

肠道微生物群调节血压的研究进展

周彬¹, 何燕², 柳陈坚¹, 李晓然^{1*}

1 昆明理工大学 生命科学与技术学院, 云南 昆明

2 昆明医科大学 附属延安医院高血压中心, 云南 昆明

周彬, 何燕, 柳陈坚, 李晓然. 肠道微生物群调节血压的研究进展[J]. 微生物学报, 2025, 65(8): 3492-3506.

ZHOU Bin, HE Yan, LIU Chenjian, LI Xiaoran. Research progress in the regulation of blood pressure by gut microbiota[J]. *Acta Microbiologica Sinica*, 2025, 65(8): 3492-3506.

摘要: 作为全球心血管疾病的主要风险因素, 高血压的危害不容忽视。近年来, 肠道微生物群在高血压发病机制中的作用逐渐成为研究热点。本综述系统探讨了肠道微生物群与高血压之间的联系, 详细阐述了肠道微生物群通过介导炎症反应、影响肠道微生物群-肠-脑轴以及产生特定代谢产物等多种途径对血压的调控机制。同时, 本文讨论了基于肠道微生物群的干预策略在高血压预防与治疗中的潜在应用价值, 揭示了肠道微生物群在治疗高血压及其并发症中的潜在靶点和证据, 为治疗方法的探索开辟了新的途径。

关键词: 肠道微生物; 高血压; 血压调控

Research progress in the regulation of blood pressure by gut microbiota

ZHOU Bin¹, HE Yan², LIU Chenjian¹, LI Xiaoran^{1*}

1 Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, Yunnan, China

2 Hypertension Center, Yan'an Hospital Affiliated to Kunming Medical University, Kunming, Yunnan, China

Abstract: As a major risk factor for cardiovascular disease worldwide, hypertension poses threats that cannot be ignored. In recent years, the role of gut microbiota in the pathogenesis of hypertension has gradually become a research hotspot. This review systematically explores the relationship between gut microbiota and hypertension and elaborates on the mechanisms of gut

资助项目: 云南省科技厅基础研究专项(202401AT070846)

This work was supported by the Basic Research Project of Yunnan Provincial Department of Science and Technology (202401AT070846).

*Corresponding author. Tel: +86-871-65920759, E-mail: starkeyran@163.com

Received: 2025-01-16; Accepted: 2025-03-31; Published online: 2025-06-10

microbiota regulation of blood pressure by mediating inflammatory responses, influencing the microbiota-gut-brain axis, and producing specific metabolites. Furthermore, this article discusses the potential application value of gut microbiota-based intervention strategies in the prevention and treatment of hypertension and reveals the potential targets and evidence of gut microbiota in the treatment of hypertension and its complications, paving a new way for the exploration of therapeutic methods.

Keywords: gut microbiota; hypertension; blood pressure regulation

心血管疾病长期以来一直是全球健康领域面临的一大挑战^[1]。高血压作为其发展的关键危险因素^[2]，影响着全球约 15 亿成年人，占总成年人口的 1/3^[3]。高血压的发病机制复杂，涉及遗传和环境等多种因素^[4]。肠道微生物群是细菌、真菌、古细菌和病毒等构成的复杂生态系统，在人类健康与疾病中的作用备受关注^[5]，该系统通过种群结构动态变化、代谢产物多样性、信号转导途径的调控以及基因表达的差异，调节宿主代谢、生理功能及免疫系统，从而维持宿主的内环境稳定，对保障宿主健康至关重要^[6]。

尽管对高血压的研究已取得显著进展，但仍面临着长期药物治疗所带来的严重副作用、器官损伤和日益增加的耐药性问题^[7]。因此，开发非药物降压策略刻不容缓。虽然肠道微生物群在高血压调控中的作用机制尚待阐明，但已有研究表明其在高血压的发生发展中扮演着重要角色^[8]。本综述旨在深入探讨该领域的研究动态，为阐明肠道微生物组在高血压发病机制中的作用提供科学理论基础。预期通过深化微生物组功能理解，发现新的治疗策略和生物标志物，为高血压的预防和治疗提供新的研究方向。

1 高血压对肠道微生物组成的影响

据估计，成年人的肠道微生物群包含大约 500–1 000 种不同的细菌种类^[9]，Eckburg 等^[10]通过宏基因组学分析揭示了肠道细菌群落主要由 6 个菌门构成：芽孢杆菌门(*Bacillota*)、拟杆

菌门 (*Bacteroidota*)、假单胞菌门 (*Pseudomonadota*)、放线菌门(*Actinobacteriota*)、梭杆菌门 (*Fusobacteriota*) 和疣微菌门 (*Verrucomicrobiota*)^[11]。肠道微生物之间的相互作用主要通过拮抗或共生关系实现，肠道菌群的失衡(即微生态失调)可能进一步导致血压失衡^[12]，其机制涉及微生物代谢物失衡、免疫调节改变、交感神经活动增强、肠道屏障破坏和炎症^[13-14]。此外，肠道菌群失衡特征为芽孢杆菌与拟杆菌(*Bacillota/Bacteroidota*, F/B)比率变化，可用作病理状况的生物标志物^[15]。一项针对 1 082 名中国成年人的肠道微生物群和血浆代谢组学的队列研究揭示了特定细菌群落(如明串珠菌科、肠杆菌科、梭杆菌属和沙雷氏菌属)以及代谢物(如亚油酸酯、棕榈酸酯、二高宁酸酯等)与宿主血压水平呈正相关^[16]。此外，患有妊娠期高血压综合征的产妇肠道微生物的组成也发生改变^[17]。Miao 等^[18]通过采用双样本孟德尔随机化方法，调查肠道菌群的 199 个微生物类群与高血压以及常见的高血压相关并发症之间的因果关系，并通过反向分析检验了反向因果关联，结果表明肠道微生物群失衡会导致高血压。Mell 等^[19]发现，与血压正常的 Wistar-Kyoto 大鼠相比，易发中风的自发性高血压大鼠 (spontaneously hypertensive rats, SHR)的肠道微生物群落存在显著差异。动物和人类研究均显示肠道菌群失调与高血压存在双向联系^[20]。越来越多的研究表明，肠道菌群失衡及其代谢产物在血压调节中起关键作用，可能与高血压的发生发展密切相关^[21](表 1)。这些研究结果说明肠

表1 高血压中的肠道微生物群变化

Table 1 Changes in gut microbiota in hypertension

Object of study	Gut microbial change	Conclusion	References
62 patients with normal blood pressure and 67 patients with hypertension	Most of the differential genus were clustered to the <i>Bacillota</i> and <i>Bacteroidetes</i> phyla, and <i>Ruminococcaceae</i> , <i>Prevotellaceae</i> , <i>Porphyromonadaceae</i> , <i>Lachnospiraceae</i> , <i>Veillonellaceae</i> families	There were significant differences in the intestinal microbiota between the hypertensive and normotensive groups	[22]
Normotension, borderline hypertension, and nocturnal hypertension	A correlation between stool metabolome and 24 hour BP levels was evidenced, with increased fecal levels of acetate, propionate, and butyrate levels in hypertension patients.	Observations support an association between gut microbiota composition and blood pressure levels, possibly <i>via</i> stool abundance of SCFAs	[23]
2 355 hypertensive (defined as having systolic blood pressure, SBP \geq 140 or diastolic blood pressure, DBP \geq 90 mmHg) and 4 644 non-hypertensive participants	The microbial genera with the most differential co-abundances included <i>Ruminococcaceae</i> UCG-002.id.11360, <i>Ruminococcaceae</i> UCG-013.id.11370, <i>Corynebacterium</i> id.449, and <i>Flavobacterium</i> id.1142	The strength of gut microbial co-abundances is associated with hypertension severity	[24]
The gut microbiome of 30 participants with resistant hypertension, 30 with controlled hypertension, and 30 nonhypertension	Compared with the controlled hypertension group, the genera <i>Rothia</i> and <i>Sharpea</i> in resistant hypertension were more abundant. Compared with the nonhypertension group, the genera <i>Escherichia - Shigella</i> , <i>Lactobacillus</i> , and <i>Enterococcus</i> were more abundant	Treatment resistance in resistant hypertension patients may be related to the gut microbiota	[25]

菌群对高血压的发病有影响，同时也揭示了通过调节肠道微生物群对血压管理带来潜在的益处。

2 肠道微生物群对血压的调控机制

肠道微生物群通过介导炎症反应、与肠-脑轴的相互作用以及代谢产物的调控，共同影响和调节血压的发生发展(图 1)。

2.1 肠道微生物群介导炎症反应影响血压

在高血压的发展过程中，潜在的炎症状态可能促进交感神经活动的增强，并导致全身血管系统和肾脏功能的改变^[26]。肠道微生物群通

过与免疫细胞的直接相互作用或通过产生代谢物调节全身免疫反应，这些代谢物可传播至远端器官，触发炎症级联反应^[27]。菌群失调导致肠道通透性增加，促使机会性病原体及其产物进入血液循环，引发炎症反应^[28-30]，这与高血压等心血管疾病的发病机制直接相关^[31]。Elijovich 等^[32]发现过量摄入膳食盐可改变肠道微生物组，激活树突状细胞，并通过还原型烟酰胺腺嘌呤二核苷酸磷酸 (reduced nicotinamide adenine dinucleotide phosphate, NADPH) 氧化酶产生活性氧 (reactive oxygen species, ROS)，进而导致高血压。Bao 等^[33]通过双样本孟德尔随机化，利用全基因组关联研究的汇总数据，证实了炎症性肠病与高血压之间存在因果关系。研究表明，神经炎症引发的交感神经兴奋能够激活骨髓中

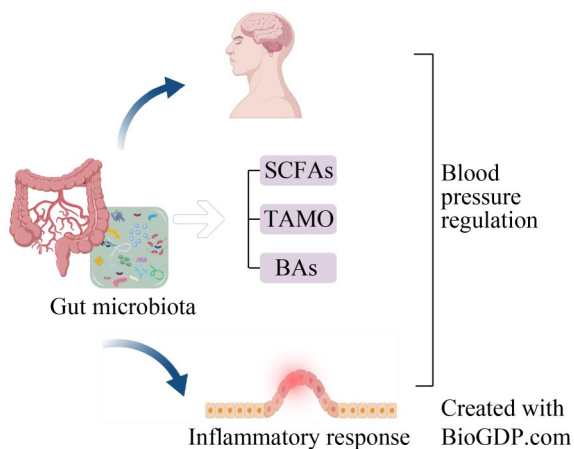


图1 肠道微生物群调控血压。肠道微生物群通过菌群失调、微生物群-肠-脑轴和代谢产物3种途径影响血压调节。菌群失调会导致肠道通透性增加, 引发炎症反应, 升高血压。微生物群-肠-脑轴通过迷走神经将信号传递至大脑, 影响中枢神经系统对血压的调节。肠道微生物产生的短链脂肪酸、胆汁酸和三甲胺N-氧化物等代谢产物也可以影响血压水平。

Figure 1 The gut microbiota regulate blood pressure. The gut microbiota affects blood pressure regulation through three pathways: dysbiosis, microbiota-gut-brain axis, and metabolites. Dysbiosis can lead to increased intestinal permeability, triggering an inflammatory response and raising blood pressure. The microbiota-gut-brain axis transmits signals to the brain through the vagus nerve, influencing the regulation of blood pressure by the central nervous system. Metabolites such as short-chain fatty acids, bile acids, and trimethylamine N-oxides produced by gut microbes can also affect blood pressure levels.

的造血干细胞, 促使它们向炎症细胞分化^[34]。这些炎症细胞随后迁移至大脑, 加剧神经炎症, 导致交感神经系统过度活跃, 这种激活状态增加了肠道黏膜的通透性, 破坏了肠道菌群的平衡^[35]。肠道菌群紊乱导致各种病原菌代谢物释放进入血液循环, 显著加剧中枢炎症并促进交感神经兴奋^[36], 从而促使心跳加快、血管收缩。

同时, 交感神经系统调节多个器官(包括外周血管系统、肾脏、骨髓和肠道)的功能, 在高血压的发作和进展中扮演着关键的病理生理角色^[37]。总之, 炎症反应调节是连接肠道菌群和高血压的重要纽带, 表明它们之间存在互动交流, 强调了肠道菌群与炎症反应之间的关联。尽管目前关于肠道菌群如何调节高血压炎症反应的机制尚不完全清楚, 但这些发现为治疗高血压提供了新的视角。

2.2 肠道微生物群-肠-脑轴调节血压

肠道微生物群-肠-脑轴构成一个复杂的双向通信网络, 其相互作用的改变被认为与血压调节密切相关, 涉及多种信号传递途径, 包括神经、激素和免疫信号^[38]。自主神经系统, 尤其是通过迷走神经, 以及由肠道神经元和神经胶质细胞组成的肠道神经系统, 在调节肠道分泌、运动和免疫反应方面起着关键作用^[39]。迷走神经作为脑干延髓的重要传出神经, 以双向神经信号传递调节着多种生理过程, 包括心率、血压、消化和炎症反应^[40], 其通过传入神经纤维感知肠道内部环境的变化, 包括对肠道微生物群代谢物和肠内分泌细胞释放激素的敏感性^[41]。肠道中的肠嗜铬细胞富含 Gpr41 和 Gpbar1 等受体, 它们识别并响应次级胆汁酸以及胰高血糖素样肽-1 等肠道菌群代谢产物^[41], 受体以旁分泌方式作用于肠嗜铬细胞, 刺激其通过色氨酸羟化酶 1 释放血清素 (5-hydroxytryptamine, 5-HT)。5-HT 通过血清素转运蛋白 (serotonin reuptake transporter, SERT) 被从血液中吸收, 并以致密颗粒的形式储存在血小板中^[42]。当 5-HT 释放到外周血和肠道神经系统中的神经元中时, 其信号活性受 5-HT 受体调节, 5-HT 受体主要是 G 蛋白偶联受体类型, 随受体亚型和细胞类型而变化^[43]。当受体被激活时, 会引发信号级联反应^[44], 增强迷走神经的传入神经活性^[45], 导致血管内皮细胞释放一氧化氮, 引起血管平滑肌松弛、血管舒张, 从而参与血压的稳定调节^[46]。在血压正常和高血压啮齿动物中的逆行

病毒追踪表明,在高血压啮齿动物中,从肠道到脑室旁核的神经连接增强^[47],这为支持微生物群-肠-脑轴作为参与高血压病理生理学的新机制的关键作用提供了直接证据。这些研究表明,微生物群紊乱对中枢心血管控制区域的影响可能是导致高血压的部分原因。

2.3 肠道菌群代谢物对血压的影响

肠道微生物群通过产生多种代谢物进入血液循环,在宿主体内发挥信号传导功能。其中,细菌合成的代谢化合物包括短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acids, BAs)及三甲胺 N-氧化物(trimethylamine-N-oxide, TMAO),对宿主细胞的生理功能产生显著影响。肠道微生物群产生的代谢物是宿主-微生物群关系的关键介质,可通过各种机制影响血压水平^[48](表 2)。

2.3.1 SCFAs 对血压的影响

SCFAs 作为肠道微生物发酵膳食纤维的主要代谢产物,在胃肠道内被肠黏膜高效吸收,它们不仅作为能量来源,还充当细胞代谢参与者以及特定受体的信号分子,在血压调节中发挥重要作用^[53-55]。乙酸盐、丙酸盐和丁酸盐是 3 种主要的 SCFAs,它们在体内以不同浓度存在,并对宿主代谢产生显著影响^[56]。在高血压大鼠中,产生丁酸盐和乙酸盐的细菌类群,如假丁酸弧菌属和粪球菌属显著减少,而产生乳酸的细菌类群,如链球菌科和苏黎世杆菌属

增加^[57]。某些 SCFAs 已被证实可作为高血压治疗的潜在靶点,它们作为多种 G 蛋白偶联受体(如 Gpr41、Gpr43 和 Gpr109a)和嗅觉受体 78 (Olf78)的配体^[58],与血管收缩和血压升高密切相关^[59]。研究表明,GPR41 和 GPR43 这 2 种受体在 SCFA 信号通路中具有功能冗余,可相互替代传递信号,GPR41/43 信号对于维持肠道上皮屏障的完整性至关重要,可防止细菌毒素如脂多糖进入血液循环,从而减少炎症,实验模型显示,缺乏 GPR41 和 GPR43 的信号传导会增加高血压的风险,并导致心肾纤维化和肥大^[60]。此外,SCFAs 还通过调节宿主免疫系统和抑制炎症反应来影响血压。大量证据表明,丁酸盐治疗可以改善血管紧张素 II 诱导的血压升高以及心脏和血管功能障碍,循环丁酸盐可以穿过血脑屏障到达调节大脑血压的关键中枢——下丘脑室旁核(paraventricular nucleus of hypothalamus, PVN)并减轻小胶质细胞活化和神经炎症^[61-62]。研究表明,微生物群衍生的乙酸盐通过调节小胶质细胞和星形胶质细胞的活动,以及抑制神经炎症和交感神经输出,从而调节血压^[63]。这些机制与高血压的发展和高血压器官损伤的进展密切相关^[64-65]。

2.3.2 TMAO 对血压的影响

TMAO 由肠道微生物群发酵膳食营养素(如胆碱和肉碱)产生,在肝脏中经黄素单加氧酶(FMO1 和 FMO3)转化而来^[66]。芽孢杆菌门和假

表2 微生物群衍生代谢物在血压调节中的作用机制

Table 2 Mechanisms of microbiota-derived metabolites in blood pressure regulation

Metabolite	Blood pressure change	Mechanisms	References
Short chain fatty acids	Lower	1. Activate Treg cells, enhance mRNA levels of Tjp1 2. Reduced expression of IL17a and IL6	[49]
Short chain fatty acids	Lower	1. Activate Olf78 to raise blood pressure 2. Activate Gpr41 to lower blood pressure	[50]
Trimethylamine-N-oxide	Increase	1. Activate the protein kinase R-like endoplasmic reticulum kinase pathway 2. Enhance Ang II-induced vasoconstriction and acute vasopressor responses	[51]
Bile acid	Lower	Inhibit nitric oxide synthase and cyclooxygenase-2 to attenuate migration and inflammatory responses of vascular smooth muscle cells	[52]

单胞菌门等特定肠道微生物携带与三甲胺产生相关的酶合成基因, 例如参与胆碱代谢和肉碱代谢的胆碱-三甲胺裂解酶(*CutC*)和肉碱加氧酶(*CntA*)基因^[67]。这些微生物对富含胆碱的饮食做出反应, 并将其转化为三甲胺, 后者在肝脏中进一步代谢为 TMAO^[68]。TMAO 导致内皮功能障碍的复杂分子机制有以下几方面。一方面, 高浓度的 TMAO 通过诱导氧化应激损害内皮细胞功能^[69]。TMAO 通过激活 TXNIP-NLRP3 炎性小体和 SIRT3-SOD2 信号通路促进活性氧生成, 活性氧进而氧化内皮细胞膜, 破坏细胞结构, 并抑制内皮型一氧化氮合酶活性, 降低 NO 生物利用度, 进而影响血管舒张功能^[70]。另一方面, TMAO 通过 NF- κ B 信号通路促进炎症因子[如肿瘤坏死因子(tumor necrosis factor, TNF)- α 和白细胞介素(interleukin, IL-1 β)]的产生, 并上调血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1) 和细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1) 的表达, 引发单核细胞黏附和泡沫细胞形成^[71]。泡沫细胞是动脉粥样硬化斑块的重要组成部分, 其形成可导致血管狭窄和血栓形成^[72], 最终促进心血管疾病的发生和发展^[73]。对 TMAO 处理的细胞进行 24 h 和 48 h 的转录组学和代谢组学分析后发现, TMAO 处理诱导了内皮功能障碍, 表现为细胞活力下降和氧化应激水平升高, 在 48 h 的处理中上调的差异表达基因主要涉及氧化应激和炎症表型的产生, 而受抑制的途径与细胞外基质(extracellular matrix, ECM)的结构组织、内皮细胞增殖和胶原蛋白代谢相关, 这些数据表明, TMAO 诱导的内皮功能障碍是通过调节参与氧化应激和炎症的分子基因特征, 从而激活内皮细胞重塑的过程^[74]。此外, 研究表明与血浆中 TMAO 浓度低的人相比, TMAO 浓度高的人患高血压的风险增加了 12%, 揭示了 TMAO 浓度与高血压风险增加之间存在正相关关系^[75]。然而, 该研究的局限性在于未充分控制参与者的遗传背景、环境和生活方式等因素。

研究还发现, TMAO 测定显示出强烈的个体内差异, 女性和男性之间的差异显著, 并且 TMAO 浓度随着时间的推移而增加^[76]。此外, 其他饮食因素(例如从补充剂或某些食物, 如蛋黄中摄入大量胆碱)已被证明会提高 TMAO 水平, 表明饮食调整可能对 TMAO 相关高血压的管理有影响^[77]。通过 16S rRNA 基因测序和液相色谱-质谱(liquid chromatograph-mass spectrometer, LC-MS)代谢组学方法对 Dahl 盐敏感大鼠模型在高血压心力衰竭情况下的肠道微生物群组成和功能进行了研究, 在该模型中, 肠道微生物群组成和代谢物变化与疾病发生相关, 尤其是 SCFAs 产生菌减少和 TMAO 增加^[78]。鉴于 TMAO 是由肠道微生物群产生的代谢物, 因此针对肠道微生物群和 TMAO 代谢途径的干预可能为预防这些相关疾病提供新的策略^[79]。

2.3.3 BAs 对血压的影响

胆汁酸是肝脏中胆固醇的代谢产物, 通过肝肠循环参与维持肠道微生物群的平衡^[80]。它们通过减少内皮素-1 表达和调节可诱导型一氧化氮合酶/内皮一氧化氮合酶途径促进血管舒张^[81]。当前研究集中于胆盐水解酶, 该酶将甘氨酸或牛磺酸结合的胆盐的 C-24-N-酰基键水解, 生成游离胆汁酸。多种肠道细菌, 包括拟杆菌属、梭状芽胞杆菌、乳杆菌属和双歧杆菌属, 均具有胆盐水解酶活性, 表明肠道菌群的失衡可能会影响胆汁酸代谢^[80,82]。初级胆汁酸由宿主合成并偶联, 但可在肠道共生细菌的作用下解偶联并转化为次级胆汁酸, 胆汁酸代谢物作为宿主核受体或 G 蛋白偶联受体的关键配体, 包括法尼醇 X 受体(farnesoid X receptor, FXR)、维生素 D 受体和 G 蛋白偶联受体 Gpbar1 (TGR5), 在血压调节中起着关键作用^[83-84]。重要的是, 肠道微生物群和胆汁酸之间的调节是相互的, 这意味着胆汁酸也可以通过直接或间接作用调节肠道微生物群, 例如破坏细菌膜或与肠道 FXR 结合, 促进抗菌肽的表达^[85]。

3 基于肠道微生物的血压干预策略

肠道微生物与高血压之间存在着密切的关联，可以作为调节血压的潜在靶点(表 3)。通过调节肠道微生物来干预高血压的多种策略(图 2)，为高血压的治疗提供了新的视角和方法。

3.1 饮食干预调节血压

饮食与肠道微生物之间的相互作用对维持血管健康具有重要意义，肠道微生物能够代谢那些未被人体消化酶分解的膳食成分，而这些膳食成分又为特定肠道微生物的生长提供了支持^[89]。同时，饮食会引起肠道微环境的改变，从而导致肠道菌群失衡及其代谢产物的变化，

这可能会触发一系列连锁反应，形成恶性循环，对患者血压产生严重影响^[90]。

3.1.1 优化饮食结构以预防高血压

地中海饮食(Mediterranean diet, MedDiet)以食物多样性和平衡性而著称^[91]。研究表明，遵循地中海饮食可能有助于改善高血压患者的整体心血管健康^[92]，包括血脂水平的优化和高血压发生率的降低^[93]。一项临床试验表明，补充燕麦麸膳食纤维可以改善 24 h 动态血压，减少患者对抗高血压药物的需求量，并通过提高双歧杆菌和螺旋菌的相对丰度来调节肠道微生物群^[94]。此外，停止高血压的饮食方法(dietary approaches to stop hypertension diet, DASH)也被证明可以降低血压^[95]。它通过促进有益菌的生

表3 基于肠道微生物的血压干预措施

Table 3 Gut microbiome-based blood pressure interventions

Interventions	Subjects of the study	Result	Conclusion	References
Mediterranean diet	European adolescents participating in the Healthy Lifestyle in Europe by Nutrition in Adolescence cross-sectional study	1. The higher adherence adolescents have to the Mediterranean diet, the lower their systolic and diastolic blood pressure levels 2. For adolescents who carry fewer alleles for the risk of high blood pressure, the Mediterranean diet can lower blood pressure levels	There is an interaction between genes and diet, and the Mediterranean diet can lower blood pressure levels in adolescents	[86]
Probiotic <i>Bifidobacterium breve</i>	Hypertension in deoxycorticosterone acetate (DOCA)-salt rats	1. Increase acetate-producing bacterial populations and intestinal acetate levels 2. Ameliorate acetylcholine-induced nitric oxide-dependent vasodilation in the aortic ring	Probiotic prevent the development of endothelial dysfunction and hypertension in DOCA salt rats	[87]
Acetate	Obstructive sleep apnea-induced hypertensive rats	1. Lower the levels of Egr1 in the heart and kidneys 2. Reverse intestinal dysbiosis and inhibits intestinal inflammation	Increasing acetate concentrations may protect OSA against adverse effects on the microbiota, gut, brain, and blood pressure	[57]
Fecal microbiota transplantation	Spontaneously hypertensive rats	1. Upregulate the expression of tight junction-related proteins 2. Promote the restoration of intestinal mucosal barrier structure and SHRs function	Butyric acid-producing bacteria can improve blood pressure regulation by promoting mucosal barrier integrity	[88]

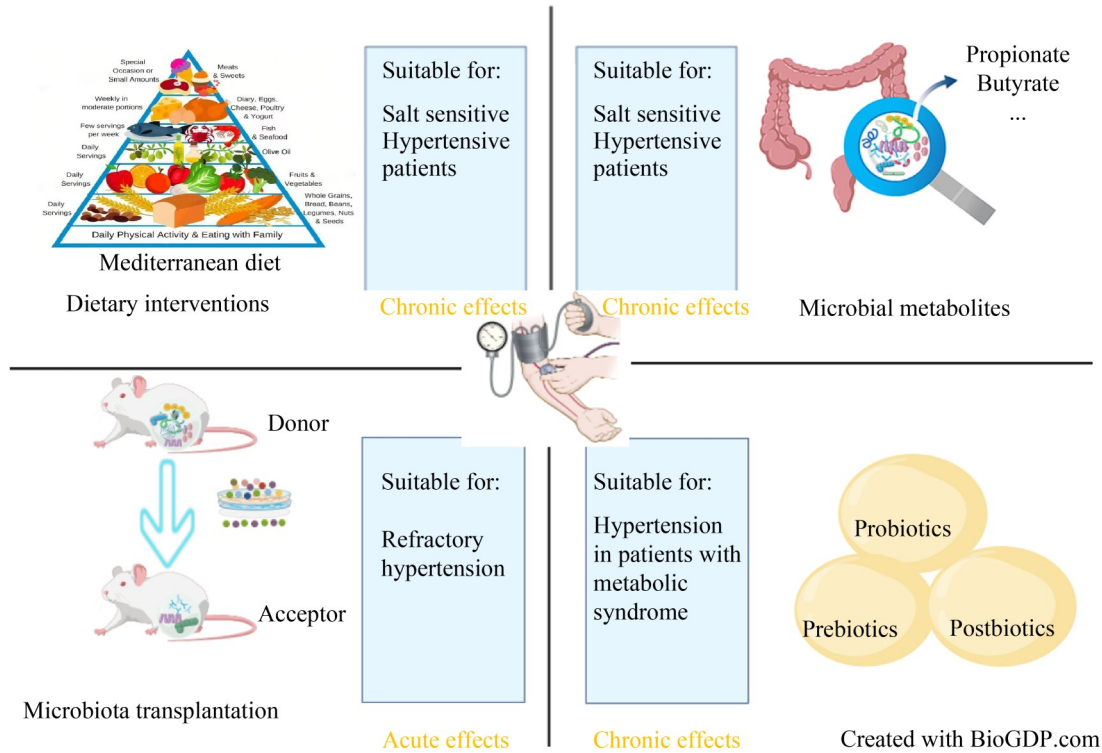


图2 肠道微生物靶向治疗高血压的方式。多种干预策略通过不同的机制调节肠道微生物群，从而调节血压。具体来说，饮食干预和微生物代谢物，如丙酸盐和丁酸盐，发挥更持久的效果，通过长期调节过程影响血压。相比之下，菌群移植调节作用较快，表现出对血压的急性效应。至于益生菌、益生元和后生元的组合，更适合代谢综合征的高血压患者，通过慢性调整来改善血压状况。

Figure 2 Targeted treatment of hypertension by gut microbiota. Multiple intervention strategies regulate blood pressure by modulating the gut microbiota through different mechanisms. Specifically, dietary interventions and microbial metabolites, such as propionate and butyrate, exert a more lasting effect, affecting blood pressure through a long-term regulatory process. In contrast, microbiota transplantation has a more rapid regulatory effect and exhibits an acute effect on blood pressure. As for the combination of probiotics, prebiotics, and postbiotics, it is more suitable for hypertensive patients with metabolic syndrome to improve blood pressure through chronic adjustments.

长、增加肠道微生物的多样性，显著影响肠道微生物群的组成和功能，进而对整体健康产生积极影响^[96]。Zambrano 等^[97]证明，富含多酚的食物能够塑造独特的微生物群，与生物多样性和健康有关。坚果的摄入促进肠道有益菌丰度增加，进而促进了对人类健康有益的 SCFAs 的产生^[98]。生活方式和饮食诱导的微生物群及其代谢物的扰动可以直接影响上皮细胞和免疫细胞的稳态，这对免疫细胞活化和血压有重大影

响^[99-100]。然而，饮食干预血压需注意个体差异，确保依从性和可持续性，以实现有效血压管理。

3.1.2 肠道微生物衍生代谢物治疗高血压

肠道微生物群及其饮食衍生代谢物可调节宿主能量稳态以防止代谢综合征的发展^[101]。研究首次证明，在妊娠和哺乳期间补充丁酸盐或丙酸盐，可以保护成年后代免受母体高果糖摄入引发的高血压风险，结果表明母体补充丁酸盐或丙酸盐能够通过增加 SCFAs 的浓度、恢复

一氧化氮的生物利用度、调节肠道微生物群组成以及降低 TMAO 水平发挥保护作用^[102]。Chakraborty 等^[103]分析了人类、高血压和无菌大鼠模型的胆汁酸谱,发现通过营养补充牛磺酸来拯救宿主足以逆转共轭胆汁酸的缺乏并改善高血压。这些研究成果为开发利用肠道微生物代谢物预防高血压的功能性食品提供了科学依据。

3.1.3 补充益生菌、益生元、后生元控制血压

益生菌(probiotics)通过改善胆固醇水平、内皮功能障碍、抑制血管紧张素转化酶活性来改善高血压^[104]。例如,长期服用发酵乳杆菌通过减轻内皮功能障碍、预防血管炎症和减轻氧化应激来降低高血压大鼠的收缩压^[105]。随机对照试验表明,益生菌辅助治疗有助于减少 110 名 1 级高血压患者药物治疗需求,并促进靶器官保护及减少心血管疾病发生^[106]。益生菌的应用通常以功能性食品原料的形式实现^[107]。例如,牛奶等高蛋白食品在益生菌独特的蛋白水解系统的作用下发酵产生具有抗高血压作用的肽类物质,这些肽类通过与血管紧张素转换酶的活性结合位点相互作用,从而触发肾素-血管紧张素系统,调节人体血压^[108]。研究表明,具有高效血管紧张素转化酶抑制活性的益生菌发酵奶部分逆转了 SHR 大鼠的血压升高现象,并通过增加粪便中产生 SCFAs 的细菌丰度以及提高乙酸、丙酸、丁酸和戊酸等 SCFAs 的水平,调节小鼠的肠道微生物群^[109-110]。本课题组从云南传统发酵食品中筛选出高效抑制血管紧张素转化酶的乳酸菌,研究成果为开发新型抗高血压发酵乳制品提供了支持^[111]。

益生元(prebiotics)是一类不可消化的食物成分,能够选择性地促进肠道中特定益生菌的生长或活性^[112]。当益生菌和益生元联合使用时,它们之间的相互作用可以产生协同效应,从而增强对宿主健康的积极影响,一些益生元不仅促进益生菌的增殖,还具备免疫调节功能,如

防止病原体损害、增强肠道屏障功能以及减少有害细菌种群^[113]。

后生元(postbiotics)被定义为“为宿主带来健康益处的无生命微生物和/或其成分的制剂”^[114]。研究发现,补充后生元可以影响肠道微生物群组成和特定微生物,从而预防高血压^[102]。后生元可能代表一种创新的治疗策略,因为其包含的细菌代谢物能够在整个肠道血管轴上发挥协同作用^[115]。

综上所述,饮食结合益生菌、益生元和后生元等多种成分,通过各自独特的机制作用于血压调节,展示了在预防和治疗高血压疾病中的显著潜力,为后续研究奠定了理论基础。

3.2 微生物群移植干预调节血压

粪菌移植(faecal microbiota transplantation, FMT)是一种新的治疗手段,通过引入健康微生物群替代患者原有菌群,从而恢复肠道平衡和生理功能^[116-117]。研究表明,通过 FMT 将正常血压供体的微生物群转移至高血压受体大鼠,显著降低了受体大鼠的血压水平、肠道炎症以及血浆中血清脂肪酶的含量^[118]。当正常血压大鼠接受高血压大鼠的 FMT 后,血压则有所上升,且肠道微生物多样性显著改变^[88]。虽然 FMT 在治疗多种疾病中显示出潜力,但其安全性问题以及患者的心理接受度仍然是临床应用面临的挑战。作为一种改进方法,洗涤菌群移植(washed microbiota transplantation, WMT)通过自动化去除粪便悬浮液中的有害颗粒,有效减少了 FMT 的不良反应,WMT 与 FMT 原理相似,但通过智能分离和洗涤技术提高了治疗的安全性^[119]。Lin 等^[120]证明 WMT 可降低患者的平均血压,且长期不良反应发生率低。然而,洗涤菌群悬浮液未在厌氧条件下制备,可能导致严格厌氧的有益细菌在好氧过程中死亡,从而促进好氧细菌的生长^[121]。因此,开展大规模的前瞻性研究对于验证这些治疗方法的有效性和安全性至关重要。这些研究将有助于进一步理解肠道微生物群与宿主健康之间的关系,并

为临床实践提供更为坚实的科学依据。

4 总结与展望

近年来,肠道微生物群与高血压之间的关联研究取得了显著进展,揭示了肠道微生物群在高血压发生发展中的重要作用。本综述基于相关文献,总结了肠道微生物群影响高血压的方式,并展望了未来肠道微生物靶向治疗高血压的研究方向。本课题组通过合理的引物设计对人体内肠道微生物群进行分析,能够更加全面地了解人体内的微生物群落结构,有助于认识肠道微生物的丰富性和多样性,未来计划将深入探讨肠道微生物群落结构变化与高血压发生发展的关系,通过高通量测序和生物信息学分析筛选出与高血压相关的关键微生物种群,并研究它们在血压调节中的作用机制,揭示特定肠道微生物对高血压的影响,寻找潜在的早期诊断指标,并为精准干预提供初步的科学依据。

该领域仍面临一系列挑战,包括体外模型与体内环境的差异、微生物组数据分析的准确性问题,以及在评估微生物生态系统复杂性时,准确解析微生物群落结构与功能关系的难点。这些挑战要求研究人员不仅要提升实验技术和数据分析方法,还需深入探究微生物组与宿主间的动态交互。因此,开发更精确的实验模型、加强跨学科合作、推动数据共享和标准化是必要的,这将有助于在未来研究中获得更可靠和有意义的成果。同时,开展广泛而严谨的临床试验对于评估肠道微生物干预措施的安全性、有效性和长期血压控制效果至关重要。此外,肠道微生物组治疗靶点的识别需达成一致,需对心脏代谢风险相关的微生物代谢物机制标志物达成共识。未来研究应揭示肠道微生物代谢物影响血压的具体机制,确定潜在治疗靶点。例如,SCFAs和TAMO等代谢物显示出治疗开发潜力应优先深入研究,调查基于个体微生物群组成的个性化干预方案,以提高治疗效果并

减少不良反应。同时,探索将不同微生物群干预措施相结合的协同效应,以验证其对血压管理的有效性。最后,为在临床实践中使用基于微生物群的疗法,建立明确的监管指南至关重要。这有助于确保其安全有效地实施,为高血压管理提供更有效的策略。

作者贡献声明

周彬:论文构思、资料检索、论文撰写和修订;何燕:论文资料检索和修订;柳陈坚:论文审阅和修订;李晓然:论文审阅和修订。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

参考文献

- [1] SAIZ LC, GORRICO J, GARJÓN J, CELAYA MC, ERVITI J, LEACHE L. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease[J]. *Cochrane Database of Systematic Reviews*, 2022, 11(11): CD010315.
- [2] FUCHS FD, WHELTON PK. High blood pressure and cardiovascular disease[J]. *Hypertension*, 2020, 75(2): 285-292.
- [3] PADMANABHAN S, DOMINICZAK AF. Genomics of hypertension: the road to precision medicine[J]. *Nature Reviews Cardiology*, 2021, 18(4): 235-250.
- [4] NAKAI M, RIBEIRO RV, STEVENS BR, GILL P, MURALITHARAN RR, YIALLOUROU S, MUIR J, CARRINGTON M, HEAD GA, KAYE DM, MARQUES FZ. Essential hypertension is associated with changes in gut microbial metabolic pathways: a multisite analysis of ambulatory blood pressure[J]. *Hypertension*, 2021, 78(3): 804-815.
- [5] JIA QJ, XIE YY, LU CM, ZHANG A, LU YM, LV SC, ZHANG JP. Endocrine organs of cardiovascular diseases: gut microbiota[J]. *Journal of Cellular and Molecular Medicine*, 2019, 23(4): 2314-2323.
- [6] HOU JL, XIANG JG, LI DL, LIU XH, PAN WC. Gut microbial response to host metabolic phenotypes[J]. *Frontiers in Nutrition*, 2022, 9: 1019430.
- [7] LI J, WEI W, MA XM, JI J, LING XM, XU ZY, GUAN YT, ZHOU LY, WU QM, HUANG WH, LIU FG, ZHAO M. Antihypertensive effects of rice peptides involve intestinal microbiome alterations and intestinal inflammation alleviation in spontaneously hypertensive rats[J]. *Food & Function*, 2025, 16(5): 1731-1759.
- [8] MARQUES FZ. Missing heritability of hypertension and

- our microbiome[J]. *Circulation*, 2018, 138(14): 1381-1383.
- [9] ABENAVOLI L, SCARPELLINI E, COLICA C, BOCCUTO L, SALEHI B, SHARIFI-RAD J, AIELLO V, ROMANO B, de LORENZO A, IZZO AA, CAPASSO R. Gut microbiota and obesity: a role for probiotics[J]. *Nutrients*, 2019, 11(11): 2690.
- [10] ECKBURG PB, BIK EM, BERNSTEIN CN, PURDOM E, DETHLEFSEN L, SARGENT M, GILL SR, NELSON KE, RELMAN DA. Diversity of the human intestinal microbial flora[J]. *Science*, 2005, 308(5728): 1635-1638.
- [11] OREN A, ARAHAL DR, GÖKER M, MOORE ERB, ROSSELLO-MORA R, SUTCLIFFE IC. International Code of Nomenclature of Prokaryotes. Prokaryotic Code (2022 Revision) [J]. *International Journal of Systematic and Evolutionary Microbiology*, 2023, 73(5a). doi: 10.1099/ijsem.0.005585.
- [12] ALHAJRI N, KHURSHEED R, ALI MT, ABU IZNEID T, AL-KABBANI O, AL-HAIDAR MB, AL-HEMEIRI F, ALHASHMI M, POTTOO FH. Cardiovascular health and the intestinal microbial ecosystem: the impact of cardiovascular therapies on the gut microbiota[J]. *Microorganisms*, 2021, 9(10): 2013.
- [13] NISSEN L, CASCIANO F, CHIARELLO E, Di NUNZIO M, BORDONI A, GIANOTTI A. Colonic *in vitro* model assessment of the prebiotic potential of bread fortified with polyphenols rich olive fiber[J]. *Nutrients*, 2021, 13(3): 787.
- [14] COOKSON TA. Bacterial-induced blood pressure reduction: mechanisms for the treatment of hypertension *via* the gut[J]. *Frontiers in Cardiovascular Medicine*, 2021, 8: 721393.
- [15] QIN YL, ZHAO J, WANG YW, BAI M, SUN SR. Specific alterations of gut microbiota in Chinese patients with hypertension: a systematic review and meta-analysis[J]. *Kidney & Blood Pressure Research*, 2022, 47(7): 433-447.
- [16] WANG YQ, WANG HJ, HOWARD AG, TSILIMIGRAS MCB, AVERY CL, MEYER KA, SHA W, SUN S, ZHANG JG, SU C, WANG ZH, FODOR AA, ZHANG B, GORDON-LARSEN P. Gut microbiota and host plasma metabolites in association with blood pressure in Chinese adults[J]. *Hypertension*, 2021, 77(2): 706-717.
- [17] 张思遥, 李晓然, 柳陈坚, 童玉云, 靳晴, 牛兆仪, 陈雪蓉. 妊娠期高血压综合征剖宫产产妇细菌群落结构变化[J]. *昆明医科大学学报*, 2019, 40(10): 154-159.
- ZHANG SY, LI XR, LIU CJ, TONG YY, JIN Q, NIU ZY, CHEN XR. Changes of microbial community structure in cesarean section maternity with pregnancy-induced hypertension[J]. *Journal of Kunming Medical University*, 2019, 40(10): 154-159 (in Chinese).
- [18] MIAO C, XU X, HUANG S, KONG L, HE Z, WANG Y, CHEN K, XIAO L. The causality between gut microbiota and hypertension and hypertension-related complications: a bidirectional two-sample Mendelian randomization analysis[J/OL]. *Hellenic Journal of Cardiology*, 2024. DOI: <https://doi.org/10.1016/j.hjc.2024.02.002>.
- [19] MELL B, JALA VR, MATHEW AV, BYUN J, WAGHULDE H, ZHANG YJ, HARIBABU B, VIJAY-KUMAR M, PENNATHUR S, JOE B. Evidence for a link between gut microbiota and hypertension in the Dahl rat[J]. *Physiological Genomics*, 2015, 47(6): 187-197.
- [20] RAZAVI AC, POTTS KS, KELLY TN, BAZZANO LA. Sex, gut microbiome, and cardiovascular disease risk[J]. *Biology of Sex Differences*, 2019, 10(1): 29.
- [21] LI J, YANG XC, ZHOU X, CAI J. The role and mechanism of intestinal flora in blood pressure regulation and hypertension development[J]. *Antioxidants & Redox Signaling*, 2021, 34(10): 811-830.
- [22] XIE D, ZHANG MS, WANG BL, LIN H, WU EQ, ZHAO HH, LI SC. Differential analysis of hypertension-associated intestinal microbiota[J]. *International Journal of Medical Sciences*, 2019, 16(6): 872-881.
- [23] HUART J, LEENDERS J, TAMINIAU B, DESCY J, SAINT-REMY A, DAUBE G, KRZESINSKI JM, MELIN P, de TULLIO P, JOURET F. Gut microbiota and fecal levels of short-chain fatty acids differ upon 24-hour blood pressure levels in men[J]. *Hypertension*, 2019, 74(4): 1005-1013.
- [24] LIU L, ZHOU QY, XU TB, DENG QF, SUN YH, FU JX, CHEN MX, CHEN XJ, MA ZC, DONG QB, MA BN, JIAO YW, ZHOU Y, WU TT, ZOU H, SHI J, WANG YF, SHENG YH, TANG LM, ZHENG C, et al. Non-differential gut microbes contribute to hypertension and its severity through co-abundances: a multi-regional prospective cohort study[J]. *iMeta*, 2025, 4(1): e268.
- [25] GUO JQ, JIA PY, GU ZL, TANG WY, WANG A, SUN YX, LI Z. Altered gut microbiota and metabolite profiles provide clues in understanding resistant hypertension[J]. *Journal of Hypertension*, 2024, 42(7): 1212-1225.
- [26] NORLANDER AE, MADHUR MS, HARRISON DG. The immunology of hypertension[J]. *Journal of Experimental Medicine*, 2018, 215(1): 21-33.
- [27] JAMA HA, BEALE A, SHIHATA WA, MARQUES FZ. The effect of diet on hypertensive pathology: is there a link *via* gut microbiota-driven immunometabolism[J]. *Cardiovascular Research*, 2019, 115(9): 1435-1447.
- [28] AHMADI S, RAZAZAN A, NAGPAL R, JAIN S, WANG B, MISHRA SP, WANG SH, JUSTICE J, DING JZ, McCLAIN DA, KRITCHEVSKY SB, KITZMAN D, YADAV H. Metformin reduces aging-related leaky gut and improves cognitive function by beneficially modulating gut microbiome/goblet cell/mucin axis[J]. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, 2020, 75(7): e9-e21.
- [29] STEVENS BR, GOEL R, SEUNGBUM K, RICHARDS EM, HOLBERT RC, PEPINE CJ, RAIZADA MK. Increased human intestinal barrier permeability plasma biomarkers zonulin and FABP2 correlated with plasma LPS and altered gut microbiome in anxiety or depression[J]. *Gut*, 2018, 67(8): 1555-1557.
- [30] THEVARANJAN N, PUCHTA A, SCHULZ C, NAIDOO A, SZAMOSI JC, VERSCHOOR CP, LOUKOV D, SCHENCK LP, JURY J, FOLEY KP, SCHERTZER JD, LARCHÉ MJ, DAVIDSON DJ, VERDÚ EF, SURETTE MG, BOWDISH DME. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction[J]. *Cell Host & Microbe*, 2017, 21(4): 455-466.e4.

- [31] BHATTACHARYYA M, GHOSH T, SHANKAR S, TOMAR N. The conserved phylogeny of blood microbiome[J]. *Molecular Phylogenetics and Evolution*, 2017, 109: 404-408.
- [32] ELIJOVICH F, LAFFER CL, SAHINOZ M, PITZER A, FERGUSON JF, KIRABO A. The gut microbiome, inflammation, and salt-sensitive hypertension[J]. *Current Hypertension Reports*, 2020, 22(10): 79.
- [33] BAO W, ZHANG Y, HUANG XJ, GU N. The role of gut microbiome in mediating the effect of inflammatory bowel disease on hypertension: a two-step, two-sample Mendelian randomization study[J]. *Frontiers in Cardiovascular Medicine*, 2024, 11: 1396973.
- [34] LANGE T, LUEBBER F, GRASSHOFF H, BESEDOVSKY L. The contribution of sleep to the neuroendocrine regulation of rhythms in human leukocyte traffic[J]. *Seminars in Immunopathology*, 2022, 44(2): 239-254.
- [35] BROWN DR. Catecholamine-directed epithelial cell interactions with bacteria in the intestinal mucosa[J]. *Advances in Experimental Medicine and Biology*, 2016, 874: 79-99.
- [36] LI J, RAIZADA MK, RICHARDS EM. Gut-brain-bone marrow axis in hypertension[J]. *Current Opinion in Nephrology and Hypertension*, 2021, 30(2): 159-165.
- [37] WANG XQ, CHEN ZZ, GENG B, CAI J. The bidirectional signal communication of microbiota-gut-brain axis in hypertension[J]. *International Journal of Hypertension*, 2021, 2021: 8174789.
- [38] FUNG TC. The microbiota-immune axis as a central mediator of gut-brain communication[J]. *Neurobiology of Disease*, 2020, 136: 104714.
- [39] NGUYEN TT, BAUMANN P, TÜSCHER O, SCHICK S, ENDRES K. The aging enteric nervous system[J]. *International Journal of Molecular Sciences*, 2023, 24(11): 9471.
- [40] HWANG YK, OH JS. Interaction of the vagus nerve and serotonin in the gut-brain axis[J]. *International Journal of Molecular Sciences*, 2025, 26(3): 1160.
- [41] EGEROD KL, PETERSEN N, TIMSHEL PN, REKLING JC, WANG YB, LIU QH, SCHWARTZ TW, GAUTRON L. Profiling of G protein-coupled receptors in vagal afferents reveals novel gut-to-brain sensing mechanisms[J]. *Molecular Metabolism*, 2018, 12: 62-75.
- [42] IMAMDIN A, van der VORST EPC. Exploring the role of serotonin as an immune modulatory component in cardiovascular diseases[J]. *International Journal of Molecular Sciences*, 2023, 24(2): 1549.
- [43] McCORVY JD, ROTH BL. Structure and function of serotonin G protein-coupled receptors[J]. *Pharmacology & Therapeutics*, 2015, 150: 129-142.
- [44] GIULIETTI M, VIVENZIO V, PIVA F, PRINCIPATO G, BELLANTUONO C, NARDI B. How much do we know about the coupling of G-proteins to serotonin receptors[J]. *Molecular Brain*, 2014, 7: 49.
- [45] PSICHAS A, REIMANN F, GRIBBLE FM. Gut chemosensing mechanisms[J]. *Journal of Clinical Investigation*, 2015, 125(3): 908-917.
- [46] ZUBCEVIC J, RICHARDS EM, YANG T, KIM S, SUMNERS C, PEPINE CJ, RAIZADA MK. Impaired autonomic nervous system-microbiome circuit in hypertension[J]. *Circulation Research*, 2019, 125(1): 104-116.
- [47] SANTISTEBAN MM, QI YF, ZUBCEVIC J, KIM S, YANG T, SHENOY V, COLE-JEFFREY CT, LOBATON GO, STEWART DC, RUBIANO A, SIMMONS CS, GARCIA-PEREIRA F, JOHNSON RD, PEPINE CJ, RAIZADA MK. Hypertension-linked pathophysiological alterations in the gut[J]. *Circulation Research*, 2017, 120(2): 312-323.
- [48] O'DONNELL JA, ZHENG TH, MERIC G, MARQUES FZ. The gut microbiome and hypertension[J]. *Nature Reviews Nephrology*, 2023, 19(3): 153-167.
- [49] CHEN H, LI JB, LI N, LIU HS, TANG JY. Increased circulating trimethylamine N-oxide plays a contributory role in the development of endothelial dysfunction and hypertension in the RUPP rat model of preeclampsia[J]. *Hypertension in Pregnancy*, 2019, 38(2): 96-104.
- [50] XIAO L, DONG JH, TENG X, JIN S, XUE HM, LIU SY, GUO Q, SHEN W, NI XC, WU YM. Hydrogen sulfide improves endothelial dysfunction in hypertension by activating peroxisome proliferator-activated receptor delta/endothelial nitric oxide synthase signaling[J]. *Journal of Hypertension*, 2018, 36(3): 651-665.
- [51] JIANG S, SHUI YJ, CUI Y, TANG C, WANG XH, QIU XY, HU WP, FEI LY, LI Y, ZHANG SP, ZHAO L, XU N, DONG F, REN XQ, LIU RS, PERSSON PB, PATZAK A, LAI EY, WEI QC, ZHENG ZH. Gut microbiota dependent trimethylamine N-oxide aggravates angiotensin II-induced hypertension[J]. *Redox Biology*, 2021, 46: 102115.
- [52] FLEISHMAN JS, KUMAR S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets[J]. *Signal Transduction and Targeted Therapy*, 2024, 9(1): 97.
- [53] JIN MC, QIAN ZY, YIN JY, XU WT, ZHOU X. The role of intestinal microbiota in cardiovascular disease[J]. *Journal of Cellular and Molecular Medicine*, 2019, 23(4): 2343-2350.
- [54] POLL BG, CHEEMA MU, PLUZNICK JL. Gut microbial metabolites and blood pressure regulation: focus on SCFAs and TMAO[J]. *Physiology*, 2020, 35(4): 275-284.
- [55] NAQVI S, ASAR TO, KUMAR V, AL-ABBASI FA, ALHAYYANI S, KAMAL MA, ANWAR F. A cross-talk between gut microbiome, salt and hypertension[J]. *Biomedicine & Pharmacotherapy*, 2021, 134: 111156.
- [56] OVERBY HB, FERGUSON JF. Gut microbiota-derived short-chain fatty acids facilitate microbiota: host cross talk and modulate obesity and hypertension[J]. *Current Hypertension Reports*, 2021, 23(2): 8.
- [57] YANG T, SANTISTEBAN MM, RODRIGUEZ V, LI E, AHMARI N, CARVAJAL JM, ZADEH M, GONG M, QI Y, ZUBCEVIC J, SAHAY B, PEPINE CJ, RAIZADA MK, MOHAMADZADEH M. Gut dysbiosis is linked to hypertension[J]. *Hypertension*, 2015, 65(6): 1331-1340.
- [58] MURALITHARAN RR, MARQUES FZ. Diet-related gut microbial metabolites and sensing in hypertension[J].

- Journal of Human Hypertension, 2021, 35(2): 162-169.
- [59] WANG L, ZHU Q, LU AH, LIU XF, ZHANG LL, XU CM, LIU XY, LI HB, YANG TX. Sodium butyrate suppresses angiotensin II-induced hypertension by inhibition of renal (pro)renin receptor and intrarenal renin-angiotensin system[J]. *Journal of Hypertension*, 2017, 35(9): 1899-1908.
- [60] MURALITHARAN RR, ZHENG T, DINAKIS E, XIE L, BARBARO-WAHL A, JAMA HA, NAKAI M, PATERSON M, LEUNG KC, MCARDLE Z, MIRABITO COLAFELLA K, JOHNSON C, QIN W, SALIMOVA E, BITTO NJ, KAPARAKIS-LIASKOS M, KAYE DM, O'DONNELL JA, MACKAY CR, MARQUES FZ. Gut microbiota metabolites sensed by host GPR41/43 microbiota metabolites sensed by host[J]. *Circulation Research*, 2025, 136(4): e20-e33.
- [61] KIM S, GOEL R, KUMAR A, QI YF, LOBATON G, HOSAKA K, MOHAMMED M, HANDBERG EM, RICHARDS EM, PEPINE CJ, RAIZADA MK. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure[J]. *Clinical Science*, 2018, 132(6): 701-718.
- [62] LI HB, XU ML, DU MM, YU XJ, BAI J, XIA WJ, DAI ZM, LI CX, LI Y, SU Q, WANG XM, DONG YY, KANG YM. Curcumin ameliorates hypertension *via* gut-brain communication in spontaneously hypertensive rat[J]. *Toxicology and Applied Pharmacology*, 2021, 429: 115701.
- [63] YIN XP, DUAN CH, ZHANG L, ZHU YF, QIU YY, SHI KY, WANG S, ZHANG XG, ZHANG HX, HAO YC, YUAN F, TIAN YM. Microbiota-derived acetate attenuates neuroinflammation in rostral ventrolateral medulla of spontaneously hypertensive rats[J]. *Journal of Neuroinflammation*, 2024, 21(1): 101.
- [64] DIXON DL, WOHLFORD GF 4th, ABBATE A. Inflammation and hypertension: causal or not[J]. *Hypertension*, 2020, 75(2): 297-298.
- [65] ZHANG RM, McNERNEY KP, RIEK AE, BERNAL-MIZRACHI C. Immunity and hypertension[J]. *Acta Physiologica*, 2021, 231(1): e13487.
- [66] FARHANGI MA, VAJDI M. Novel findings of the association between gut microbiota-derived metabolite trimethylamine oxide and inflammation: results from a systematic review and dose-response meta-analysis[J]. *Critical Reviews in Food Science and Nutrition*, 2020, 60(16): 2801-2823.
- [67] RATH S, RUD T, PIEPER DH, VITAL M. Potential TMA-producing bacteria are ubiquitously found in *Mammalia*[J]. *Frontiers in Microbiology*, 2020, 10: 2966.
- [68] FALONY G, VIEIRA-SILVA S, RAES J. Microbiology meets big data: the case of gut microbiota-derived trimethylamine[J]. *Annual Review of Microbiology*, 2015, 69: 305-321.
- [69] SINGH GB, ZHANG Y, BOINI KM, KOKA S. High mobility group box 1 mediates TMAO-induced endothelial dysfunction[J]. *International Journal of Molecular Sciences*, 2019, 20(14): 3570.
- [70] SUN XL, JIAO XF, MA YR, LIU Y, ZHANG L, HE YZ, CHEN YH. Trimethylamine N-oxide induces inflammation and endothelial dysfunction in human umbilical vein endothelial cells *via* activating ROS-TXNIP-NLRP3 inflammasome[J]. *Biochemical and Biophysical Research Communications*, 2016, 481(1/2): 63-70.
- [71] YANG SJ, LI XY, YANG F, ZHAO R, PAN XD, LIANG JQ, TIAN L, LI XY, LIU LT, XING YW, WU M. Gut microbiota-dependent marker TMAO in promoting cardiovascular disease: inflammation mechanism, clinical prognostic, and potential as a therapeutic target[J]. *Frontiers in Pharmacology*, 2019, 10: 1360.
- [72] ZHENG Y, LI YP, RIMM EB, HU FB, ALBERT CM, REXRODE KM, MANSON JE, QI L. Dietary phosphatidylcholine and risk of all-cause and cardiovascular-specific mortality among US women and men[J]. *The American Journal of Clinical Nutrition*, 2016, 104(1): 173-180.
- [73] SHANMUGHAM M, BELLANGER S, LEO CH. Gut-derived metabolite, trimethylamine-N-oxide (TMAO) in cardio-metabolic diseases: detection, mechanism, and potential therapeutics[J]. *Pharmaceuticals*, 2023, 16(4): 504.
- [74] SHANMUGHAM M. Time dependent activation of molecular signatures is associated with trimethylamine N oxide induced endothelial dysfunction in human microvascularendothelial cells[J]. *Physiology*, 2023, 38(S1): 5754780.
- [75] GE XY, ZHENG L, ZHUANG RL, YU P, XU ZC, LIU GY, XI XL, ZHOU XH, FAN HM. The gut microbial metabolite trimethylamine N-oxide and hypertension risk: a systematic review and dose-response meta-analysis[J]. *Advances in Nutrition*, 2020, 11(1): 66-76.
- [76] ALMER G, ENKO D, KARTIOSUO N, NIINIKOSKI H, LEHTIMÄKI T, MUNUKKA E, VIIKARI J, RÖNNEMAA T, ROVIO SP, MYKKÄNEN J, LAGSTRÖM H, JULA A, HERRMANN M, RAITAKARI OT, MEINITZER A, PAHKALA K. Association of serum trimethylamine-N-oxide concentration from childhood to early adulthood with age and sex[J]. *Clinical Chemistry*, 2024, 70(9): 1162-1171.
- [77] BÖCKMANN KA, FRANZ AR, MINARSKI M, SHUNOVA A, MAIWALD CA, SCHWARZ J, GROSS M, POETS CF, BERNHARD W. Differential metabolism of choline supplements in adult volunteers[J]. *European Journal of Nutrition*, 2022, 61(1): 219-230.
- [78] LI L, ZHONG SJ, HU SY, CHENG B, QIU H, HU ZX. Changes of gut microbiome composition and metabolites associated with hypertensive heart failure rats[J]. *BMC Microbiology*, 2021, 21(1): 141.
- [79] JANEIRO MH, RAMÍREZ MJ, MILAGRO FI, ALFREDO MARTÍNEZ J, SOLAS M. Implication of trimethylamine N-oxide (TMAO) in disease: potential biomarker or new therapeutic target[J]. *Nutrients*, 2018, 10(10): 1398.
- [80] WAHLSTRÖM A, SAYIN SI, MARSCHALL HU, BÄCKHED F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism[J]. *Cell Metabolism*, 2016, 24(1): 41-50.
- [81] VARELA-TRINIDAD GU, DOMÍNGUEZ-DÍAZ C, SOLÓRZANO-CASTANEDO K, ÍÑIGUEZ-

- GUTIÉRREZ L, HERNÁNDEZ-FLORES TJ, FAFUTIS-MORRIS M. Probiotics: protecting our health from the gut[J]. *Microorganisms*, 2022, 10(7): 1428.
- [82] SONG ZW, CAI YY, LAO XZ, WANG X, LIN XX, CUI YY, KALAVAGUNTA PK, LIAO J, JIN L, SHANG J, LI J. Taxonomic profiling and populational patterns of bacterial bile salt hydrolase (BSH) genes based on worldwide human gut microbiome[J]. *Microbiome*, 2019, 7(1): 9.
- [83] CHAKRABORTY S, LULLA A, CHENG X, MCCARTHY C, YEO JY, MANDAL J, ALIMADADI A, SAHA P, YEOH BS, MELL B, JIA W, PUTLURI V, PUTLURI N, SREEKUMAR A, WENCESLAU CF, KUMAR MV, MEYER KA, JOE B. Abstract P238: bile acid metabolites modulate hypertension[J]. *Hypertension*, 2020, 76(Suppl_1): AP238-AP238.
- [84] ISHIMWE JA, DOLA T, ERTUGLU LA, KIRABO A. Bile acids and salt-sensitive hypertension: a role of the gut-liver axis[J]. *American Journal of Physiology Heart and Circulatory Physiology*, 2022, 322(4): H636-H646.
- [85] URDANETA V, CASADESÚS J. Interactions between bacteria and bile salts in the gastrointestinal and hepatobiliary tracts[J]. *Frontiers in Medicine*, 2017, 4: 163.
- [86] PÉREZ-GIMENO G, SERAL-CORTES M, SABROSO-LASA S, ESTEBAN LM, WIDHALM K, GOTTRAND F, STEHLE P, MEIRHAEGHE A, MUNTANER M, KAFATOS A, GUTIERREZ A, MANIOS Y, ANASTASIOU CA, GONZALEZ-GROSS M, BREIDENASSEL C, CENSI L, de HENAUW S, LABAYEN I, BUENO-LOZANO G, RUPÉREZ AI, et al. Interplay of the Mediterranean diet and genetic hypertension risk on blood pressure in European adolescents: findings from the HELENA study[J]. *European Journal of Pediatrics*, 2024, 183(5): 2101-2110.
- [87] ROBLES-VERA I, deLa VISITACIÓN N, TORAL M, SÁNCHEZ M, ROMERO M, GÓMEZ-GUZMÁN M, YANG T, IZQUIERDO-GARCÍA JL, GUERRA-HERNÁNDEZ E, RUIZ-CABELLO J, RAIZADA MK, PÉREZ-VIZCAÍNO F, JIMÉNEZ R, DUARTE J. Probiotic *Bifidobacterium breve* prevents DOCA-salt hypertension[J]. *FASEB Journal*, 2020, 34(10): 13626-13640.
- [88] XU XH, JIN H, LI XL, YAN CL, ZHANG QJ, YU XY, LIU ZJ, LIU SF, ZHU FF. Fecal microbiota transplantation regulates blood pressure by altering gut microbiota composition and intestinal mucosal barrier function in spontaneously hypertensive rats[J/OL]. *Probiotics and Antimicrobial Proteins*, 2024. DOI: 10.1007/s12602-024-10344-x.
- [89] MILLER JC, BABU AKS, PETERSEN C, WANKHADE UD, ROBESON MS 2nd, PUTICH MN, MUELLER JE, O'FARRELL AS, CHO JM, CHINTAPALLI SV, JALILI T, SYMONS JD, BABU PVA. Gut microbes are associated with the vascular beneficial effects of dietary strawberry on metabolic syndrome-induced vascular inflammation[J]. *Molecular Nutrition & Food Research*, 2022, 66(22): e2200112.
- [90] 肖礼其, 杨莉, 崔赛仙, 张娅袁, 王玉路, 何燕. 高盐诱导肠道菌群紊乱调节盐敏感性血压的机制研究[J]. *中国全科医学*, 2023, 26(29): 3704-3709.
- XIAO LQ, YANG L, CUI SX, ZHANG YY, WANG YL, HE Y. Advances in the association of high salt-induced gut microbiota disturbances with salt-sensitive blood pressure[J]. *Chinese General Practice*, 2023, 26(29): 3704-3709 (in Chinese).
- [91] CAPURSO A. The Mediterranean diet: a historical perspective[J]. *Aging Clinical and Experimental Research*, 2024, 36(1): 78.
- [92] DAIDONE M, di CHIARA T, del CUORE A, CASUCCIO A, SALAMONE G, Di RAIMONDO D, TUTTOLOMONDO A. Mediterranean diet and hypertension: relationship between adherence to a Mediterranean diet and arterial hypertension[J]. *BMC Nutrition*, 2025, 11(1): 44.
- [93] LI J, GUASCH-FERRÉ M, CHUNG W, RUIZ-CANELA M, TOLEDO E, CORELLA D, BHUPATHIRAJU SN, TOBIAS DK, TABUNG FK, HU J, ZHAO T, TURMAN C, FENG YA, CLISH CB, MUCCI L, HEATHER ELIASSEN A, COSTENBADER KH, KARLSON EW, WOLPIN BM, ASCHERIO A, et al. The Mediterranean diet, plasma metabolome, and cardiovascular disease risk[J]. *European Heart Journal*, 2020, 41(28): 2645-2656.
- [94] XUE Y, CUI LL, QI JD, OJO O, DU XJ, LIU YY, WANG XH. The effect of dietary fiber (oat bran) supplement on blood pressure in patients with essential hypertension: a randomized controlled trial[J]. *Nutrition, Metabolism and Cardiovascular Diseases*, 2021, 31(8): 2458-2470.
- [95] THEODORIDIS X, CHOURDAKIS M, CHRYSOULA L, CHRONI V, TIRODIMOS I, DIPLA K, GKALIAGKOUSI E, TRIANTAFYLLOU A. Adherence to the DASH diet and risk of hypertension: a systematic review and meta-analysis[J]. *Nutrients*, 2023, 15(14): 3261.
- [96] MERRA G, NOCE A, MARRONE G, CINTONI M, TARSITANO MG, CAPACCI A, de LORENZO A. Influence of Mediterranean diet on human gut microbiota[J]. *Nutrients*, 2020, 13(1): 7.
- [97] ZAMBRANO AK, CADENA-ULLAURI S, RUIZ-POZO VA, TAMAYO-TRUJILLO R, PAZ-CRUZ E, GUEVARA-RAMÍREZ P, FRIAS-TORAL E, SIMANCAS-RACINES D. Impact of fundamental components of the Mediterranean diet on the microbiota composition in blood pressure regulation[J]. *Journal of Translational Medicine*, 2024, 22(1): 417.
- [98] FITZGERALD E, LAMBERT K, STANFORD J, NEALE EP. The effect of nut consumption (tree nuts and peanuts) on the gut microbiota of humans: a systematic review[J]. *The British Journal of Nutrition*, 2021, 125(5): 508-520.
- [99] AVERY EG, BARTOLOMAEUS H, MAIFELD A, MARKO L, WIIG H, WILCK N, ROSSHART SP, FORSLUND SK, MÜLLER DN. The gut microbiome in hypertension: recent advances and future perspectives[J]. *Circulation Research*, 2021, 128(7): 934-950.

- [100] De CABO R, MATTSON MP. Effects of intermittent fasting on health, aging, and disease[J]. *New England Journal of Medicine*, 2019, 381(26): 2541-2551.
- [101] NISHIDA A, ANDO Y, KIMURA I, MIYAMOTO J. Involvement of gut microbial metabolites derived from diet on host energy homeostasis[J]. *International Journal of Molecular Sciences*, 2022, 23(10): 5562.
- [102] TAIN YL, HOU CY, CHANG-CHIEN GP, LIN SF, TZENG HT, LEE WC, WU KLH, YU HR, CHAN JYH, HSU CN. Reprogramming effects of postbiotic butyrate and propionate on maternal high-fructose diet-induced offspring hypertension[J]. *Nutrients*, 2023, 15(7): 1682.
- [103] CHAKRABORTY S, LULLA A, CHENG X, YEO JY, MANDAL J, YANG T, MEI X, SAHA P, GOLONKA RM, YEOH BS, MELL B, JIA W, PUTLURI V, PIYARATHNA DWB, PUTLURI N, SREEKUMAR A, MEYER K, VIJAY-KUMAR M, JOE B. Conjugated bile acids are nutritionally re-programmable antihypertensive metabolites[J]. *Journal of Hypertension*, 2023, 41(6): 979-994.
- [104] QI D, NIE XL, ZHANG JJ. The effect of probiotics supplementation on blood pressure: a systemic review and meta-analysis[J]. *Lipids in Health and Disease*, 2020, 19(1): 79.
- [105] ROBLES-VERA I, TORAL M, DE LA VISITACION N, SANCHEZ M, ROMERO M, OLIVARES M, JIMENEZ R, DUARTE J. The probiotic *Lactobacillus fermentum* prevents dysbiosis and vascular oxidative stress in rats with hypertension induced by chronic nitric oxide blockade[J]. *Molecular Nutrition & Food Research*, 2018, 62(19): e1800298.
- [106] MÄHLER A, WILCK N, RAUCH G, DECHEND R, MÜLLER DN. Effect of a probiotic on blood pressure in grade 1 hypertension (HYPRO): protocol of a randomized controlled study[J]. *Trials*, 2020, 21(1): 1032.
- [107] RASHIDINEJAD A, BAHRAMI A, REHMAN A, REZAEI A, BABAZADEH A, SINGH H, JAFARI SM. Co-encapsulation of probiotics with prebiotics and their application in functional/synbiotic dairy products[J]. *Critical Reviews in Food Science and Nutrition*, 2022, 62(9): 2470-2494.
- [108] TER ZY, CHANG LS, BABJI AS, ZAINI NAM, FAZRY S, SARBINI SR, PETERBAUER CK, LIM SJ. A review on proteolytic fermentation of dietary protein using lactic acid bacteria for the development of novel proteolytically fermented foods[J]. *International Journal of Food Science & Technology*, 2024, 59(3): 1213-1236.
- [109] KONG CY, LI ZM, MAO YQ, CHEN HL, HU W, HAN B, WANG LS. Probiotic yogurt blunts the increase of blood pressure in spontaneously hypertensive rats *via* remodeling of the gut microbiota[J]. *Food & Function*, 2021, 12(20): 9773-9783.
- [110] JIANG YH, WU J, TIAN L, LIU Y, ZHAO F, HE ZJ, MAO YC, JIA J, GUAN TW. The therapeutic effects of fermented milk with lactic acid bacteria from traditional Daqu on hypertensive mice[J]. *Journal of Dairy Science*, 2024, 107(2): 742-758.
- [111] 程龙, 龚福明, 李晓然, 向新, 罗义勇, 柳陈坚. 具有高效 ACE 抑制活性乳酸菌的筛选及其益生特性研究[J]. *现代食品科技*, 2015, 31(11): 127-134, 119.
- CHENG L, GONG FM, LI XR, XIANG X, LUO YY, LIU CJ. Screening and potential probiotic properties of lactic acid bacteria with high angiotensin-I converting enzyme-inhibition activity[J]. *Modern Food Science and Technology*, 2015, 31(11): 127-134, 119 (in Chinese).
- [112] PATEL AK, SINGHANIA RR, AWASTHI MK, VARJANI S, BHATIA SK, TSAI ML, HSIEH SL, CHEN CW, DONG CD. Emerging prospects of macro- and microalgae as prebiotic[J]. *Microbial Cell Factories*, 2021, 20(1): 112.
- [113] PARADA VENEGAS D, deLa FUENTE MK, LANDSKRON G, GONZÁLEZ MJ, QUERA R, DIJKSTRA G, HARMSSEN HJM, FABER KN, HERMOSO MA. Short chain fatty acids (SCFAs) - mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases[J]. *Frontiers in Immunology*, 2019, 10: 277.
- [114] SALMINEN S, COLLADO MC, ENDO A, HILL C, LEBEER S, QUIGLEY EMM, SANDERS ME, SHAMIR R, SWANN JR, SZAJEWSKA H, VINDEROLA G. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics[J]. *Nature Reviews Gastroenterology & Hepatology*, 2021, 18(9): 649-667.
- [115] FLORI L, BENEDETTI G, MARTELLI A, CALDERONE V. Microbiota alterations associated with vascular diseases: postbiotics as a next-generation magic bullet for gut-vascular axis[J]. *Pharmacological Research*, 2024, 207: 107334.
- [116] ZHANG L, LIU Y, WANG XZ, ZHANG X. Physical exercise and diet: regulation of gut microbiota to prevent and treat metabolic disorders to maintain health[J]. *Nutrients*, 2023, 15(6): 1539.
- [117] BLANCO C. The influence of the gut microbiome on obesity[J]. *Journal of the American Association of Nurse Practitioners*, 2020, 32(7): 504-510.
- [118] ORAL M, ROBLES-VERA I, deLa VISITACIÓN N, ROMERO M, YANG T, SÁNCHEZ M, GÓMEZ-GUZMÁN M, JIMÉNEZ R, RAIZADA MK, DUARTE J. Critical role of the interaction gut microbiota-sympathetic nervous system in the regulation of blood pressure[J]. *Frontiers in Physiology*, 2019, 10: 231.
- [119] ZHANG T, LU GC, ZHAO Z, LIU YF, SHEN Q, LI P, CHEN YY, YIN HR, WANG HQ, MARCELLA C, CUI B, CHENG L, JI GZ, ZHANG FM. Washed microbiota transplantation *vs.* manual fecal microbiota transplantation: clinical findings, animal studies and screening[J]. *Protein Cell*, 2020, 11(4): 251-266.
- [120] LIN DJ, HU DX, SONG YL, HE XX, WU L. Long-term efficacy of washed microbiota transplantation in overweight patients[J]. *European Journal of Clinical Investigation*, 2024, 54(10): e14260.
- [121] ZHONG HJ, ZENG HL, CAI YL, ZHUANG YP, LIU YL, WU QP, HE XX. Washed microbiota transplantation lowers blood pressure in patients with hypertension[J]. *Frontiers in Cellular and Infection Microbiology*, 2021, 11: 679624.