

Gut microbiota and microbiota-derived metabolites in cardiovascular diseases

Xiaofeng Chen¹, Hua Zhang^{2,3,4}, Sichong Ren⁵, Yangnan Ding⁶, Naznin Sultana Remex⁷, Md. Shenuarin Bhuiyan^{7,8}, Jiahua Qu⁹, Xiaoqiang Tang^{2,3,4}

¹Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, China;

²Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, State Key Laboratory of Biotherapy, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China;

³Key Laboratory of Chronobiology (Sichuan University), National Health Commission of China, Chengdu, Sichuan 610041, China;

⁴Sichuan Birth Defects Clinical Research Center, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China;

⁵Department of Nephrology, Clinical Medical College and The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan 610500, China;

⁶Clinical Laboratory, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China;

⁷Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA 71103, USA;

⁸Department of Pathology and Translational Pathobiology, Louisiana State University Health Sciences Center, Shreveport, LA 71103, USA;

⁹Department of Pathology, University of California, San Francisco, CA 94117, USA.

Abstract

Cardiovascular diseases, including heart failure, coronary artery disease, atherosclerosis, aneurysm, thrombosis, and hypertension, are a great economic burden and threat to human health and are the major cause of death worldwide. Recently, researchers have begun to appreciate the role of microbial ecosystems within the human body in contributing to metabolic and cardiovascular disorders. Accumulating evidence has demonstrated that the gut microbiota is closely associated with the occurrence and development of cardiovascular diseases. The gut microbiota functions as an endocrine organ that secretes bioactive metabolites that participate in the maintenance of cardiovascular homeostasis, and their dysfunction can directly influence the progression of cardiovascular disease. This review summarizes the current literature demonstrating the role of the gut microbiota in the development of cardiovascular diseases. We also highlight the mechanism by which well-documented gut microbiota-derived metabolites, especially trimethylamine N-oxide, short-chain fatty acids, and phenylacetylglutamine, promote or inhibit the pathogenesis of cardiovascular diseases. We also discuss the therapeutic potential of altering the gut microbiota and microbiota-derived metabolites to improve or prevent cardiovascular diseases.

Keywords: Gut microbiota; Metabolites; Heart failure; Coronary artery disease; Atherosclerosis; Aneurysm; Thrombosis; Hypertension

Introduction

Cardiovascular diseases, including heart failure (HF), coronary artery disease, atherosclerosis, thrombosis, aneurysm, and hypertension, are the most common health care burden and the leading cause of death worldwide.^[1,2] With the advent of high-throughput sequencing and various omics technologies, recent studies have highlighted the molecular role of the gut microbiota in the development of cardiovascular diseases.^[3] Atherosclerosis, the most common cause of cardiovascular disease, results in a complex cascade of events

occurring within the arterial wall, involving rheology, lipid metabolism, and inflammation.^[4] Previous studies have indicated that gut microbiota could enhance the permeability of the intestine, thus regulating intestinal integrity and inflammatory responses.^[5,6] A major portion of the current research is focused on understanding the role of the gut microbiome in the pathogenesis of atherosclerosis, including the correlation between the presence of harmful inflammation-associated microbes and a decreased level of some beneficial bacteria.^[7,8] Direct manipulation of the mouse gut

Xiaofeng Chen, Hua Zhang, and Sichong Ren contributed equally to this work.

Correspondence to: Dr. Xiaoqiang Tang, Key Laboratory of Birth Defects of MOE, State Key Laboratory of Biotherapy, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: tangxiaoqiang@scu.edu.cn; txiaoqiang@yeah.net

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microbiome reportedly retards the progression of atherosclerotic plaque.^[9] Moreover, a series of metabolites generated by the gut microbiota participate in the pathogenesis of cardiovascular diseases.^[10] Among them, trimethylamine N-oxide (TMAO) aggravates atherosclerosis and thrombosis, while short-chain fatty acids (SCFAs) fermented by microbiota maintain cardiovascular health.^[11] Similarly, recent studies demonstrated common traits of the gut microbe's capacity to produce butyrate and elevate circulating TMAO levels to regulate coronary artery disease and HF. In addition, alterations in the gut microbiota and microbiota-derived metabolites improve the symptoms of cardiovascular disease.^[3,12,13] However, the underlying molecular mechanisms and other unknown metabolites require further exploration. This review summarizes the role of the gut microbiota in the physiology and pathology of cardiovascular diseases as well as the relationship between the gut microbiota and microbiota-derived metabolites and cardiovascular diseases including HF, atherosclerosis, aneurysm, thrombosis, and hypertension. Moreover, we discuss the possibility of modifying microbiota and microbiota-derived metabolites as a therapeutic strategy for attenuating cardiovascular diseases.

Role of Gut Microbiota in Physiology and Pathology

The human gut is a dynamically balanced microecosystem in which over 2000 species and 100 trillion microbes, mainly bacteria, viruses, and fungi, live and coevolve with us.^[14] Bacteria account for the majority of the total gut microbe species, with over 90% being *Bacteroidetes* and *Firmicutes*, followed by *Actinobacteria*, *Tenericutes*, and *Proteobacteria*.^[15] The gut microbiota generally settles in the oxygen-free and nutrient-rich ascending colon, an optimal environment to live. The gut microbiota gradually colonizes and matures from birth.

The gut microbiota can degrade ingredients from nutrition and generate vitamin B and vitamin K to promote the host's growth, metabolism, and developmental processes. Simultaneously, SCFAs generated through the fermentation of dietary fiber by the gut microbiota protect the host in various ways, ranging from providing energy for enterocytes to regulating the immune system.^[16] Moreover, microbes maintain intestinal development and integrity by secreting signals for epithelial renewal and inducing intestinal vascular remodeling.^[17] Taken together, gut microbiota and microbiota-derived metabolites play a significant role in maintaining the host's health.

Alteration of the composition and function of gut microbiota, known as gut dysbiosis, is caused by intestinal inflammation, cold, stimulus, antibiotic abuse, and other factors. Increasing studies have reported that gut dysbiosis is associated with many diseases, including human cancer, irritable bowel syndrome, cardiovascular disease, and even the more recently emerged coronavirus disease 2019 (COVID-19). Gut dysbiosis leads to impaired gut barrier integrity, increases intestinal inflammation, and further enhances microbial products and metabolites absorbed by the host's circulation, promoting the progression of cardiovascular diseases.^[18] The mechanical insights into the role of gut microbiota in cardiovascular diseases range

from the modulation of inflammation, immunity, and vascular function to the regulation of reactive oxygen species (ROS) and lipid metabolism.^[18] Overall, the gut microbiota is involved in the pathophysiological processes of diseases, including cardiovascular diseases.

Gut Microbiota-derived Metabolites

The gut microbiota generates a series of small molecule metabolites, such as TMAO, SCFA, and phenylacetylglutamine [Figure 1]. Dietary quaternary amines, including phosphatidylcholine, choline, carnitine, and betaine, are converted to trimethylamine (TMA) under the action of microbial choline TMA-lyase (cutC/D) and L-carnitine oxygenase (CntA/B) enzymes in the gut.^[19] Subsequently, TMA is absorbed by the liver via the portal circulation, where it is oxidized to produce TMAO, mainly by hepatic flavin-containing monooxygenase (FMO1). Finally, TMAO is excreted in the urine through the kidney and cleared from the body.^[20] Several studies have demonstrated an association between TMAO and the development of cardiovascular diseases, chronic renal insufficiency, type 2 diabetes (T2D), insulin resistance, non-alcoholic fatty liver disease, and certain cancers.^[21-23]

SCFAs are composed largely of acetate, propionate, and butyrate produced by the microbial fermentation of indigestible dietary fiber.^[13] SCFAs may function by directly binding to fatty acid receptors (such as G protein-coupled receptor 41 [GPR41], GPR42, GPR43, OLFR78, GPR109A, and GPR164), inhibiting histone deacetylase enzymatic activity, resulting in increased protein acetylation, and acting as substrates for protein acylation to play roles in the pathophysiological state.^[13] It is well-known that gut microbiota-derived SCFAs are causally associated with various diseases, including T2D, obesity, multiple sclerosis, and cardiovascular diseases.^[10,24,25]

Other important metabolites generated by the gut microbiota are lipopolysaccharide (LPS), a component of the gram-negative bacterial cell membrane, and phenylacetylglutamine (PAGln), a product of phenylalanine. All these metabolites play an essential role in the development of cardiovascular diseases.^[11,26] Thus, deepening our knowledge of the action model of microbial metabolites in various diseases might contribute to a better understanding and management of associated diseases.

Role of Gut Microbiota in Cardiovascular Diseases

Recent research demonstrated that alterations in the gut microbial community and microbiota-derived metabolites could play a role in the development and progression of cardiovascular diseases, including HF, coronary heart disease (CHD), atherosclerosis, thrombosis, aneurysm, and hypertension. The host-microbiota interactions modulate the inflammatory and metabolic pathways of the body, and their alteration may contribute to the pathogenesis of multiple immune-mediated and metabolic diseases closely related to the cardiovascular system.^[27] Here we summarize the recent advances in our understanding of the interplay between the gut microbiota, microbiota-derived metabolites, and pathogenesis of cardiovascular diseases.^[28-30]

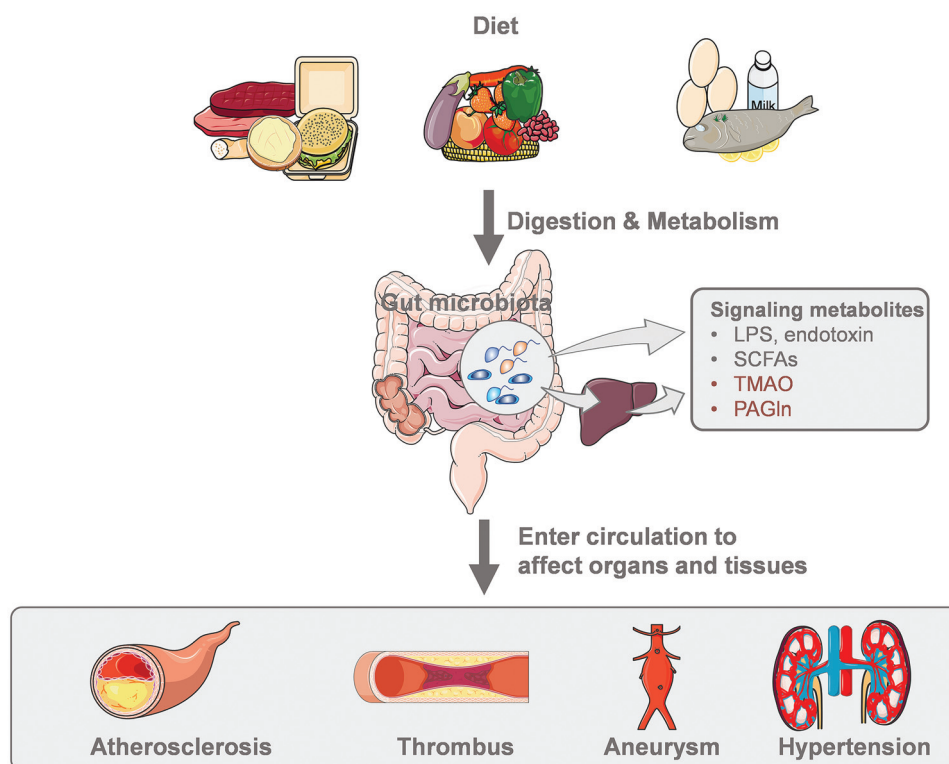


Figure 1: Gut microbiota-derived metabolites regulate vascular diseases. TMA is produced from dietary phosphatidylcholine, choline, and carnitine by microbial TMA lyases, such as CutC/D and Cnt A/B, in the gut. TMA then enters the liver via portal vein circulation and is oxidized by FMOs to produce TMAO. Dietary fiber can be fermented by gut microbiota to generate SCFAs, mainly acetate, propionate, and butyrate. Dietary phenylalanine can be converted into phenylacetic acid by the microbial *porA* gene, with further production of PAGln and phenylacetylglutamine in the liver. LPS: lipopolysaccharide; TMA: trimethylamine; FMOs: Flavin monooxygenases; PAGln: Phenylacetylglutamine; SCFAs: Short-chain fatty acids; TMAO: Trimethylamine N-oxide.

Gut microbiota and metabolites in HF

Several studies have found an association between alterations in the composition of the intestinal microbiota and the development of HF. Studies of patients with chronic HF demonstrated a decreased number of beneficial bacterial communities and a significantly increased number of pathogenic bacteria, such as *Shigella*, *Campylobacter*, *Salmonella*, and *Candida* species.^[31] The significantly decreased number of beneficial bacterial communities observed in patients with HF include *Blautia*, *Erysipelotrichaceae*, *Collinsella*, and *Ruminococcaceae*.^[32] A nationwide study in the United States also reported an increased number of pathogenic bacteria, such as *Clostridium difficile*, in the fecal samples of patients with chronic HF. This pathogenic bacterial infection was associated with remarkably higher hospital mortality rates among patients with HF.^[33] Moreover, a 16S ribosomal DNA (rDNA) analysis-based study showed that 22 hospitalized patients with HF had decreased levels of SCFA-producing bacteria, including *Eubacterium rectale* and *Dorea longicatena*.^[34] Similarly, a decrease in the butyrate-producing bacterial community was also reported in the guts of patients with chronic HF. Butyrate exercises anti-inflammatory roles in the gut mucosa by increasing the production of regulatory T cells.^[35,36] In addition, a significant upregulation of microbial genes responsible for bacterial LPS biosynthesis and TMAO generation was observed in patients with chronic HF.^[37]

Gut microbes can generate many metabolites, including TMAO and uremic toxins. Elevated levels of these gut

metabolites can contribute to HF and chronic kidney disease progression.^[38] The systemic circulatory level of TMAO depends on gut microbes and hepatic and renal functions.^[28] A clinical study of over 4000 participants showed higher fasting plasma TMAO levels on elective coronary angiography associated with major adverse cardiac events (MACE) over a 3-year period.^[39] Another more recent clinical study showed that plasma TMAO levels were increased in patients with acute and chronic HF, suggesting a predictive value for poor prognosis and an over three-fold increased risk of mortality^[40] [Figure 2]. Another gut microbiota-generated metabolite, SCFA, plays a role in the host's immune system and regulates the host's blood pressure by modulating renin secretion by the olfactory receptor, Olfr78, in the glomerular paracycles of the kidney.^[40] SCFAs such as acetate, propionate, and butyrate are produced by the gut microbiota from dietary fiber [Figure 2], and have protective roles in maintaining gut barrier function.^[41] SCFAs also reportedly play an important role in repairing cardiac injury after myocardial infarction by increasing CX3CR1⁺ monocyte infiltration in the peri-infarct areas. Thus, SCFAs can prevent the development and progression of the inflammation that leads to HF.^[42]

Overall, HF development and progression are associated with a decrease in SCFA-generating microbes and an increase in TMA-generating microbes [Figure 2]. A recent study identified that alterations in gut microbiota composition through a diet that is rich in fiber have a protective role in the development of hypertension and HF

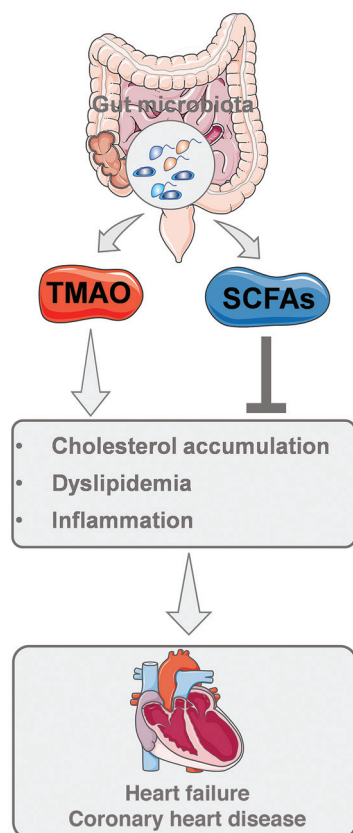


Figure 2: Roles of gut microbiota-generated metabolites, TMAO, and SCFA, in HF and CHDs. Gut microbiota-derived metabolites, TMAO, are produced from dietary sources of phosphatidylcholine, choline, and carnitine, and SCFAs such as acetate, propionate, and butyrate are produced from dietary fiber. Increased levels of TMAO and decreased levels of SCFA in the host serum are associated with HF and CHDs through regulation of cholesterol accumulation, circulatory and liver levels of lipids, lipid transportation, and activation or inhibition of inflammatory pathways. CHD: Coronary heart disease; HF: Heart failure; SCFAs: Short-chain fatty acids; TMAO: Trimethylamine N-oxide.

in mice,^[43] so alterations in gut microbiota composition and metabolites can be used therapeutically to treat patients with HF.

Gut microbiota and metabolites in CHD

CHD, another major cardiovascular disease-causing mortality, affects approximately one-third of the global population. Imbalances in the gut microbiota community are directly linked to the pathogenesis of CHD^[44] [Figure 2]. The levels of metabolic TMAO, produced by the gut microbe population, in the blood are strongly correlated with and a major risk factor for CHD. Cholesterol accumulation is a potential risk factor for CHD, and TMAO has been shown to increase cholesterol accumulation in cells by inducing CD36 receptor and scavenger receptor A expression.^[20] TMAO can also inhibit cholesterol transport in macrophages by decreasing the expression of Cyp7a1, an enzyme responsible for bile acid (BA) synthesis, leading to cholesterol accumulation and foam cell formation. Inflammation is another major risk factor for CHD [Figure 2], and studies suggest that TMAO can rapidly stimulate the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa beta (NF- κ B) signaling axis of inflammation in vascular

endothelial and smooth muscle cells. This further activates the downstream signaling molecules of this axis, including cell adhesion molecules.^[45] Moreover, higher TMAO levels may upregulate the expression of SMAD3 protein, a key molecule in the transforming growth factor-beta pathway.^[46] Thus, the gut microbial metabolite TMAO plays an important role in promoting vascular inflammation-mediated endothelial activation and the upregulation of cell adhesion molecules, leading to CHD.^[47] SCFAs also play a role in providing an energy supply to gut epithelial cells, promoting intestinal mucosal repair, and blocking inflammatory regulatory factors, including Toll-like receptor 4 (TLR4), NF- κ B, and interleukin-6 (IL-6) expression levels.^[48,49] SCFAs also have inhibitory effects on hepatic adipose synthetase activity, resulting in the maintenance of cholesterol levels in the blood and liver.^[50] Therefore, SCFAs can decrease serum levels of cholesterol and lipid accumulation in the host species. Reduced SCFA production may lead to dyslipidemia, while SCFA levels increased by probiotics can reduce serum cholesterol levels, suggesting a protective role of SCFA in inhibiting the risk factors of CHD.^[51]

Gut microbiota and metabolites in atherosclerosis

Atherosclerosis, a sophisticated and multifactorial vascular disease that contributes to the global epidemic of cardiovascular diseases, is a major cause of death worldwide.^[52,53] Dyslipidemia, hypertension, diabetes, and genetic factors are the major risk factors for the development and progression of atherosclerosis, which is driven by the accumulation of low-density lipoprotein in the artery accompanying proliferative fibrous tissue and calcinosis to form atheroma and characteristic plaques.^[54] Inflammation, immunity, and metabolism are also actively involved in the development of atherosclerosis.^[54,55]

Accumulating evidence indicates that the gut microbiota plays an essential role in the initiation and progression of atherosclerosis pathogenesis^[56] [Table 1]. The first study to demonstrate the role of bacteria in the inflammatory responses of atherosclerosis was based on the observation that bacterial DNA existed in the atherosclerotic plaques of humans and the composition of bacteria was positively related to leukocyte content.^[57] Subsequent studies using high-throughput sequencing and omics techniques have reported that gut microbiota associated with inflammation (e.g., *Acidaminococcus*) was increased in patients with carotid atherosclerosis, whereas the levels of beneficial bacteria (e.g., *Anaerostipes*) and butyrate-producing bacteria (e.g., *Clostridium XVIII/XIVa/XIVb*) were higher in healthy controls.^[8] Inflammation is a well-known key contributor to the pathogenesis of atherosclerosis. Indeed, a recent study demonstrated that the pathogenic bacteria *Porphyromonas gingivalis* (*P. gingivalis*) aggravated atherosclerosis progression in ApoE^{-/-} mice through the innate immune Toll-like receptor 2 (TLR2)-mediated inflammatory response. In this study, *P. gingivalis* activated macrophages and increased the levels of proinflammatory cytokines (interleukin-1 beta [IL-1 β], IL-6, and tumor necrosis factor-alpha [TNF- α]), whereas deletion of TLR2 reversed the inflammatory process.^[58] Similarly, the proinflammatory bacteria trans-

Table 1: Gut microbiota involved in vascular diseases.

Diseases	Means of altering the microbiota	Effects	Refs
Atherosclerosis	Traditional Chinese medicine formula-Dingxin recipe (DXR)	Increased <i>Muribaculaceae</i> and <i>Ruminococcaceae</i> , decreased <i>Erysipelotrichaceae</i> , improved lipid metabolism, and attenuated atherosclerosis	[163]
Atherosclerosis	Nutritional supplement-L-alpha GPC	Increased <i>Parabacteroides</i> , <i>Ruminococcus</i> , and <i>Bacteroides</i> ; decreased <i>Akkermansia</i> , <i>Lactobacillus</i> , and <i>Roseburia</i> ; increased proinflammatory chemokine (C-X-C motif) ligand 13 (CXCL13) and tissue inhibitor of metalloproteinases-1 (TIMP-1); activated the nuclear factor kappa B (NF-κB) and MAPK pathway; and promoted atherosclerosis	[164]
Atherosclerosis	Probiotics such as <i>Lactobacillus acidophilus</i> ATCC 4356 and <i>Pediococcus acidilactici</i> R037	Combated gut dysbiosis, improved the inflammatory microenvironment, and attenuated atherosclerosis	[165]
Atherosclerosis	Natural substance (Ginkgolide B)	Increased <i>Bacteroides</i> , decreased <i>Helicobacter</i> , maintained the integrity of the intestinal barrier, and attenuated atherosclerosis	[71]
Atherosclerosis	Polyphenols	Increased <i>Oscillospira</i> and <i>Ruminococcus</i> , decreased <i>Allobaculum</i> , inhibited inflammatory cytokines, maintained the integrity of the intestinal barrier, and attenuated atherosclerosis	[166]
Atherosclerosis	Flavonoid	Increased <i>Bifidobacterium</i> , promoted BA excretion, and attenuated atherosclerosis	[167]
Atherosclerosis	Isoquinoline alkaloid (BBR)	Increased <i>Akkermansia</i> , decreased proinflammatory cytokines and chemokines, and attenuated atherosclerosis	[168]
Atherosclerosis	Carbamate fungicide (Propamocarb)	Increased <i>Peptostreptococcaceae</i> , <i>Ruminococcaceae</i> , <i>Paeniclostridium</i> , <i>Allobaculum</i> , and <i>Clostridioides</i> , affected lipid metabolism and the inflammatory response, and promoted atherosclerosis	[169]
Aneurysm	Drinking water with an antibiotic cocktail for 3 weeks	Reduced the bacterial load, changed the diversity of bacterial sub-populations, reduced eNOS activity, and promoted cerebral endothelial dysfunction	[170]
Aneurysm	None	Increased the genus <i>Campylobacter</i> and <i>Campylobacter ureolyticus</i> in patients with ruptured aneurysms	[171]
Aneurysm	None	Decreased <i>Akkermansia</i> and <i>Parvibacter</i> , and increased <i>Odoribacter</i> , <i>Helicobacter</i> , <i>Ruminococcus</i> , <i>Megamonas</i> , <i>Bacteroides</i> , <i>Alistipes</i> , and <i>Alloprevotella</i> in abdominal aortic aneurysm mice	[172]
Aneurysm	FMT	Increased <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Ruminococcus</i> , and <i>Blautia</i> , and decreased <i>Faecalibacterium</i> , <i>Eubacterium</i> , <i>Collinsella</i> , and <i>Lactobacillus</i> in patients with UIA; the UIA microbiota was able to induce UIA in mice	[98]
Thrombosis	Isoquinoline alkaloid- BBR	Increased <i>Lactobacillus</i> , decreased <i>Bacteroidetes</i> , reduced the TMAO level, and decreased thrombosis potential	[116]
Thrombosis	None	Increased <i>Prevotella</i> in hyperglycemic patients with STEMI, increased coronary thrombus burden	[104]
Thrombosis	Ldlr ^{-/-} mice fed a HFD	Increased <i>Clostridiaceae</i> , <i>Staphylococcaceae</i> , <i>Bacillales</i> , <i>Streptococcaceae</i> , and <i>Clostridiales</i> ; decreased <i>Lactobaicillaceae</i> , <i>Proteobacteria</i> , and <i>Betaproteobacteria</i> ; modulated the plasma lipoprotein profile; reduced vascular inflammation; and promoted AT	[107]
Hypertension	Captopril	Increased <i>Bifidobacterium</i> and <i>Akkermansia</i> ; decreased <i>Proteobacteria</i> , <i>Cyanobacteria</i> , <i>Escherichia-Shigella</i> , <i>Eubacterium nodatum</i> , and <i>Ruminococcus</i> in hypertensive rats; reduced blood pressure	[173]
Hypertension	Curcumin	Increased <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> , <i>Ruminococcaceae</i> , <i>Ruminococcus</i> , and <i>Roseburia</i> and reduced blood pressure	[174]
Hypertension	FMT	Increased <i>Bifidobacterium</i> and reduced portal hypertension	[175]
Hypertension	Potassium alginate oligosaccharides	Decreased <i>Prevotella</i> and <i>Phascolarctobacterium</i> , and reduced hypertension	[176]

AT: Arterial thrombosis; BBR: Berberine; BA: Bile acid; eNOS: Endothelial nitric oxide synthase; FMT: Fecal microbiota transplantation; GPC: Glycerolphosphorylcholine; HFD: High-fat western diet; MAPK: Mitogen-activated protein kinase; STEMI: ST-segment elevation myocardial infarction; UIA: Unruptured intracranial aneurysm.

mitted from *Caspase1*^{-/-} to *Ldr*^{-/-} mice increased circulating leukocyte and inflammatory cytokines and accelerated the atherosclerosis phenotype.^[59] This study also reported that *Akkermansia muciniphila* could inhibit the development of atherosclerosis by maintaining the integrity of the gut barrier.^[60] In addition, cyclic D- and L- α -peptides could remodel the Western diet gut microbiota state to a low-fat diet gut microbiota state in mice, and the administration of D- and L- α -peptides inhibited the formation of atherosclerosis. However, treatment with antibiotics in these mice reversed its anti-atherosclerotic effect,^[9] indicating that gut microbiota participation in atherosclerosis and direct shaping of the gut microbial community could retard the progression of atherosclerosis. But in the clinical trials, conclusions about the effect of antibiotics on atherosclerosis are inconsistent. Some studies indicated antibiotics could prevent the progression of atherosclerosis,^[61,62] while other studies showed antibiotics only temporarily exerted a protective effect on atherosclerosis.^[63] As such, more clinical researches need to uncover the role of antibiotics on atherosclerosis.

Aside from the gut microbiota itself, the microbiota-derived metabolite TMAO has also been demonstrated to participate in atherosclerosis^[18,22] [Figure 3]. Numerous independent clinical studies documented increased plasma TMAO levels in association with an increased risk of cardiovascular diseases. Indeed, preclinical animal studies have shown that dietary supplementation with choline or TMAO aggravated atherosclerotic plaque lesions with an increased level of proatherogenic macrophage scavenger receptors (CD36 and SR-A1) and macrophage foam cell formation in ApoE^{-/-}

mice.^[28] Similar studies have shown that circulating TMAO levels are positively correlated with elevated carotid intima-media thickness and atherosclerosis in humans independent of traditional cardiovascular risk factors.^[64,65] The consumption of L-carnitine, the precursor of TMAO, or γ -butyrobetaine, the intermediate product of bacterial metabolism of L-carnitine to TMAO, was sufficient to promote atherosclerosis.^[20,66] In addition, the reduction of TMAO by the suppression of choline TMA-lyase (CutC) by 3,3-dimethylbutanol (DMB) has been shown to alleviate the progression of atherosclerosis.^[67] Moreover, the natural polyphenol resveratrol, isoquinoline alkaloid berberine (BBR), ginkgolide B, and the probiotic *Lactobacillus plantarum* ZDY04 and *Enterobacter aerogenes* ZDY01 have all been shown to reshape the gut microbiota to reduce TMAO synthesis and retard atherosclerosis in ApoE^{-/-} mice.^[68-73] More importantly, a recent clinical trial of Taurisolo[®], a novel nutraceutical formulation from grape pomace polyphenols, reported an effective anti-atherosclerotic role by reducing the circulating TMAO level.^[74] Therefore, several published studies suggested that gut microbiota-derived TMAO is detrimental to the development of atherosclerosis. Mechanistically, the published literature demonstrated that TMAO could directly stimulate vascular inflammatory signaling pathways, including MAPK, extracellular signal-related kinase, and NF- κ B signaling.^[45] The NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome is an important contributor to vascular inflammation, and TMAO activates the NLRP3 inflammasome through ROS-thioredoxin interacting protein (TXNIP) or sirtuin 3 (SIRT3)-superoxide dismutase 2 (SOD2)-mitochondrial

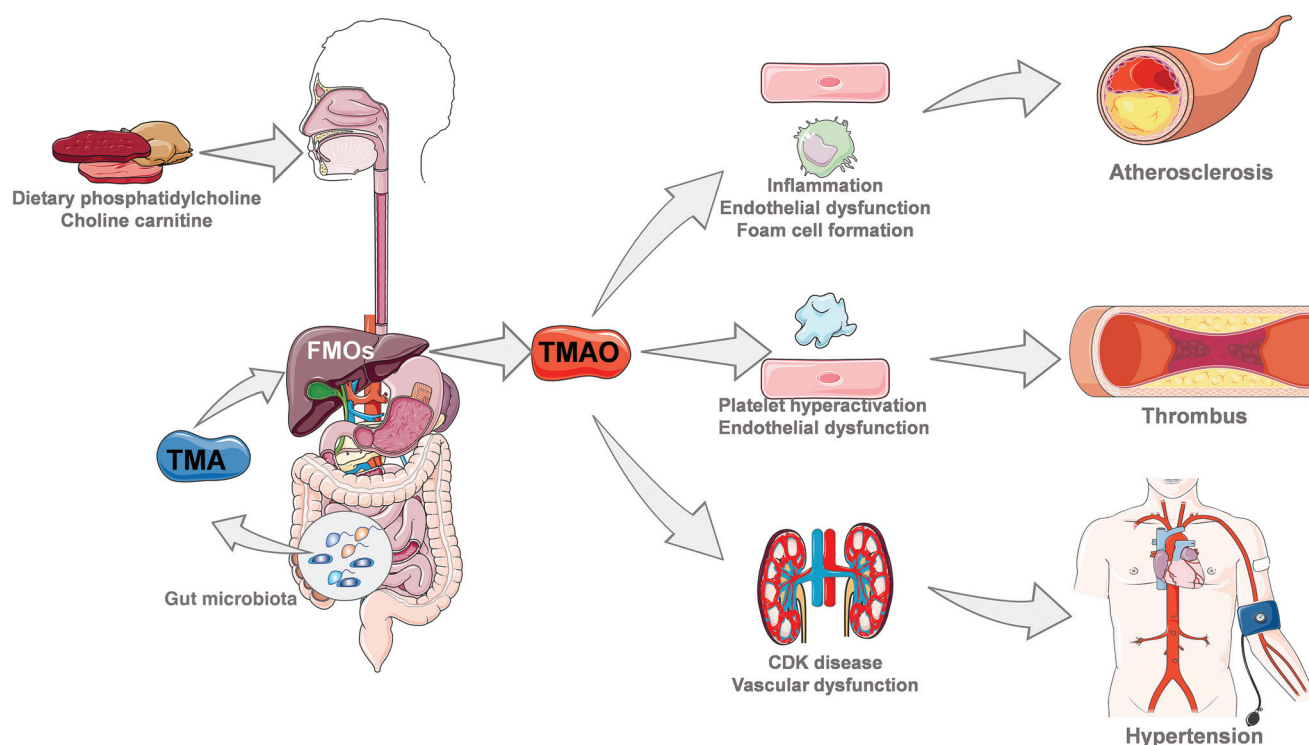


Figure 3: TMAO participates in vascular diseases. High levels of TMAO can decrease reverse cholesterol transport and BA metabolism and increase vascular inflammation and cell pyroptosis, contributing to atherosclerosis. TMAO activates platelets and increases the release of TFs to promote thrombosis. TMAO increases blood pressure by increasing inflammation, oxidative stress, and water reabsorption. BA: Bile acid; TF: Tissue factor; TMAO: Trimethylamine N-oxide; CDK: chronic kidney disease; TMA: trimethylamine; FMOs: Flavin monooxygenases.

reactive oxygen species (mtROS) signaling pathways, which ultimately leads to the release of inflammatory cytokines, including IL-1 β and IL-18. In contrast, suppression of NLRP3 reverses the proinflammatory and proatherogenic phenotype of TMAO.^[75-77] In addition, excessive cholesterol contributes to the development of atherosclerosis, and BA metabolism from cholesterol is an effective way to clear excess cholesterol and arrest atherosclerosis. TMAO decreases the Cyp7a1 level to repress BA metabolism by irritating the nuclear receptor farnesoid X receptor and small heterodimer partner.^[78] In terms of immunity, TMAO could activate the CD36/MAPK/c-Jun N-terminal kinase (JNK) pathway to promote foam cell formation^[79] as well as increase macrophage M2 polarization and efferocytosis.^[80] Moreover, oxidative stress induced by TMAO may increase ROS production via dehydrogenase complex subunit B to enhance cell pyroptosis.^[77,81,82] Overall, TMAO may contribute to the pathogenesis of atherosclerosis by regulating inflammation, cholesterol accumulation, host immunity, and oxidative stress.

SCFAs are involved in the pathogenesis of atherosclerosis [Table 2]. Indeed, an early experiment showed that SCFA treatment decreased the levels of several pivotal genes implicated in cholesterol biosynthesis.^[83] Subsequent studies reported that butyrate derived from the fermentation of pectin reduced the atherosclerotic lesion area by almost half compared to the corresponding control by repressing cholesterol absorption; this was reversed by supplementation with antibiotic.^[84] A similar study demonstrated that oral butyrate could induce adenosine 5'-triphosphate (ATP)-binding cassette sub-family A member 1 expression and activity in macrophages through the specificity protein 1 pathway, enhancing reverse cholesterol transport to inhibit atherosclerosis.^[85] Propionate-regulated intestinal cholesterol metabolism prevents aortic atherosclerotic lesions by increasing regulatory T-cell numbers and IL-10 expression to inhibit the gut cholesterol transporter Niemann-Pick C1-like 1.^[86] Moreover, butyrate supplementation in ApoE^{-/-} mice

reduced the atherosclerotic lesion area by almost half, accompanied by a reduction in proinflammatory TNF- α and IL-1 β levels and decreased NF- κ B activation.^[87] Several other studies also demonstrated that SCFAs may prevent atherosclerosis by inhibiting inflammation.^[88,89] In addition, oxidative stress is a significant contributor to the development of atherosclerosis; therefore, treatment with antioxidants may be a promising therapeutic strategy. Indeed, treatment with butyrate resulted in lower superoxide and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase levels in atherosclerotic ApoE^{-/-} mice.^[90] More importantly, germ-free ApoE^{-/-} mice colonized with the butyrate-producing bacteria *Roseburia* demonstrated decreased atherosclerotic plaque sizes, indicating a causal relationship between bacterial butyrate and atherosclerosis.^[91,92] Collectively, SCFAs regulate plaque cholesterol metabolism, inflammation, and oxidative stress to attenuate the progression of atherosclerosis, providing a novel preventive and therapeutic target for atherosclerosis.

Gut microbiota and metabolites in aneurysms

Aneurysm refers to a permanent and localized dilatation of a vessel, leading to an arterial blood vessel diameter that is >50% of that of the normal vessel.^[93] Aneurysms are among the most common vascular diseases that cause disability and mortality. Aneurysms can occur in any artery of the body and are classified as abdominal aortic aneurysm, thoracic aortic aneurysm, intracranial aneurysm, aortic dissecting aneurysm, and peripheral aneurysm. Aneurysms are most common in people >50 years old, with common etiologies including atherosclerosis, injury, infection, and immune disease.^[94] Smooth muscle cell apoptosis, inflammation, excessive oxidative stress, and abnormalities of the extracellular matrix are implicated in the pathogenesis of aneurysms.^[95]

In recent years, it was recognized that gut microbiota played an important role in aneurysms [Table 1]. Some

Table 2: Potential roles of SCFAs in atherosclerosis and hypertension.

SCFAs	Effects	Mechanisms	Refs
Propionate	Inhibits atherosclerosis	<ul style="list-style-type: none"> Regulates intestinal cholesterol metabolism via increasing the number of regulatory T-cells and IL-10 expression 	[86]
Butyrate	Inhibits atherosclerosis	<ul style="list-style-type: none"> Reduces proinflammatory cytokines and inhibits NF-κB Reduces oxidative stress through downregulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase Inhibits intestinal cholesterol absorption via up-regulating ATP-binding cassette sub-family A member 1 (ABCA1) 	[85,86,87,91]
Acetate	Decreases blood pressure	<ul style="list-style-type: none"> Reduces the levels of cardiac and renal Egr1, and downregulates the rennin-angiotensin system Reverses gut dysbiosis and inhibits gut inflammation 	[43,133]
Propionate	Increases blood pressure Decreases blood pressure	<ul style="list-style-type: none"> Increases renin secretion through binding to Olfr78 Decreases renin secretion through binding to Gpr41, and maintains the homeostasis of regulatory T cells 	[177] [134,177]
Butyrate	Decreases blood pressure	<ul style="list-style-type: none"> Inhibits the renin-angiotensin system and renin release Increases butyrate production capacity, linked to serum PAI-1 levels 	[121,136]

ATP: Adenosine 5'-triphosphate; Gpr41: G protein-coupled receptor 41; IL: Interleukin; NF- κ B: Nuclear factor-kappa beta; Olfr78: Olfactory receptor; PAI-1: Plasminogen activator inhibitor; SCFAs: Short-chain fatty acids.

reports stated that bacterial DNA exists in ruptured and unruptured intracranial aneurysms (UIAs).^[96] A previous study subjected mice to intracranial aneurysm induced by hypertension and the injection of elastase and found that deletion of the entire gut microbiota of these mice through gavage of an antibiotic cocktail could decrease intracranial aneurysm formation. In these mice, depletion of the gut microbiota significantly inhibited macrophage infiltration and inducible nitric oxide synthase as well as expression of the inflammatory cytokines IL-1 β and IL-6.^[97] Although interruption of the entire gut microbiota was not an optimal strategy, it suggested a close relationship between gut microbiota and aneurysms. Furthermore, a fecal transplantation experiment indicated that intestinal flora contributed to intracranial aneurysms.^[98] Mice who received a fecal graft from Chinese patients with UIA had a higher probability of intracranial aneurysm formation and rupture than the controls. Researchers also found that *Hungatella bathewayi* was positively related to the serum taurine level, that oral *Hungatella bathewayi* rescued the taurine concentration, and that taurine supplementation repressed the incidence and rupture of intracranial aneurysms.^[98] In addition to the gut microbiota, there is limited evidence demonstrating the involvement of gut microbiota-derived metabolites in the progression of aneurysms. Some studies have shown that TMA or butyrate influences vascular smooth muscle cell (VSMC) viability,^[99,100] which may be involved in aneurysm pathology. Taken together, these studies suggest a potential influence of gut microbiota on aneurysm pathology. However, the current research on the role of gut microbiota in aneurysms is limited, and more studies are needed to explore the effect of specific enteric bacteria on aneurysm pathobiology and should be further validated by human studies.

Gut microbiota and metabolites in thrombosis

Thrombosis is a devastating vascular disease that accounts for 25% of deaths worldwide.^[101] Generally, a thrombus is a blood clot similar to a plug, which serves to block blood flow. The delicate balance between bleeding and clotting, thrombosis, and thrombolysis maintains the metabolic activity of the human body. However, hypercoagulability or weakened anticoagulant function leads to slow blood flow, coagulation factor lesions, and impaired vascular function, which leads people prone to thrombus formation. Thrombi are composed of many components, including cellulose, tissue factor (TF), fibrinogen, and fibrin, as well as platelets, red blood cells, and other blood cells, including lymphocytes in the blood.^[102] Thrombosis can also occur in arteries or veins, where it is termed arterial thrombosis (AT) and venous thrombosis (VT), respectively. Arterial thrombi are enriched in platelets, whereas venous thrombi mainly contain fibrin and red blood cells.^[103] Hypertension, smoking, diabetes, age, and obesity are established risk factors for thrombosis. Platelet activation and propagation, endothelial inflammation, enhanced TF activity, and thrombin generation are involved in the development of thrombosis.

Recently, an increasing number of studies have demonstrated that the gut microbiota modulates thrombosis^[104]

[Table 1]. Indeed, gnotobiotic mice showed reduced thrombus growth mediated by the symbiotic gut microbiota through platelet TLR2 signaling and modulation of hepatic von Willebrand factor (VWF) expression and circulating VWF levels, further affecting platelet deposition, while cecal microbial transplantation reversed this phenotype.^[105] In addition, microbial recolonization research showed that gut microbiota comprising the *cutC* gene was able to increase platelet responsiveness and thrombosis risk. In contrast, *cutC* deficiency resulted in decreased thrombosis potential.^[106] Similarly, high-fat western diet (HFD)-fed low-density lipoprotein receptor-deficient gnotobiotic mice subjected to ferric chloride treatment in a mouse model of carotid artery injury showed diminished atherosclerotic plaque rupture-stimulated thrombus development compared to corresponding controls, indicating that gut microbiota promoted AT.^[107] In addition, hyperglycemia can influence the thrombosis potential of patients with ST-segment elevation myocardial infarction (STEMI). A clinical study demonstrated distinguishable thrombus microbiota between patients with STEMI with or without hyperglycemia, and proposed that thrombus microbiota might affect thrombosis potential.^[104] And it is well-known that patients with atrial fibrillation (AF), the most common arrhythmia in hospitalized patients, easily form thrombi in the atria. Accumulating evidence has demonstrated gut microbiota dysbiosis contributed to AF.^[108-110] Moreover, COVID-19 has also been identified to enhance the incidence of arterial and venous thrombosis, partly because of gut microbiota dysbiosis.^[111]

The microbial metabolite TMAO is widely involved in the development of thrombosis [Figure 3]. Zhu *et al*^[47] demonstrated that circulating TMAO concentration was a predictor of incident thrombosis risk even after adjusting for traditional cardiovascular risk factors. They clarified that TMAO could increase human platelet reactivity and platelet adhesion *in vitro* and elevated TMAO enhanced thrombus formation *in vivo* in a mouse model of carotid artery injury (FeCl₃). Dietary choline consumption also increased platelet deposition and reduced occlusion time. By analyzing 117 patients with AF with or without thrombi, Gong *et al*^[112] found that circulating TMAO expression was much higher and platelet reactivity was increased in patients with thrombi. In addition, an *in vitro* experiment on vascular endothelial cells showed that TMAO increased thrombosis via promoted TF activity and thrombin generation, accompanied by the heightened activity of the NF- κ B signal cascade.^[113] Interestingly, interrupting enzymes responsible for TMAO production, such as microbial choline-trimethylamine lyase (CutC) or flavin-containing monooxygenase 3 (FMO₃), was sufficient to influence the TMAO levels, platelet responsiveness, and thrombosis risk.^[106,114,115] More importantly, shaping the gut microbes by BBR to decrease TMAO levels could reduce AT.^[116] Collectively, gut microbiota-derived TMAO has an obvious prothrombotic effect.

In recent studies using untargeted metabolomics, researchers identified a novel microbial metabolite named PAGln from dietary phenylalanine (Phe), which was associated with the incidence of MACE even after adjusting for traditional cardiovascular risk factors. Subsequent studies

revealed that PAGln increased platelet responsiveness and platelet aggregation induced by different agonists *in vitro*. PAGln also enhanced platelet clot formation and thrombosis risk in an FeCl₃-induced carotid artery injury mouse model. Mechanically, the microbial genes *porA* and *fldH* were implicated in the production of PAGln and the prothrombotic effect of PAGln mediated through G protein-coupled receptors (GPCRs), including $\alpha 2A$, $\alpha 2B$, and $\beta 2$ adrenergic receptors.^[117] These findings indicate that the novel metabolite PAGln might act as a therapeutic target to prevent and treat thrombosis-related diseases.

Gut microbiota and metabolites in hypertension

Hypertension is a major risk factor for cardiovascular disease, which affects 240 million patients in China and causes 9.4 million deaths worldwide each year.^[53,118] Heredity, a high-salt diet, less activity, a sedentary lifestyle, and environmental factors contribute to hypertension. In recent years, it has been increasingly recognized that the gut microbiota is closely linked to hypertension^[119] [Table 1]. A recent study showed significant microbial alterations in spontaneous hypertensive rats, rats infused with angiotensin II (Ang II), and human hypertensive patients. These correlations were confirmed by a reduction in microbial composition and diversity, an increase in the *Firmicutes/Bacteroidetes* (F/B) ratio, and a decrease in butyrate- and acetate-generating bacteria. They also remodeled the gut microbiota with oral minocycline, which could decrease the F/B ratio to rebalance the gut microbiota and attenuate hypertension.^[120] In addition, by analyzing the intestinal microbiota component of obese women with early pregnancy, investigators demonstrated lower levels of the butyrate-producing bacteria genus *Odoribacter* in obese women and further demonstrated that the level of butyrate-generating bacteria was positively linked to pregnancy-induced hypertension.^[121] Similarly, several other studies reported reduced microbiota diversity and imbalanced harmful and beneficial bacteria in hypertensive patients, which indicated the profound role of gut microbiota dysbiosis in hypertension.^[122,123] More importantly, germ-free mice that received fecal microbiota transplantation (FMT) from patients affected by hypertension displayed higher blood pressure,^[122] while the administration of the probiotic *Bifidobacterium breve* CECT7263 reportedly repressed hypertension in rats induced by deoxycorticosterone acetate (DOCA) salt.^[124] Germ-free mice that received normal gut microbiota from the cecal content of conventionally raised mice were able to prevent Ang II-induced arterial hypertension.^[125] These findings indicate a strong relationship between gut microbiota and hypertension pathology. However, most studies focused on describing the phenotype, and the underlying mechanism of gut microbiota in hypertension remains to be explored.

For TMAO [Figure 3], increased plasma TMAO was observed in the reduced uterine perfusion pressure (RUPP) rat model of preeclampsia (PE). Since PE is always accompanied by hypertension, supplementation with DMB, a non-lethal TMA inhibitor, could lower TMAO levels and reduce the blood pressure of RUPP rats.^[126]

Pre-treatment with DMB in pregnant rats might inhibit the transmission of programmed hypertension induced by a high-fructose diet from their mothers to adult male offspring.^[127,128] In addition, TMAO may increase hypertension in rats by up-regulating aquaporin-2 levels in the kidney medulla to stimulate an increase in water reabsorption.^[129] The study also reported that TMAO aggravated Ang II-induced hypertension; this phenotype was reversed by treatment with antibiotics.^[130] However, an early study showed that TMAO did not influence blood pressure in normotensive rats and that TMAO prolonged the hypertensive effect of Ang II.^[131] Moreover, a slight increase in circulating TMAO about four to five times had no destructive roles in the circulatory system and instead displayed protective roles in diastolic function in the pressure-overloaded heart.^[132] Given the controversial effect of TMAO on hypertension and the lack of a target receptor for TMAO, future studies should test different doses of TMAO and the direct sensor of TMAO in hypertension.

As previously discussed, SCFAs fermented by the gut microbiota are closely related to maintaining blood pressure^[3] [Table 2]. Gut microbiota-derived SCFAs mainly contain acetate, propionate, and butyrate, and a high-fiber diet generates SCFAs via microbial fermentation. This high-fiber content elevated the biomass of acetate-producing bacteria to reduce hypertension in mice induced by DOCA, and direct administration of acetate showed a similar effect on blood pressure regulation.^[43] Similarly, elevated levels of acetate through prebiotic, probiotic, or acetate replenishment exert antihypertensive effects, indicating that microbial acetate is a central modulator of blood pressure.^[133] In addition, supplementation with propionate reduced Ang II-induced hypertension in a murine model.^[134] As for butyrate, plasma butyrate was negatively associated with portal hypertension,^[135] and promoting butyrate-producing bacteria and increasing butyrate-producing ability could improve blood pressure in pregnant women.^[121] More importantly, several studies have shown that oral butyrate prevents the development of hypertension.^[136,137] In addition, our recent research indicated that SCFAs, such as crotonate, are involved in the pathogenesis of cardiovascular disease by modulating protein crotonylation, and other SCFAs widely participate in cardiovascular diseases via acylation.^[12,13] However, it remains to be elucidated whether microbial SCFAs regulate blood pressure through acylation. Taken together, these data prove the significant role of microbial SCFAs in blood pressure regulation, although further experiments are needed to verify the clinical application of SCFAs and the underlying epigenetic mechanism.

Therapeutic application

Gut microbiota modulation

As discussed above, the gut microbiota plays a significant role in cardiovascular diseases; therefore, manipulating it seems a promising strategy to improve the symptoms of cardiovascular diseases. Dietary intervention efficiently changes the quantity and richness of the gut microbiota. A

Mediterranean diet (MD) rich in cereals, fruits, vegetables, and legumes, a healthy dietary type, could increase the number of some bacteria to ferment fiber and elevate SCFA levels.^[138] A clinical trial demonstrated that MD improved endothelial function and vascular homeostasis compared to the low-fat diet, suggesting that following a MD produced vascular protective effects.^[139] Similar studies have demonstrated that adherence to an MD significantly influences the gut microbiota and prevents the deterioration of vascular diseases.^[140,141] In contrast, the Western diet, which was rich in meat and fat, showed elevated counts of *Firmicutes* and reduced counts of *Bacteroidetes*, leading to gut microbiota dysbiosis, compared to mice fed a standard diet, which contributed to arterial stiffness and endothelial dysregulation.^[142]

The use of probiotics and prebiotics efficiently modulates gut microbiota abundance and function. The administration of probiotics consists in introducing a collection of active microorganisms beneficial for the host, thus resulting in maintaining the balance of intestinal flora, promoting the digestion and absorption of nutrients, improving immunity, maintaining gut health, and enhancing antioxidant capacity.^[143] Replenishment with *Lactobacillus acidophilus* ATCC 4356 was demonstrated to have anti-oxidative stress and anti-inflammatory effects to reduce atherosclerotic lesion areas in ApoE^{-/-} mice.^[144] Several probiotics, such as VSL#3, a mixture of probiotics containing eight strains of *Lactobacillus rhamnosus*, and GR-1 were found to attenuate atherosclerosis supported by decreased atherosclerotic lesions and reduced proinflammatory soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM1), soluble E-selectin (sE-selectin) adhesion molecules and reduced proinflammatory TNF- α and IL-1 β cytokine levels in HFD-induced ApoE^{-/-} mice.^[145-147] Some studies indicated that replenishment with probiotics could promote vascular endothelial function, inhibit inflammation, improve vascular oxidative stress and arterial stiffness, and increase platelet functionality, suggesting the protective role of probiotic in atherosclerosis and thrombosis.^[148-151] Classical prebiotics includes oligosaccharides, microalgae, polysaccharides, inulin, and natural plants, which are not digested or absorbed by the host; rather, they selectively promote the metabolism and proliferation of beneficial bacteria in the body, thereby improving the host's health.^[152] An earlier murine experiment showed that inulin could prevent atherosclerosis; however, recent reports indicated that inulin could regulate the intestinal microbiota but had no effect on atherosclerosis or even aggravated atherosclerosis development.^[153-155] Supplementation with gum arabic was associated with lower thrombosis and platelet deposition in water-pipe smoking-stimulated mice.^[156] Moreover, 12 weeks of administration of oligofructose in adults with obesity reportedly reduced the expression of plasminogen activator inhibitor-1, a cause of thrombosis.^[157] However, the underlying mechanism of action of probiotics and prebiotics on cardiovascular diseases remains to be explored.

FMT is the transfer of stool fluid from healthy people after certain treatments into a patient's intestinal tract to

reconstruct the gut microbiota. FMT has become the treatment recommended by domestic and international medical guidelines and consensus for *C. difficile* infection, and an increasing number of studies have demonstrated that FMT is an effective treatment for inflammatory bowel disease, intractable constipation, metabolic disease, intestinal immune deficiency, intestinal allergy, and other diseases in clinical trials.^[158] In terms of vascular diseases, in some animal studies, FMT from patients with UIA evoked UIA in mice, accompanied by a reduced abundance of *Hungatella hathewayi*.^[98] In addition, heightened platelet hyper-responsiveness and thrombosis risk were transmitted to mice who received fecal microflora with high choline TMA-lyase activity, suggesting that some pathogens may exist in the feces.^[106] In addition, FMT from atherosclerosis-prone mice aggravated atherosclerosis in atherosclerosis-resistant mice.^[159] However, these findings were in preclinical animal studies, and endotoxins or infectious agents introduced by FMT were important factors limiting its application. Therefore, more research is needed to explore the mechanisms and safety of FMT in cardiovascular diseases.

Gut microbiota-derived metabolite modulation

Among the identified gut microbiota-derived metabolites, the widely reported detrimental metabolites, such as TMAO and PAGln, and beneficial metabolites, such as SCFAs, demonstrated the potential ability to target microbial metabolites as promising therapeutic strategies. For example, the knockdown of FMO₃, an important enzyme responsible for TMAO production, prevented the progression of atherosclerosis in mice.^[160] The administration of DMB in drinking water, an inhibitor of microbial TMA lyases, was reported to repress TMA production and circulating TMAO levels in mice fed choline or carnitine diets, which ultimately inhibited atherosclerotic plaque areas in mice.^[67] Similarly, oral administration of DMB inhibited platelet aggregation and thrombosis risk in mice. Subsequent studies reported that two efficient CutC/D inhibitors, fluoromethylcholine and iodomethylcholine, were sufficient to lower TMA and TMAO levels to attenuate platelet deposition and thrombosis potential without altering bleeding time.^[161] More interestingly, numerous Chinese medicine or natural substances, such as BBR, Hawthorn fruit extract, and *Alisma orientalis* beverage, exert a TMAO lowering effect to protect mice from atherosclerosis.^[69,81,162] As most of these studies used murine models, future clinical trials are needed to validate the efficiency of the interruption of microbial metabolites to prevent and treat cardiovascular disease.

Concluding Remarks and Future Perspectives

Accumulating evidence demonstrates that gut microbiota plays a significant role in the physiology and pathology of the cardiovascular system. The gut microbiota itself maintains host health and gut homeostasis, which in turn contributes to the initiation and progression of cardiovascular diseases by regulating inflammation, immunity, and oxidative stress. The existence of bacteria in atherosclerotic plaques and aneurysms proves a compelling rationale for studying the

association of microbes with these diseases. Although differences in microbe composition and diversity are found between healthy and diseased patients, the specific bacteria and their potential mechanisms remain indistinct. Future studies using metagenomics can identify potential functional bacteria and metabolomics to determine the differential metabolites responsible for cardiovascular diseases. In addition, the incorporation of transcriptomic and proteomic studies will facilitate the determination of the underlying mechanism of the role of gut microbiota in cardiovascular diseases. Diet manipulation, FMT, probiotics, and prebiotics that regulate gut microbiota composition and function may be beneficial therapeutic strategies for patients with cardiovascular diseases. However, future studies should also consider the safety of FMT and some contrary conclusions about prebiotic use. Therefore, the application of the drug microbiome in clinical practice requires more fundamental research. In addition to gut microbes, microbial metabolites could regulate the development of cardiovascular diseases, providing a new avenue for exploiting possible pharmacological targets for improving cardiovascular diseases. In terms of microbiota-derived metabolites, alterations in the production of TMAO or enhanced generation of fermented SCFAs sufficiently impact the pathogenesis of cardiovascular diseases. Therefore, future studies require the identification of novel microbial metabolites in cardiovascular diseases in the clinical setting and the facilitation of the translation of these metabolite-related modulations in cardiovascular diseases.

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Conflicts of interest

None.

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