

# Research Progress on the Correlation Between Hypertension and Gut Microbiota

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**Abstract:** Among cardiovascular diseases, hypertension is the most important risk factor for morbidity and mortality worldwide, and its pathogenesis is complex, involving genetic, dietary and environmental factors. The characteristics of the gut microbiota can vary in response to increased blood pressure (BP) and influence the development and progression of hypertension. This paper describes five aspects of the relationship between hypertension and the gut microbiota, namely, the different types of gut microbiota, metabolites of the gut microbiota, sympathetic activation, gut-brain interactions, the effects of exercise and dietary patterns and the treatment of the gut microbiota through probiotics, faecal microbiota transplantation (FMT) and herbal remedies, providing new clues for the future prevention of hypertension. Diet, exercise and traditional Chinese medicine may contribute to long-term improvements in hypertension, although the effects of probiotics and FMT still need to be validated in large populations.

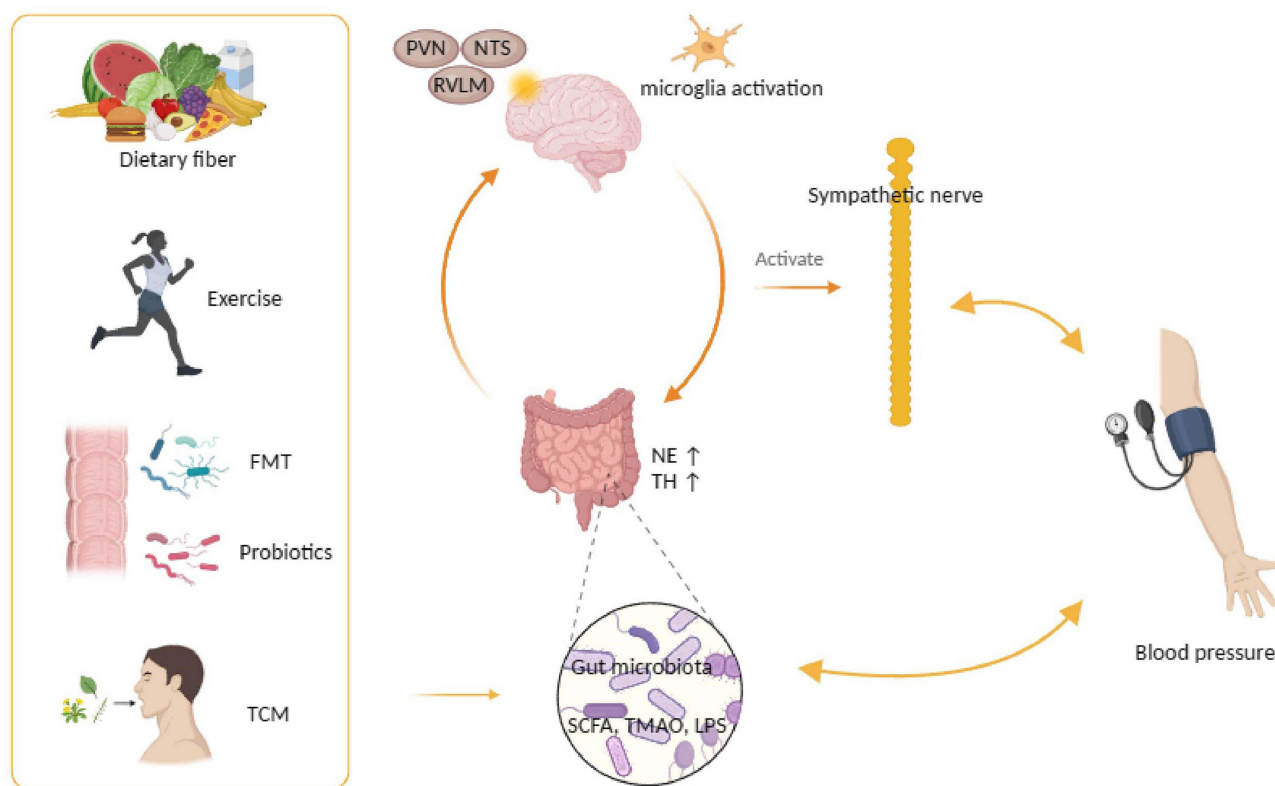
**Keywords:** blood pressure, metabolites, gut-brain, treatment

## Introduction

Cardiovascular disease (CVD) has been a major threat to global health during the last 30 years. Hypertension is the primary risk factor for CVD and has become a global public health crisis.<sup>1,2</sup> High SBP (systolic blood pressure) was the top Level 2 risk factor for attributable fatalities in 2019, accounting for 10.8 million (95% uncertainty interval [UI] 9.51–12.1) deaths (19.2% [16.9–21.3] of all deaths in 2019).<sup>3</sup> High BP is caused by a complex combination of genetic, nutritional, and environmental variables, although the exact interactions among these factors is yet to be elucidated. To date, the precise reason for the rising incidence rate has not been elucidated. One study demonstrated that only a small portion of hypertension was caused by heredity and a much greater proportion of cases is caused by complex environmental factors.<sup>4</sup>

Recently, there has been significant interest in the gut microbiota's potential to affect host health.<sup>5–7</sup> There are trillions of microbial cells in the human intestine, predominantly bacteria and viruses. These cells are collectively commonly referred to as gut microbiota and are an important part of our ecosystem.<sup>5</sup> The gut is an important site for the absorption and digestion of nutrients and the production of metabolites. Therefore, the daily diet and the nutritional status of the body have a significant impact on the formation of the gut microbiota.<sup>8</sup> The gut microbiota is linked to a variety of disorders, including hypertension, atherosclerosis, and type 2 diabetes mellitus (T2DM).<sup>9–11</sup> This paper comprehensively examines the complex relationship between the gut microbiota and hypertension, providing a diverse perspective on the treatment of hypertension by analysing the effects of various types of gut microbiota, gut microbiota metabolites, sympathetic activation and gut-brain interactions, and exercise and dietary patterns, as well as the positive effects of probiotics, FMT, and traditional Chinese medicine (TCM) on BP. The aim of this paper is to offer a comprehensive and systematic review of the latest scientific developments in the field of hypertension and gut microbiota research, and to provide insights into the potential value of TCM in regulating the gut microbiota to prevent and treat hypertension. This

## Graphical Abstract



study not only provides valuable academic references for researchers and medical practitioners, but also provides a practical scientific basis for public health policy makers and the public.

## Different Gut Microbiota and Hypertension

The gut microbiota contains a high proportion of bacteria from Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria.<sup>12</sup> Table 1 summarises existing studies of different gut microbiota phyla in hypertension or individuals with higher BP, including study type, study subjects, sequencing methods, and variation in gut microbiota phyla.

## Gut Microbiota Imbalance

The uniformity, abundance, and diversity of the microbial community in the intestine are critical indicators reflecting the imbalance of the intestinal microbiota. In a healthy intestinal ecosystem, Bacteroidetes and Firmicutes are the dominant bacterial groups, and thus, the Firmicutes/Bacteroidetes (F/B) ratio can be regarded as a potential biomarker for pathological states.<sup>13</sup> A study based on high-throughput sequencing technology using fecal samples from patients with grade 3 hypertension and healthy controls revealed that the gut microbiota of hypertensive patients exhibited significant decreases in abundance, diversity, and uniformity, with a notable increase in the F/B ratio. This increase was accompanied by an elevation in the abundance of *Prevotella\_9*, *Megasphaera*, *Parasutterella*, and *Escherichia Shigella*, while the abundance of *Bacteroides* and *Faecalibacterium* decreased.<sup>14</sup> The significant increase in the F/B ratio has been further validated in animal model studies.<sup>15,29</sup> However, in cross-bred spontaneously hypertensive rat (SHR), this difference became particularly prominent, suggesting that relying solely on the F/B ratio as a predictor of disease status may have limitations.<sup>30</sup> Therefore, a comprehensive analysis of the gut microbiota is crucial for accurately assessing pathological states such as hypertension.

**Table I** Studies on Gut Microbiota Composition in Hypertension

Refs.	Study Subjects	Sequencing Method	Upregulate or Downregulate Microorganism phylum and Microorganism Genus
Qin et al <sup>13</sup> (2022)	China population	/	Bacteroidetes↓: Bacteroidetes↓ Firmicutes↑↓: Firmicutes↑, Genus Megasphaera↑, Faecalibacterium↓, Roseburia↓, Ruminococcus↓ Proteobacteria↑: Escherichia-Shigella↑, Klebsiella↑ Actinobacteria↓: genus Bifidobacterium↓
Mushtaq et al <sup>14</sup> (2019)	China population	High-throughput sequencing	Bacteroidetes↑↓: Prevotella_9↑, Bacteroides↓ Firmicutes↑↓: Megasphaera↑, Faecalibacterium↓ Proteobacteria↑↓: Parasutterella↑, Escherichia-Shigella↑
Yan et al <sup>15</sup> (2020)	Rats	16S	Bacteroidetes↓: Bacteroidetes↓ Firmicutes↑: Firmicutes↑ Proteobacteria↑: Proteobacteria↑ Actinobacteria↑: Actinobacteria↑
Dinakris et al <sup>16</sup> (2022)	Adult Australia population	16S	Bacteroidetes↑: Prevotella spp↑, Alistipes spp↑ Firmicutes↑: Clostridium spp↑, Lactobacillus spp↓ Gut microbial richness and evenness ↓
Han et al <sup>17</sup> (2021)	SHR	16S/HPLC System	Bacteroidetes↑: Prevotella_9↑ Firmicutes↑: Phascolarctobacter↑
Fang et al <sup>18</sup> (2022)	China patients with hypertension hospitalized	Metagenomic sequencing data	Bacteroidetes↑: Prevotella↑
Li et al <sup>19</sup> (2019)	Rural areas of Henan, China	16S	Firmicutes↓: Clostridium perfringens 1↓, Romboutsia↓, Ruminococcus 2↓ Proteobacteria↓: Intestinibacter↓
Galla et al <sup>20</sup> (2020)	Dahl salt-sensitive rats	16S	Bacteroidetes↑: Prevotella↑ Firmicutes↑↓: Ruminococcus↑, Clostridium↑, Dorea↑, Veillonellaceae↑, Blautia↓ Lachnospiraceae↑, Blautia↓ Proteobacteria↑↓: Pseudomonas↑; Sutterella↓ Actinobacteria↓: genuses Bifidobacterium↓
Dan et al <sup>21</sup> (2019)	Adult China population	16S	Firmicutes↓: Clostridium perfringens 1↓, Romboutsia↓, Ruminococcus 2↓ Proteobacteria↓: Intestinibacter↓
Yan et al <sup>22</sup> (2017)	Adult China population	Whole-metagenome shotgun sequencing	Bacteroidetes↑: Parabacteroides↑ Firmicutes↓: Clostridium↓, Streptococcus↓, Faecalibacterium↓, Roseburia↓ Proteobacteria↑: Klebsiella↑, Salmonella↑ Actinobacteria↑: Eggerthella↑
Su et al <sup>23</sup> (2018)	China patients with hospitalized	/	Proteobacteria↑: Escherichia coli↑, Salmonella↑, Shigella↑
Lakshmanan et al <sup>24</sup> (2021)	Childhood	16S	Actinobacteria↓: Bifidobacteria↓

**Abbreviations:** 16S, 16S rRNA sequencing; HPLC System, High-Performance Liquid Chromatography System; SHR, spontaneous hypertensive rats.

Recent studies have shown that the gut microbiota can be regulated and balanced through diet and TCM, thereby increasing the numbers of Akkermansia, Bifidobacterium, and Bacteroides, and reducing the F/B ratio, which can help lower BP.<sup>31,32</sup> In addition, oral administration of butyrate or acetate has been observed to prevent increases in BP and the F/B ratio in animal models.<sup>33</sup> These results indicate that hypertension is associated with an unhealthy gut microbiota, and

improving the gut microbiota may be a future target for the treatment of hypertension. Moreover, increases in the F/B ratio have also been observed in obesity and diabetes.<sup>34,35</sup>

## Bacteroidetes

Bacteroidetes play an important role in protein metabolism in the gut and are strongly implicated in the development of hypertension. Most Bacteroidetes are gram-negative bacilli. The genera *Bacteroides* and *Prevotella* form a major part of the phylum Bacteroidetes, and their activities have a significant role in the decomposition and transformation of food.<sup>36</sup> *Bacteroides* are the most abundant genus of bacteria in the gut and are thought to be a major source of short-chain fatty acids (SCFA) and an important contributor to the metabolism of dietary fibre and host-derived polysaccharides.<sup>37</sup> Additionally, *Prevotella* contributes to the utilisation of plant materials in the rumen.<sup>38</sup> *Prevotella* is found in the mouth, vagina, and intestine and can mediate intestinal mucosal inflammation, improve intestinal permeability and promote systemic inflammation.<sup>39,40</sup> Many studies have found a significant increase in the presence of *Prevotella* in the stool of hypertensive patients.<sup>16–18</sup> Both *Bacteroides* and *Prevotella* play an essential function in protein metabolism and possibly also in the metabolism of carcinogens and xenobiotics.

## Firmicutes

There is a wide range of genera of bacteria in Firmicutes that have been strongly associated with hypertension. The majority of Firmicutes are gram-positive bacteria, including the *Ruminococcus*, *Clostridium*, and *Veillonellaceae* families. The abundance of *Clostridium perfringens* 1, *Romboutsia*, *Ruminococcus* 2, and *Intestinibacter* was found to be negatively correlated with SBP and diastolic blood pressure (DBP) in hypertensive patients receiving antihypertensive treatment.<sup>19</sup> In addition, a decrease in the relative abundance of *Ruminococcus* was observed in the gut following a high-fat diet; *Ruminococcus* is the main producer of butyrate in the body.<sup>41</sup> Butyrate is an SCFA that plays an active role in maintaining the overall health of the gut.<sup>42</sup> Furthermore, in Dal salt-sensitive rats, the abundance of *Veillonellaceae* was positively correlated with BP,<sup>20</sup> whereas *Enterococci* were more common in normotensive individuals.<sup>21</sup>

## Proteobacteria

Proteobacteria have various shapes, are mainly defined by ribosomal ribonucleic acid (RNA) sequences and are commonly disorganised in the gut of hypertensive people. Proteobacteria are gram-negative bacteria, including species such as *Klebsiella* and *Salmonella*. The guts of patients with hypertension exhibit more *Klebsiella* and *Salmonella* bacteria than those of normotensive people.<sup>22</sup> *Klebsiella* is a pathogen commonly found in the human intestinal tract and can cause a variety of infectious diseases, such as pneumonia, diarrhoea, and urinary tract infections.<sup>43,44</sup> Furthermore, Su et al found dysbiosis of the gut microbiota in the intestines of hypertensive patients treated with antibiotics, resulting in large numbers of pathogenic gram-negative bacteria, such as *Salmonella*.<sup>23</sup>

## Actinobacteria

The key genera of the Actinobacteria phylum, including *Bifidobacterium* and *Mycobacterium*, are both Gram-positive bacteria and crucial for the gut health of hypertensive patients. *Bifidobacterium* plays a significant role in reducing the production of lipopolysaccharide (LPS), maintaining the balance of the gut microbiota, and preserving the intestinal barrier function.<sup>45</sup> A meta-analysis targeting the Chinese population has indicated that hypertensive patients suffer from impaired gut microbial diversity, manifesting as an increased F/B ratio, increased abundances of phylum Firmicutes, genus *Megasphaera*, *Escherichia*\_Shigella, *Klebsiella*, and decreased abundances of Bacteroidaceae, *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus*.<sup>13</sup> Additionally, a notable decrease in *Bifidobacterium* abundance has been observed in *Ruminococcus*-T1DM (type 1 diabetes mellitus) patients with high BP.<sup>24</sup> This reduction in *Bifidobacterium* abundance is closely associated with an increased susceptibility to *Mycobacterium tuberculosis* among hypertensive patients. Therefore, *Mycobacterium tuberculosis* infection may serve as a common risk factor for both hypertension and tuberculosis.<sup>46,47</sup>

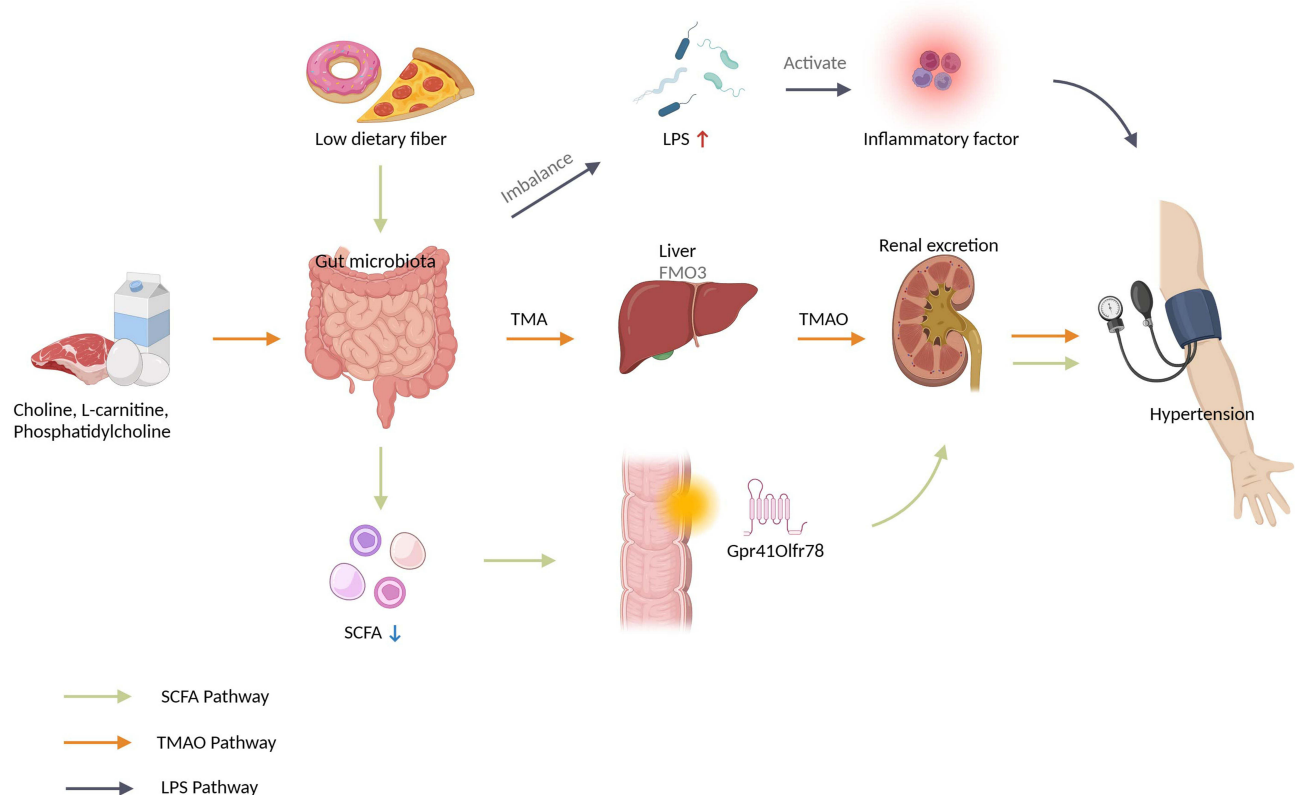
## Metabolites of the Gut Microbiota

### Short-Chain Fatty Acids

SCFA, as important metabolites of the gut microbiota, play a crucial role in the prevention of CVD such as hypertension.<sup>32,48–51</sup> Studies have revealed that gut microbiota that produce SCFA are associated with reduced BP, while elevated concentrations of SCFA in feces are related to increased BP.<sup>52</sup> In particular, butyrate can inhibit the production of proinflammatory cytokines, exert an anti-inflammatory effect, and affect BP by regulating the gut microbiota and the renin-angiotensin system.<sup>53–57</sup> In recent years, there have been numerous reports on the use of specific probiotics or foods to improve butyrate-producing bacteria, helping to reduce the F/B ratio and BP in subjects.<sup>58–60</sup> Additionally, SCFA receptors such as G-protein coupled receptors (mainly GPR41 and GPR43) and olfactory receptor 78 (Olf78) play important roles in BP regulation.<sup>61,62</sup> SCFA regulate the gut microbiota and affect BP levels by influencing these receptors and exerting anti-inflammatory effects.<sup>62–65</sup> Therefore, optimizing the gut microbiota, especially by increasing the production of SCFA, may provide new strategies for the prevention and treatment of CVD such as hypertension (Figure 1).

### Trimethylamine N-Oxide

The concentration of trimethylamine N-oxide (TMAO) in the intestine is closely related to the BP of hypertensive patients, and its production is associated with the composition of the gut microbiota, diet, and disturbance of the intestinal blood barrier (Figure 1). TMAO is mainly generated by the oxidation of trimethylamine (TMA) by the gut microbiota, and its metabolic pathway differs in different regions of the intestine.<sup>66–69</sup> Although the underlying mechanism between TMAO and hypertension is not fully understood, it has been confirmed that TMAO in the plasma can accelerate the formation of foam cells, enhance oxidative stress and proinflammatory responses, and reduce the production of anti-inflammatory cytokines.<sup>70</sup> In



**Figure 1** Effect of metabolites of gut microbiota on hypertension.

**Notes:** In Figure 1, the SCFA pathway, the TMAO pathway, and the LPS pathway are indicated by different coloured arrows, respectively. Created with BioRender.com.

**Abbreviations:** SCFA, short-chain fatty acid; TMA, trimethylamine; FMO3, flavin-containing monooxygenase 3; TMAO, trimethylamine N-oxide; LPS, lipopolysaccharide; Gpr41, G-protein coupled receptor 41; Olf78, olfactory receptor 78.

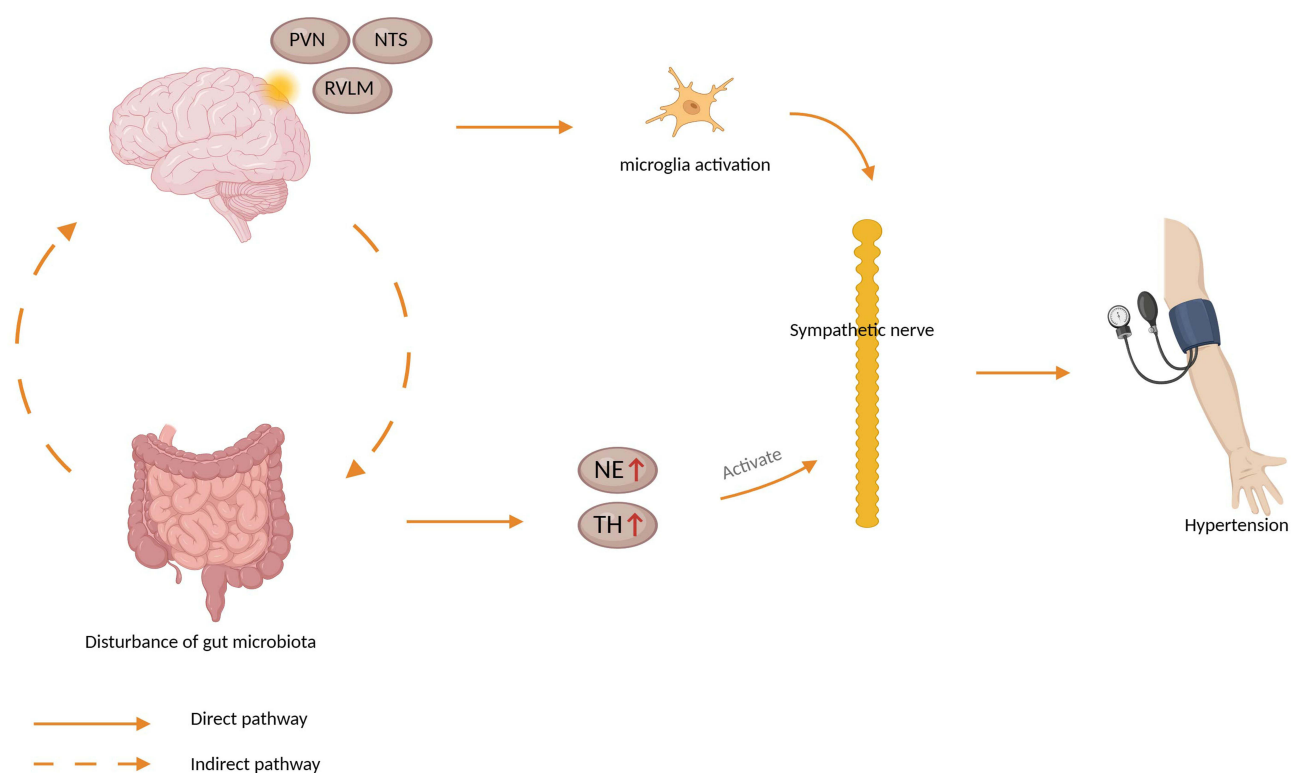
hypertensive patients, due to the decreased intestinal barrier function, the inflammation in the body also increases when the concentration of TMAO rises.<sup>71,72</sup> Multiple studies have shown that the level of plasma TMAO is associated with the risk of hypertension and other diseases, and there is a dose-dependent relationship.<sup>73–77</sup> Animal models have demonstrated that specific intestinal microbiota are highly positively correlated with plasma TMA, TMAO levels, and the degree of atherosclerotic lesions, while certain bacterial flora show a negative correlation.<sup>78</sup> Therefore, the production of TMAO may be influenced by individual differences in the gut microbiota, as indicated by the relationship between the F/B ratio and the degree of response to dietary precursors of TMAO.<sup>79</sup>

## Lipopolysaccharide

LPS, commonly known as endotoxin, is a component of the bacterial wall of gram-negative bacteria and a key factor in triggering inflammation.<sup>80,81</sup> In hypertensive patients with gut microbiota imbalance, the proliferation of gram-negative bacteria leads to an increase in LPS concentration, which then binds to Toll-like receptor 4 (TLR4) to activate the innate immune response. LPS forms a complex with LPS-binding protein (LBP), enters the blood from the intestine, interacts with CD14 on monocytes, and activates TLR4, thereby triggering the production of proinflammatory cytokines such as Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and IL-6.<sup>81,82</sup> Butyrate, on the other hand, can inhibit the inflammatory response triggered by LPS.<sup>83</sup> Studies have shown that prenatal exposure to LPS can induce oxidative stress, impair the ability to eliminate salt load, and lead to hypertension in multiple generations.<sup>84</sup> Additionally, low-dose aspirin can reduce LPS-induced hypertension and related inflammatory responses in mice.<sup>85</sup> Therefore, the systemic effects of LPS are closely related to the pathophysiology of hypertension (Figure 1).

## Interaction Between Sympathetic Activation and the Gut-Brain

The imbalance of the gut microbiota exacerbates the progression of hypertension by activating the sympathetic drive and promoting neuroinflammation (as shown in Figure 2). Overactive sympathetic activity can directly or indirectly promote



**Figure 2** Interaction between sympathetic activation and the gut-brain axis.

**Note:** Created with BioRender.com.

**Abbreviations:** PVN, paraventricular nucleus; NTS, nucleus of the solitary tract; RVLM, rostral ventrolateral medulla; NE, norepinephrine; TH, tyrosine hydroxylase.



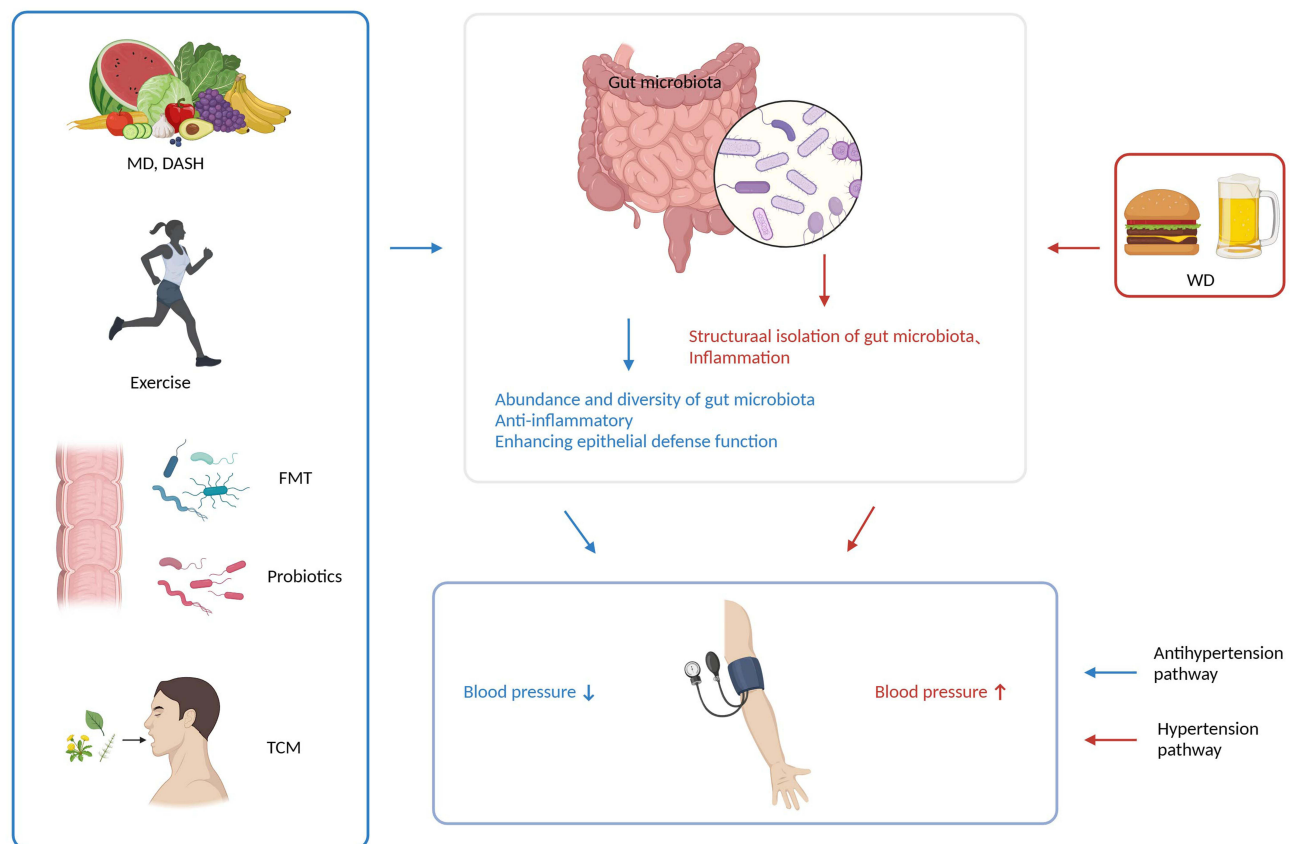
the development of hypertension and organ damage by stimulating low-grade systemic inflammation. Dysfunction of the gut-brain axis has been observed in animal models of hypertension.<sup>86</sup> Additionally, increased sympathetic activation has been observed in the early stages of hypertension.<sup>87,88</sup> Experiments involving FMT have confirmed the stimulatory effect of the gut microbiota on the sympathetic drive.<sup>89–91</sup> Simultaneously, reducing sympathetic activity is crucial for alleviating structural changes in the cardiovascular system and mitigating hypertension.<sup>92,93</sup>

## Different Hypertension Concomitant Factors

As previously stated, hypertension is caused by a variety of complex environmental factors. At present, the impact of exercise and diet on hypertension has attracted significant attention (Figure 3). Tables 2 and 3 summarise the interactions between exercise and diet and hypertension or higher BP, including study type, study population, intervention type, sequencing method, changes in gut microbiota and postintervention impact.

## Exercise Changes Gut Microbiota

Exercise, as a non-pharmacological intervention, has shown significant results in the treatment and prevention of hypertension. Several studies have focused on athlete populations to reveal positive associations between their healthy BP status and the diversity of their gut microbiota, particularly the association between Prevotella counts and exercise duration and intensity.<sup>25,26</sup> Although the extreme dietary and behavioural patterns of elite athletes limit the generalizability of the findings, studies in the general population have similarly shown that a combination of aerobic and resistance training can be effective in lowering BP and promoting gut microbiota diversity, with an increase in metabolites of beneficial microbes, such as short-chain fatty acids. These metabolites have biological activities such as



**Figure 3** Effects of exercise, dietary pattern, and treatment on hypertension.

**Notes:** In Figure 3, the anti-hypertensive pathway and the pathway leading to hypertension are indicated by blue and red arrows, respectively. Created with BioRender.com.

**Abbreviations:** MD, Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; FMT, fecal microbiota transplantation; WD, Western diet.

**Table 2** The Effect of Exercise on Gut Microbes

Refs.	Study Subjects	Sequencing Method	Microbiota Changes	Intervention methods	Post-Intervention Impact
Barton et al <sup>25</sup> (2018)	Professional international rugby union players	HILIC chromatography profiling	Athletes excreted proportionately higher levels of the metabolite SCFA, TMAO	/	Fitness and overall health contribute to gut microbial diversity.
Kulecka et al <sup>26</sup> (2020)	Polish elite athletes (endurance sports)	16S	Prevotella, and Veillonella genus ↑	/	Increase the diversity of gut microbes and optimize the structure of gut microbes.
Zhong et al <sup>27</sup> (2022)	Elderly women	16S	Alpha diversity; members of the order Coriobacteriales; Asaccharobacter, Collinsella and Fusicatenibacter↑; risk of metabolic syndrome↓	8-week exercise training	Regulate the structure of gut microbes, reduce the risk of CVD, and enhance physical functions.
Wu et al <sup>28</sup> (2023)	Middle-aged and elderly people in China	16S	BP and heart rate levels ↓, immune-inflammatory factors (IL-6, IL-10) ↓, F/B ratio ↓, abundance of Escherichia-Shigella ↓, Bacteroides ↑	12 weeks of LZJ training.	Improvement of inflammation and structure of the gut microbiota

**Abbreviations:** SCFA, Short-chain fatty acids; TMAO, Trimethylamine N-oxide; 16S, 16S rRNA sequencing; CVD, Cardiovascular Disease; IL-6, Interleukin-6; IL-10, Interleukin-10; F/B, Firmicutes/Bacteroidetes ratio; LZJ, Liuzijue.

anti-inflammatory and antioxidant properties that can directly or indirectly influence BP regulatory mechanisms.<sup>27</sup> In addition, forms of exercise through harmonising the breath have shown significant positive effects in the treatment of hypertension. Among them, Liuzijue training (LZJ), a traditional exercise therapy that integrates breathing meditation with physical activity, has unique advantages in the prevention and improvement of hypertension. Compared with aerobic training, LZJ can effectively reduce BP, regulate immune homeostasis, and optimise the composition of the gut microbiota, and it is more easily applicable to the general population.<sup>28</sup> In addition, yoga, Pilates, and traditional Chinese exercises (Tai Chi, Baduanjin, and Wuqinxi) are all complementary interventions for hypertension that focus on soothing exercise modalities that harmonise the breath, enhance flexibility, and promote inner peace and focus. It has been shown in many trials to help with BP control are safe and effective for hypertensive patients, and can be used as one of the means of rehabilitation.<sup>105–108</sup> However, the role of these exercises in improving the gut microbiota still needs to be further explored in depth.

Although limited by sample size and confounding factors, the current study needs to further validate the beneficial effects of exercise on the gut microbiota in a large population. Given the specific physiological status of hypertensive patients, such as sympathetic hyperexcitability and exercise-induced BP elevation, exercise regimens should be more carefully tailored and individualised.<sup>109–111</sup> In conclusion, despite the limitations of the study, the potential of exercise as a non-pharmacological therapy for hypertension has been preliminarily established, and future studies should further explore its specific applications and mechanisms in different populations.

## Diet Regulates Blood Pressure and Gut Microbiota

There is a close relationship between diet and gut microbiota, inflammation, and BP levels.<sup>94–96</sup> High salt/fat intake and changes in the composition and function of gut microbiota can lead to cardio-metabolic diseases, including hypertension, obesity, T2DM, and dyslipidemia.<sup>112</sup> Among them, the Western diet (WD) contains little fiber, vitamins, minerals, or other plant-derived compounds (such as antioxidants), but is rich in refined sugar, salt, white flour, processed meat, animal fat, and food additives.<sup>113</sup> This diet, rich in high salt, high fat, and processed foods, leads to gut microbiota imbalance, triggers inflammation, and increases the risk of hypertension.<sup>97,98</sup> Experiments have shown that a high-salt diet reduces the abundance of Lactobacillus and the level of butyrate (a protective SCFA) in the intestines of mice, inducing a pro-inflammatory state.<sup>114,115</sup> On the other hand, the Mediterranean diet (MD) and Dietary Approaches to



**Table 3** The Effect of Diet on Gut Microbes

Refs.	Study Subjects	Sequencing Method	Microbiota Changes	Intervention Methods	Post- Intervention Impact
Le et al <sup>60</sup> (2022)	Healthy prehypertensive men and women aged 40–70 years, London	SMSeq	Gut microbiome gene richness and abundance of butyrate-producing species (eg, <i>Lawsonibacter asaccharolyticus</i> , <i>Intestinimonas butyriciproducens</i> ) ↑	Aronia berry (poly)phenol	Improved vascular function in middle-aged people with prehypertension.
David et al <sup>94</sup> (2014)	Healthy adults	16S/GC	Beta diversity, bile-tolerant microbes ( <i>Alistipes</i> , <i>Bilophila</i> , <i>Bacteroides</i> ) ↑; SCFAs, Firmicutes metabolizing plant polysaccharides ( <i>Roseburia</i> , <i>E. rectale</i> , <i>R. bromii</i> ) ↓	Animal-based diet	A changed diet might cause the gut microbiome to adapt quickly.
Wan et al <sup>95</sup> (2020)	China healthy adults	16S	<i>Bacteroides</i> , <i>Clostridium</i> , <i>Bifidobacterium</i> and <i>Lactobacillus</i> ↑	High fat intake for 6 months	Alter the composition of intestinal microbiota, and damage colonic and cardiac metabolic health.
Cho <sup>96</sup> (2021)	Korean children (aged 7 to 18 years)	16S	In the fat loss group: Firmicutes phylum, Clostridia class, Bacteroidetes phylum and microbial richness ↓ In fat gain group: Firmicutes phylum, Clostridia class, Lachnospiraceae family, and <i>Eubacterium hallii</i> group genus ↓	Lifestyle modifications	After weight loss, lifestyle adjustments alter the composition, diversity, and predicted functions of gut microbiota in obese children.
Andújar et al <sup>97</sup> (2022)	6 weeks old male mice	16S	Butter group: Proteobacteria, Desulfovibrionaceae family ↑, <i>Lactobacillus</i> ↓ Extra virgin olive oil group: Desulfovibrionaceae family, <i>Bacteroides finnegoldii</i> ↑, <i>Lactobacillus</i> ↓	Standard diet or one of two high fat diets containing either butter or extra virgin olive oil	Changes in the structure of the gut microbiota as a result of diet.
Vileigas et al <sup>98</sup> (2019)	Male Wistar rats (60 days old)	/	/	CD, WDF, or WDS for 41 weeks.	Both WDF and WDS notably increased obesity and BP, with WDF also causing mild cardiac systolic dysfunction.
Filippou et al <sup>99</sup> (2020)	Adults with and without Hypertension	/	/	DASH	DASH significantly reduced SBP and DBP, regardless of baseline BP.
Li et al <sup>100</sup> (2020)	Spanish PREDIMED cohort and US NHS/HPFS cohort	HT LC-MS/MS	/	MD	A metabolome favoring healthy cardiometabolism ↑
Schwingshackl et al <sup>101</sup> (2019)	Hypertensive and pre-hypertensive adult patients	/	/	DASH, Low-Fat, and 13 other diets	DASH diet was most effective in reducing SBP and DBP.
Jennings et al <sup>102</sup> (2019)	Elderly people in Europe	/	/	MD	Sex differences: Males only responded to SBP and pulse pressure; females showed arterial stiffness effects, not peripheral BP.
Nagpal et al <sup>103</sup> (2018)	Healthy adult female cynomolgus macaques	16S	<i>Bacteroides</i> , Proteobacteria, Fibrobacteres, Spirochaetes, Clostridiaceae, <i>Lactobacillus</i> , <i>Faecalibacterium</i> , <i>Oscillospira</i> ↑ Firmicutes and Verrucomicrobia; F/B ↓	MD	There were significant changes in the metabolome, improving cardiac metabolic health.
Belanger et al <sup>104</sup> (2023)	Adults with elevated BP or hypertension	/	/	12 weeks of the DASH diet	DASH gradually decreased hs-cTnI and hs-CRP, potentially reducing subclinical heart injury.

**Abbreviations:** SMSeq, Shotgun metagenomics sequencing; 16S, 16S rRNA sequencing; GC, Gas chromatography; SCFA, Short-chain fatty acids; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry; hs-CRP, high-sensitivity C-reactive protein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CD, Control diet; WDF, Western diet fat; WDS, Western diet sugar; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; HT LC-MS/MS, High-throughput liquid chromatography-tandem mass spectrometry; MD, Mediterranean diet; WD, Western diet; F/B, Firmicutes / Bacteroidetes ratio; hs-cTnI, high-sensitivity cardiac troponin I.

Stop Hypertension (DASH) diet, characterized by low fat and high fiber, can effectively lower BP and improve cardiovascular health.<sup>99–101</sup> Studies have shown that these dietary patterns increase gut microbial diversity, promote the growth of beneficial bacteria, reduce inflammatory markers, and effectively improve cardiovascular health.<sup>102–104,116</sup> In summary, optimizing dietary patterns, especially reducing the intake of high-salt and high-fat foods and increasing the consumption of fiber-rich foods, is crucial for maintaining the balance of gut microbiota, reducing inflammation, and preventing hypertension.

## Microbial Targeted Therapy

### Probiotics

Probiotics have positive effects, including controlling intestinal flora, inhibiting inflammation, and boosting epithelial defence. This includes microorganisms that can produce SCFA, such as bifidobacteria, enterococci, and lactobacilli.<sup>117,118</sup> Probiotics improve the structural and functional integrity of the gut wall and guard against neuroinflammation within the cardiac regulatory nucleus, which help to reduce hypertension. Probiotic (Kefir) intervention studies revealed higher serum LPS concentrations in SHR than in WKY rats and differences in the jejunal wall. The authors also reported decreased IL-6 and TNF- $\alpha$  protein density and abrogation of the activation of microglia in the hypothalamic paraventricular nucleus and medulla oblongata ventrolateral.<sup>119</sup> A meta-analysis revealed that probiotic supplementation resulted in modest but significant reductions in SBP and DBP in hypertensive patients, an effect that was related to treatment duration, dose, and age of the subjects but not to the use of single or multiple strains. In addition, probiotic supplementation had beneficial effects on lowering BMI and blood glucose.<sup>120</sup> Moreover, the beneficial effect of probiotics may be transmitted to offspring. In a rat trial of maternal flora-targeted therapy, probiotic or prebiotic therapy not only prevented elevated BP due to a perinatal high-fat diet and elevated BP in adult male offspring but also reduced maternal F/B, plasma TMAO levels, and TMAO to TMA ratios, as well as faecal concentrations of propionate and acetate in offspring, and increased the abundance of the genera *Lactobacillus* and *Akkermansia*.<sup>121</sup> In summary, probiotics contribute to lowering BP by improving gut health and reducing inflammation, and these findings reveal the potential value of probiotics as a non-pharmacological treatment for the prevention and treatment of hypertension.

## Faecal Microbiota Transplantation

The gut microbiota plays a critical role in the onset and progression of hypertension. FMT, which has attracted much interest in recent years, has been shown to not only directly alter the diversity of the gut flora and the proportion of cells that restore health but also to have fewer side effects and lower rates of recurrence and reinfection.<sup>122</sup> According to a recent study, there was a significant decrease in SBP after 2 weeks of FMT from losartan-treated SHR to untreated SHR.<sup>123</sup> Additionally, resveratrol can improve glucose imbalance and hypertension by affecting the gut flora.<sup>124</sup> Researchers transplanted the gut microbiota of resveratrol-fed healthy mice into obese mice and improved glucose homeostasis in obese mice within 11 days. Hypertensive mice exhibited lower SBP within two weeks of FMT. Moreover, FMT was more effective than oral resveratrol for the same duration.<sup>125</sup>

However, individual differences are large, and the best FMT method, including donor screening and preparation, has not been determined.<sup>125,126</sup> Patients with a history of resting ulcerative disease develop ulcerative colitis after FMT, which may be because the new gut microbiota triggers an immune response.<sup>127</sup> This suggests that there are differences in the interactions of gut microbiota between individuals. Furthermore, the gut microbiota is hereditary and has been connected to several diseases (such as diabetes and colorectal cancer), with a theoretical risk of inadvertently promoting the development of these diseases.<sup>128,129</sup> Moreover, the long-term impact of FMT is unclear, as most studies have been followed up for less than one year, and the hypothetical long-term adverse consequences of potentially harmful bacterial metastasis are unclear. As a result, to employ FMT effectively, a deeper understanding of the link between hypertension and gut flora in various individuals is needed.

## Traditional Chinese Medicine

TCM has demonstrated remarkable efficacy in the clinical treatment of hypertension. Primarily through oral intervention, it effectively prevents and controls hypertension by regulating the structure and proportion of intestinal microbiota,

thereby optimizing the immune function and metabolic mechanism of the body.<sup>130,131</sup> Research has shown that TCM plays a crucial role in regulating and balancing intestinal flora. It can increase the number of beneficial bacteria such as *Akkermansia*, *Bifidobacterium*, and *Bacteroides*, and reduce the F/B ratio, creating a healthy environment for the intestine.<sup>30</sup> For instance, Huanglian Jiedu Decoction (HJD) effectively prevents hypertension by increasing the diversity of SHR microbiota, reducing the frequency of *S. solidus* and enriching the abundance of *Lactobacilli* spp.<sup>132</sup> Moreover, it is noteworthy that HJD can significantly reduce the levels of inflammatory factors such as TNF- $\alpha$  and IL-8, effectively suppressing immune and inflammatory responses.<sup>133,134</sup> Simultaneously, it significantly alters the gene expression profile of SHR, involving multiple cellular functions like smooth muscle contraction regulation, endothelial cell Ca(2+) balance, and nitric oxide (NO) pathways.<sup>135</sup> In addition to HJD, the active components of Taohong Siwu Decoction (TSD) also demonstrate remarkable effects in the treatment of cardiovascular diseases. According to a meta-analysis, the combination of TSD and antihypertensive drugs can significantly enhance the antihypertensive effect, providing better treatment outcomes for hypertensive patients.<sup>136</sup> The BuYang HuanWu decoction not only significantly enhances the gene expression of *Bifidobacterium* in the gut, but also reduces the gene expression of *Escherichia coli*, *Clostridium*, and *Enterococcus*. Moreover, it can significantly lower serum TMAO levels.<sup>137</sup>

It is worth mentioning that TCM can not only improve hypertension in combination with Western medicine but also alone, with effects superior to the use of Western medicine alone. Cheqianzi Cuduotang capsules can assist or be used in combination with Western medicine to improve hypertension symptoms by improving the intestinal microecology of elderly hypertensive patients, and its effect is even better than using Western medicine alone.<sup>138</sup> In animal experiments, *Eucommia ulmoides*-*Tribulus terrestris* herbs have a positive impact on BP and inflammatory levels in elderly SHR, outperforming valsartan in maintaining the diversity of intestinal microbiota. Their antihypertensive mechanism is related to changes in the composition and diversity of intestinal microbiota.<sup>139</sup> Additionally, Quanduzhong capsules, which contain extracts of *Eucommia globulus*, extract are very effective for patients with Grade 1 hypertension with low to moderate risk, reducing office SBP, DBP, and the 24-hour average coefficient of variation of DBP determined by 24-hour ambulatory BP monitoring.<sup>140</sup>

Compared with Western medicine, TCM formulas have the unique advantage of attacking multiple targets simultaneously. Zhengganxifeng decoction (ZGXFD) has been widely used in the clinical treatment of hypertension. Studies have shown that ZGXFD can significantly improve the structure of intestinal microbiota, reduce the F/B ratio and the ratio of cocci to bacilli (C/B), while maintaining the integrity of the intestinal mechanical barrier and increasing the proportion of bacteria that produce SCFA, providing a new strategy for hypertension treatment.<sup>141</sup> Moreover, Zhijing powder can also regulate the signaling pathway of hypertension receptors, improve oxidative stress, and lower BP in rats with hypertension induced by cold stimulation and high salt intake.<sup>142</sup>

Regarding TCM decoctions for lowering BP, which include but are not limited to the examples mentioned above, their inclusion of a variety of medicinal materials allows for a combination effect of numerous bioactive components and pharmacological actions. This enables TCM decoctions to modulate the human body through multiple targets and pathways, thereby more comprehensively regulating physiological functions and achieving better antihypertensive effects. Moreover, there is literature suggesting that single TCMs may reduce the number of *Bifidobacterium pseudolongum*.<sup>143</sup> Therefore, from the perspective of species diversity, TCM decoctions have better health benefits than single TCM preparations.

In summary, TCM has demonstrated remarkable efficacy and potential in the clinical treatment of hypertension (Figure 3). Compared with probiotics and FMT, TCM comprehensively regulates the body through various approaches and possesses more human experimental evidence and therapeutic effects, thus often becoming the preferred option for chronic disease treatment. It not only improves the symptoms of hypertensive patients but also enhances their quality of life, paving a new way for the treatment of hypertension.

## Perspectives

The bacteria in the gut can create and secrete a wide range of compounds, allowing the gut microbiota to modulate hypertension in a variety of ways, frequently in collaboration. Therefore, a variety of therapies, such as dietary modification, exercise, probiotics, TCM and FMT, are being or will be used in the clinical setting to mitigate the development of hypertension (see Figure 3 for developmental pathways). However, due to heterogeneity, some therapies

remain to be investigated in the general population. For example, when considering the gut microflora of professional athletes and the general population, it would be unrealistic to expect the general population to train in the same way as professional athletes and thus achieve a similar improvement in their gut microbiota. Moreover, the effects of probiotics vary depending on the disease and strain, and a protocol to lower BP using probiotics can only be achieved using specific probiotics. Moreover, although the results of animal experiments using probiotics have been satisfactory, human evidence is sparse and equivocal, and the function of certain strains is often unclear. As a result, probiotics are currently used for the primary prevention of hypertension and as a supplement to established medications for hypertension and do not reach the therapeutic threshold. In conclusion, diet, exercise and TCM may be effective ways to improve the gut microbiota in the long term, whereas the effectiveness of probiotics and FMT to improve the gut microbiota remains to be validated in large populations.

## Conclusions

In recent years, there has been significant discussion regarding the relationship between the composition of the gut microbiota and the development of hypertension. The homogeneity of the distribution of microbiota in the gut, as well as the abundance and diversity in the gut, are important indicators of dysbiosis of the intestinal microbiota. For example, a decrease in mimetic bacteria and an increase in F/B can directly or indirectly contribute to a variety of diseases, including hypertension. Although the relationship between gut microbiota composition and elevated BP has not been thoroughly established, patients with an imbalanced gut microbiota are at higher risk for hypertension. Therefore, improving the gut microbiota may be a target for future hypertension treatment. Because most of our knowledge of these mechanisms comes from studies in animals and because there may be differences between the gut microbiota of animals and humans, caution should be exercised in extrapolating the results of animal experiments to humans. In the future, translating the various influences involved in hypertension to humans will remain a challenge. To better target potential therapeutic interventions, future studies with more representative population cohorts are needed to demonstrate the strengths and weaknesses of gut flora structure and function.

## Abbreviations

BP, blood pressure; FMT, faecal microbiota transplantation; CVD, Cardiovascular disease; SBP, Systolic blood pressure; T2DM, type 2 diabetes mellitus; TCM, traditional Chinese Medicine; F/B, Firmicutes/Bacteroidetes; SHR, Spontaneously hypertensive rat; SCFA, short-chain fatty acids; DBP, Diastolic blood pressure; RNA, Ribonucleic Acid; LPS, Lipopolysaccharide; T1DM, Type 1 diabetes mellitus; GPR, G-protein coupled receptors; Olfr78 olfactory receptor 78; TMAO, Trimethylamine N-oxide; TMA, trimethylamine; TLR4, Toll-like receptor 4; LBP, LPS-binding protein; TNF- $\alpha$ , Tumour necrosis factor- $\alpha$ ; IL-1, interleukin-1; LZJ, Liuzijue training; WD, Western diet; MD, Mediterranean diet; DASH, Dietary approach to stop hypertension; HJD, Huanglian Jiedu Decoction; TSD, Taohong Siwu Decoction; ZGXFD, Zhengganxifeng decoction; C/B, the ratio of cocci to bacilli.

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## Author Contributions

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## Disclosure

The authors report no conflicts of interest in this work.

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