[110,111]

LPS, a bacterial cell wall component, may be a factor influencing hypertension by gut microbiota. Upregulation of LPS biosynthesis was observed in hypertension group.[6,48,77,112,113] LPS can increase gut and neuroinflammation response in hypertension,[114] which may be a mechanism connecting gut microbiota with hypertension.[115] It is well known that high-salt diet is the major trigger of hypertension in humans,[116] which induces activation of Th17 cells[117,118] and increases the BP.[119,120] There are associations between Th17 cells and

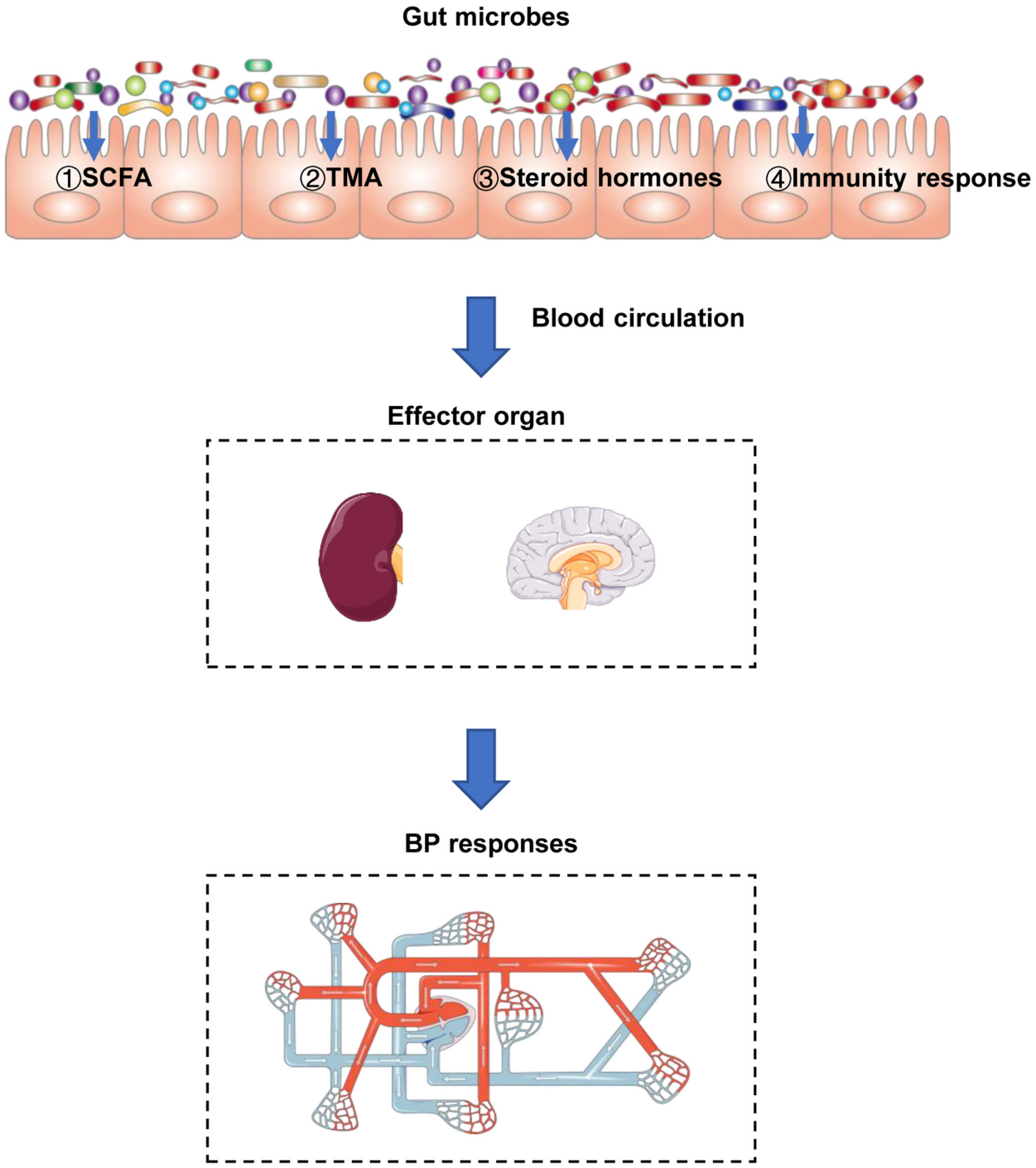

FIGURE 2 The potential mechanisms involved in the regulation between gut microbes and hypertension.

gut microbiota.[21] In addition, IL-6 is an important cytokine in the regulation of BP, which is responsive to Ang II to raise BP.[121] Another study demonstrated an increase of pro-inflammatory cytokines in peripheral blood samples in patients with hypertension associated with changes in the structure of gut microbiota.[25] These results suggest that gut microbiota could regulate BP through interaction with the immune system.

4 | TREATMENT OF HYPERTENSION BASED ON GUT MICROBES

Maintaining and recovering the homeostasis of the gut microbiota environment may be a possible therapeutic approach to treating hypertension.[122,123] Use of FMT, probiotics, prebiotics, and antibiotics can reduce BP in hypertensive animals and patients, or aid the

protective function of antihypertensive drugs.[124–126] The widely used methods based on regulation of gut microbes are listed as follows.

4.1 | FMT

FMT from hypertensive rats,[20,38–40] mice,[41,42] and humans[6] to normotensive animals elevated BP with increase of plasma IL-17,[41] T-cell activation, aortic T-cell infiltration, and impaired endothelial function,[38] suggesting that FMT can be used to confirm the roles of gut microbiota in hypertension.

Transferring fecal samples from normotensive to hypertensive animals reduced BP significantly in recipients.[38,43] A recent Chinese clinical study confirmed the effect of FMT in humans. Patients were treated with washed microbiota transplantation, which indicated that FMT had a BP-lowering effect in patients with hypertension.[127] Another study demonstrated that FMT from healthy donor mice fed resveratrol to hypertensive mice had beneficial effects in significantly lowering systolic BP during diet-induced obesity.[128] Xia et al. showed that FMT from exercised SHRs, which maintain lower BP, into SHRs alters gut microbiota and decreases BP.[129]

It is important to note that the complexity of the microbiota can produce unexpected results such as increased BP in Dahl salt-sensitive rats receiving fecal transplants from salt-resistant normotensive rats.[9] A recent study on inter-strain fecal transplant in rats showed no effect on BP and did not produce long-term changes in gut bacteria composition.[130]

4.2 | Probiotics and prebiotics

Much interest has been focused on the effective use of a wide variety of probiotic strains.[131–133] Probiotics can exert an antihypertensive effect through reducing blood glucose levels and insulin resistance by improving cholesterol levels, endothelial dysfunction, and inflammatory responses.[134–136]

The antihypertensive probiotic most widely reported is *Lactobacillus*. *Lactobacillus fermentum* CECT5716 is a potential antihypertensive probiotic that can reduce BP through multiple mechanisms such as by impairing endothelium-dependent relaxation, abolishing the increased superoxide levels, and restoring the imbalanced Th17/Treg ratio in SHRs,[66,137] tacrolimus-induced hypertension rats,[138] systemic lupus erythematosus mice,[139,140] and NZBWF1 mice.[141] Other *Lactobacillus* strains have been studied. After daily administration of *Lactobacillus casei* to SHRs for 8 weeks, antihypertensive and vascular protection effects were observed.[142] *Lactobacillus coryniformis* CECT5711, with immunomodulatory properties, could reduce BP in obese mice.[143] In a controlled, randomized, double-blinded trial, BP in healthy smokers was decreased after treatment with *Lactobacillus plantarum* 299v.[144] However, the potency for antihypertensive activity of probiotics depends on strains. For example, various strains of *Lactobacillus plantarum* show inconsistent activities.[145] The recombinant *Lactobacillus plantarum* NC8 strain was also shown to decrease BP in SHRs by restoring nitric oxide and reducing endothelin and Ang II.[97] *Lactobacillus plantarum* DSM 15313 was found to ferment dietary intake of blueberries and lower BP in L-NAME-induced hypertensive animals.[146] In a 2020 study, administration of *Lactobacillus plantarum* WJL during pregnancy and lactation in dams was reported to reduce BP and prevent cardiovascular dysfunction in male offspring of rats.[147] However, another strain from *Lactobacillus plantarum*, HEAL19, failed to ameliorate hypertension in L-NAME-induced rats.[148]

Bifidobacterium is another probiotic with antihypertensive effects. Treatment with *Bifidobacterium breve* CECT7263 prevented hypertension with restored renal damage, Th17 and Treg content, and endothelial dysfunction in lupus model induced mice,[140] SHRs,[66] and DOCA-salt induced rats.[149] *Bifidobacterium longum* supplementation increases the level of ACE2 and mas receptor in obese mice, supporting its potential beneficial effects in reducing BP.[150]

Nevertheless, some gut microbes, such as *Enterococcus faecalis*, can exacerbate hypertension. Rats receiving live *Enterococcus faecalis* exhibited higher BP and enhanced renal injury.[92] Emerging evidence has suggested that *Enterococcus faecalis* induced pulmonary hypertension syndrome with cardiac injury in young chickens.[151–153]

4.3 | Antibiotics

The first evidence for involvement of gut microbiota in hypertension etiology was obtained in rats on the effect of antibiotic therapy on BP.[12] In hypertensive animals and patients, antibiotics can alleviate hypertension. For example, minocycline[8] and an antibiotics cocktail[154] blunt hypertension in Ang-II-induced hypertensive rats. Vancomycin treatment can attenuate microbiota dysbiosis and reduce BP in fructose-induced salt-sensitive rats.[47] Vancomycin and minocycline reduce systolic BP in older SHRs.[155] Doxycycline decreased systolic BP, abundance of lactate-producing bacteria, and levels of lactate in plasma of DOCA-salt rats.[156] A cocktail of antibiotics-induced alteration of the gut microbiota improved PAH in SU5416/hypoxia rats.[157] Vancomycin inhibited the increase in BP and reduced Th17 infiltration in aortas in imiquimod-treated mice[41] and NZBWF1 mice.[42] Moreover, depletion of gut microbiota by antibiotic (polymyxin B and neomycin) administration dramatically ameliorated gut barrier disruption, renal injury, and BP elevation in high-salt-intake-induced mice.[158] In a clinical study, a 69-year-old patient with a long history of hypertension (44 years) had lower BP after combined antibiotic treatment.[159] However, in healthy rats, treatment with antibiotics resulted in elevated BP level,[155,160] indicating that the roles of antibiotics in regulation of BP are bidirectional.

4.4 | Dietary supplements

Diverse dietary supplements influence BP. Gut microbiota respond significantly to dietary supplements, and long-term diets

shape the gut microbiota.[161] Previous studies have indicated that dietary fiber,[70,162,163] mousse supplementation with whey protein hydrolysate and pumpkin pectin,[164] low-saturated-fat diet,[165] polyphenols,[166] extra virgin olive oil-enriched diet,[167] garlic oil,[168,169] potassium alginate oligosaccharides,[170] and vitamin K2[171] reshaped the gut microbial community, providing beneficial effects on BP regulation in animal models or patients with hypertension.

In addition, herbal medicines have been observed to regulate BP, associated with modulating the gut microbial community. For example, prevention of hypertension via resveratrol was related to restoration of aryl hydrocarbon receptor signaling, TH17-mediated inflammation, NO pathway, and gut microbiota in high-fructose-diet rats,[172,173] chronic kidney disease-induced hypertensive rats,[174] postnatal high-fat diet and L-NAME-induced hypertensive rats,[57] and hypertensive rats with combined asymmetric dimethylarginine and trimethylamine-*N*-oxide exposure.[175] Resveratrol ameliorated hypertension by promoting the enrichment of beneficial bacteria.[57,172,176] Curcumin also restored BP by altering the composition of gut microbial community and improving gut pathology and integrity in SHRs.[177] Quinoa protein intervention decreased BP significantly and changed the microbial community structure in SHRs compared with nonhypertension rats.[178] A growing body of evidence has indicated that berberine and its derivatives could reduce BP in patients with hypertension, and its mechanism may be attributed to inhibition of renin-angiotensin system activity,[179] decreased levels of aldosterone,[179,180] reduced arterial stiffness,[181] and improved endothelial function[180] in rats. Wu et al. indicated that Sanoshashinto and berberine-baicalin combination improved hypertension and left ventricular hypertrophy by altering gut microbiota.[182] Baicalin lowered BP and increased the amount of SCFAs by changing the gut microbiota in SHRs.[183] Some compound herbal formulae have good antihypertension effects and improve the gut dysbiosis. The combination of *Astragalus membranaceus* and *Salvia miltiorrhiza* treatment reduced BP steadily and ameliorated the imbalance of gut microbial structure in SHRs.[184] Zhengganxifeng decoction reduced BP, maintained the integrity of the gut barrier, and elevated the proportion of SCFA-producing bacteria by decreasing the expression of ACE in lungs of SHRs.[185]

5 | CONCLUSIONS AND PROSPECTS

Several studies have suggested that the dysbiosis of gut microbiota and hypertension is causally related in animals and humans. Using germ-free animal or cross-fostering method, dysbiosis of gut microbiota has been confirmed to lead to changes in BP. Lower diversity and increased F/B ratio may be used as indicators of gut microbial dysbiosis in hypertension, yet the exceptions should be noted. Studies on the composition of gut microbiota have suggested that *Lactobacillus*, *Roseburia*, *Coprococcus*, *Akkermansia*, and *Bifidobacterium* might be the potential microbe reducing BP, while *Streptococcus*, *Blautia*, and *Prevotella* might be potential harmful microbes for hypertension. The potential mechanisms involved in the regulation between gut microbiota and hypertension through SCFAs, TMAO, hormonal regulation, and immunity response should be further studied. FMT is an easy method based on gut microbes to improve hypertension, although safety and effectiveness are still a challenge. Though many microbes were considered to regulate BP, only a small number were used to improve hypertension. The commonly used probiotics are *Lactobacillus* and *Bifidobacterium*, which validates the effectiveness of antihypertension in various animal models and humans. In addition, evidence suggests that antibiotics and dietary supplements can be used to regulate BP.

Previous studies have provided enough evidence that gut microbes can regulate BP. However, there is still a long way to go before gut microbes can be applied to improve hypertension. We are not sure how to assess which therapeutic method based on gut microbes is appropriate for which patient. There are not enough indicators available to estimate the dysbiosis of patients with hypertension or to what extent we should use therapeutic methods based on gut microbes. Besides, the interaction between gut microbe and response from immunity in hypertension should be further investigated as immunity plays important roles in both gut microbe and hypertension. Though many researchers are optimistic that probiotics can be used to improve diseases, the number of probiotics is limited in hypertension. In recent decades, *Lactobacillus* and *Bifidobacterium* have remained the commonly used probiotics in diseases, including hypertension. It is urgent to develop new probiotics to improve hypertension with safety and specificity. Many bacteria were reported to be associated with hypertension, but as an important group in the gut, fungi, especially yeast, should be studied. In addition, we can obtain a vast amount of information on microbial communities through metagenome, transcriptome, metabolome, and proteome using high-throughput sequencing. Nonetheless, more work should be focused on identifying novel strains with antihypertension function, which have great value in human health.

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CONFLICT OF INTEREST

The authors have no conflicts of interest. Dong Yan is an Editorial Board member of AMEM and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

AUTHOR CONTRIBUTIONS

Dong Yan conceived and wrote the draft of the manuscript. Ye Sun, Xiaoyue Zhou, and Wenhao Si organized the references to make the tables and figures. Jieyu Liu, Min Li, Minna Wu revised the manuscript. All authors contributed significantly in the preparation of the manuscript. All authors approve of the submission of this manuscript. All authors commented on the manuscript.

ETHICS STATEMENT

The ethic statement is not applicable.

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SUPPORTING INFORMATION

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