Gut microbiota: Implications in pathogenesis and therapy to cardiovascular disease (Review)

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Abstract. The gut microbiota refers to the diverse bacterial community residing in the gastrointestinal tract. Recent data indicate a strong correlation between alterations in the gut microbiota composition and the onset of various diseases, notably cardiovascular disorders. Evidence suggests the gut-cardiovascular axis signaling molecules released by the gut microbiota play a pivotal role in regulation. This review systematically delineates the association between dysbiosis of the gut microbiota and prevalent cardiovascular diseases, including atherosclerosis, hypertension, myocardial infarction and heart failure. Furthermore, it provides an overview of the putative pathogenic mechanisms by which dysbiosis in the gut microbiota contributes to the progression of cardiovascular ailments. The potential modulation of gut microbiota as a preventive strategy against cardiovascular diseases through dietary interventions, antibiotic therapies and probiotic supplementation is also explored and discussed within the present study.

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1. Introduction

The human gut microbiota constitutes a highly intricate community comprised of ~500-1,000 bacterial species (1). Despite this diversity, a substantial discrepancy exists in the abundance of each bacterial type. Notably, a mere 30-40 species contribute to >99% of the total bacterial population, with the remaining species collectively constituting less than 1% (2). Crucially, the gut microbiota plays a pivotal role in essential physiological functions including immunity (3), metabolism (4), inflammation (5) and cell proliferation (6). These microorganisms not

only interact extensively with the intestinal epithelium but also engage in communication with diverse organ systems. It is estimated that the cumulative weight of gut bacteria in an adult can range between 1.0-1.5 kg, housing an immense population of ~10^{14} bacteria (7). The intestinal genome contains millions of genes, 100 times more than the human genome and contains various gene clusters associated with metabolic processes, immune responses and multiple signaling pathways (8). Beyond their influence on body mass and metabolism, the gut microbiota is intricately linked to variety of diseases, including, but not limited to, inflammatory bowel disease, diabetes, obesity, gastrointestinal cancer, cirrhosis, hyperuricemia and autoimmune disorders (9-11). The significance of a healthy gut microbiota as a crucial determinant of overall health cannot be understated, as alterations in its composition strongly correlate with changes in an individual's health status. The National Institutes of Health (NIH) has undertaken a substantial commitment to human microbiome research, investing a substantial $15 billion since 2008. This extensive investment has facilitated comprehensive population studies focusing on microbial populations across various tissues such as the skin, respiratory tract, gastrointestinal tract, urinary tract and vaginal tract (12). Since the commencement of the NIH Human Microecology Program and the EU Intestinal Microecology Program, gut microbiota has attracted much attention and has become an international research hotspot. Now, a number of countries in the world have launched human microbiome projects, including Canada, Australia, France, North Korea and Ireland (13).

Advancements in molecular biology techniques have greatly expanded our understanding of gut microbiota. Techniques such as fluorescence *in situ* hybridization, polymerase chain reaction denaturing gradient gel electrophoresis, gene chips and sequencing have played a vital role. These techniques have enabled more detailed and accurate analyses of gut microbiota. Specifically, next-generation sequencing and macrogenomics have been revolutionary, notably advancing the study of the gut microbiome. These advances mark a significant leap forward in this field of research (14,15).

The morbidity and mortality of cardiovascular diseases have been increasing globally, posing a serious threat to human health. Consequently, there is a pressing need for early preventive measures and innovative treatment strategies for cardiovascular diseases. This has become a focal point of research in the field. Recent studies exploring the relationship between gut microbiota and various diseases have shed light on the crucial role these microbes play in human health (16-18). Recent investigations have highlighted a connection between gut microbiota and cardiovascular disease (19,20). Modulating gut microbiota is anticipated as a potential emerging therapeutic approach for managing cardiovascular conditions (21,22).

Due to of the multiple functions of the gut microbiota, scientists have focused on comprehensive studies of this intricate ecosystem. The traditional approach to study microorganisms is to analyze the physiological functions of individual strains or groups of bacteria using *in vitro* culture. However, numerous species within the gut microbiota can only thrive within the human body and are challenging to culture *in vitro*. Consequently, traditional methods face limitations when addressing the complexity of the gut microbiota. However, with the advancement of sequencing technology, especially the increasing maturity of macrogenomics, the composition and complexity of gut microbiota were clarified. This breakthrough enables a more profound exploration of the relationship between the gut microbiota and human health, overcoming the constraints of traditional methodologies.

The present review provided a systematic exploration of the link between imbalances in gut microbiota and various cardiovascular diseases, such as atherosclerosis, hypertension, heart failure and myocardial infarction. Drawing from recent clinical research and biological studies, it delineates the association between dysbiosis of gut microbiota and the onset, as well as the advancement, of cardiovascular diseases. Emphasizing this connection, the present review underscores the potential of modulating gut microbiota as a viable therapeutic avenue for managing cardiovascular conditions.

2. Methods

To generate the initial list of studies in this review, literature searches were conducted on PubMed using specific keywords such as 'gut microbiome' or 'gut microbiota' combined with terms in the category of cardiovascular diseases such as 'Atherosclerosis', 'Hypertension', 'Heart failure' and 'Cardiac infarction'. These searches were performed to identify the most recent research papers published within the last decade (10 years). Papers published within the past 5 years were prioritized to ensure the inclusion of the most current findings in the present review. Additionally, the inclusion of the papers published in high impact journals and those with higher citation numbers were prioritized. Through these specific criteria, the literature collection process collected ~200 reviews and research papers. To ensure the relevance of the information presented in the present review, papers published within the last 10 years were excluded if they had subsequent updates. Research articles older than 10 years were included if they keep having recent citations or ongoing significance within the field. This selection process helped us compile a comprehensive and up-to-date set of literature for the present review.

3. Effects of gut microbiota on cardiovascular diseases

Composition of microbiota and linkage with cardiovascular diseases. The gut microbiota is composed of four main phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. Saprophytes and Bacteroidetes constitute the majority of the intestinal community in healthy adults and the ratio of Firmicutes:Bacteroidetes is considered an indicator of the health of the gut microbiota (23,24). However, microbial composition varies from person to person and is dynamically sensitive to host factors and environmental parameters (25). Notably, increased abundance of host opportunistic pathogens (e.g., *E. coli*, *Clostridium lambda*, *C. carinii* and *Eggerthella lenta*) and decreased short-chain fatty acid (SCFA)-producing bacteria (e.g., *Roseburia*, *Faecalibacterium* and *Eubacterium rectale*) are both associated with an increased risk of cardiovascular diseases (26). Thus, both the type of microorganism and their relative abundance are potential risk factors that may alter susceptibility to developing cardiovascular diseases.

Atherosclerosis. Atherosclerosis is the most important and common group of atherosclerotic vascular diseases and the pathogenesis of this disease has been discussed in various theories (27), including the lipid infiltration theory, thrombosis theory, smooth muscle cell cloning theory, inflammation theory and infection theory. In recent years, most researchers have supported the endothelial injury response theory, suggesting that the main risk factors for the disease ultimately damage the intima and that the formation of atherosclerotic lesions is the result of the inflammatory response of the arteries to intimal damage (28). Inflammation plays a key role in the onset and progression of atherosclerosis (29). Currently, bacteria are considered to be a contributing factor to the disease.

In the intestine of patients with symptomatic atherosclerosis, there are changes in some genera, such as an increase in *Corynebacterium*, and in healthy controls, there were more *Rhodobacter* and *Eubacterium*. This difference suggests that changes in gut microbiota may be associated with atherosclerosis (30). In addition, some researchers have identified *Aeromonas*, *Veronella* and *Streptococcus* in atherosclerotic plaques in both animal and patient studies (31-33).

In an animal study, it was discovered that the gut microbiota's role in metabolizing and absorbing bile acids and cholesterol significantly influences blood cholesterol levels. These cholesterol levels, in turn, represent crucial factors contributing to the development of atherosclerosis (34). The mechanisms that affect cholesterol metabolism include the production of cholesterol oxidase, inhibition of hepatic lipid synthase activity, regulation of cholesterol redistribution in blood and liver and influence on bile salt hepato-intestinal circulation (35). In addition, the generation of gut microbiota-dependent trimethylamine N-oxide (TMAO) alters the main pathway of cholesterol removal in the body (36). TMAO is a substance that is metabolized in the liver after trimethylamine (TMA) is absorbed in the intestine (37). Trenteseaux *et al* (38) found that in mice, TMAO could cause intracellular accumulation of cholesterol by increasing the expression of proatherosclerotic CD36 and scavenger receptor A. TMAO also decreases Cyp7a1 expression, which is an important enzyme for bile acid synthesis, inhibits cholesterol transport and causes intracellular cholesterol accumulation and foam cell formation, thus becoming a risk factor for atherosclerosis (38).

Karlsson *et al* (30) compared the macrogenomes of gut microbiota in patients with stroke and healthy individuals and found significant differences. The macrogenome of patients with stroke had an abundance of peptidoglycan biosynthesis genes, which is the main component of the cell wall of Gram-positive bacteria, accounting for ~40-90% of the cell wall weight and supporting the structure of the cell wall (39). Peptidoglycan has pro-inflammatory properties and has been demonstrated to be an immune enhancer of the human immune system, stimulating the release of immunomodulatory substances such as TNF-α, IL-1 and IL-6 from mononuclear phagocytes and endothelial cells (40,41). By contrast, in healthy controls the gene encoding phytoene synthase is enriched, which is required for the synthesis of carotenoids (42), acting as antioxidants (43) and having anti-angina and anti-stroke effects (44), confirming that changes in human gut microbiota are associated with atherosclerosis and stroke.

In addition to correlation analyses, numerous studies are also investigating potential mechanisms that establish a connection between atherosclerosis and gut microbiota. An animal study showed that the ability of gut microbiota to reduce cholesterol levels (45). The mechanism involves: i) Co-precipitation; bacteria produce bile salt hydrolases, which break down conjugated bile salts into free bile salts. At a pH of 5.5, this process leads to the co-precipitation of cholesterol and bile acids, thereby reducing the ability of cholesterol entering the bloodstream (46); ii) Cholesterol uptake by bacteria; bacterial cells uptake cholesterol, representing the primary ways of cholesterol removal by these microorganisms. While the capacity for cholesterol uptake varies among bacterial strains, this process contributes to reducing serum cholesterol concentrations (47). These mechanisms associated with gut microbiota and atherosclerosis also suggest potential therapeutic targets for the prevention and treatment of atherosclerosis.

Hypertension. Hypertension is a progressive cardiovascular syndrome with both genetic and environmental causes, leading to changes in cardiac and vascular function and structure (48). Except for genetic causes and environmental factors, gut microbiota also contributes to the progression of hypertension (49). The first evidence suggesting the role of the gut microbiota in development of hypertension was the effect of antibiotic treatment on blood pressure observed in rats (50). In 2015, Yang *et al* (51) reported that dysbiosis of gut flora may be associated with hypertension with the finding of increasing of fecal microbiota variability in both rat model and patient. It has been reported that the microbial profiles of the pre-hypertensive and hypertensive populations were similar, with significant overgrowth of *Prevotella* and *Klebsiella* in both groups. These findings were established through experiments involving the transplantation of fecal microbiota from patients with hypertension into germ-free mice (52). The abundance of butyrate-producing *Odoribacter* spp. and butyrate production were inversely correlated with blood pressure levels in women at higher risk of developing pregnancy-induced hypertension and preeclampsia (53,54).

Antibiotics for hypertension are a new discovery in the cardiovascular field and are not yet well supported by clinical studies (55). An effective animal study conducted on rats demonstrated the potential use of broad-spectrum antibiotics, including vancomycin, rifampicin and levofloxacin, in aiding the treatment of resistant hypertension, suggesting indirect evidence that antibiotics can improve gut microbiota and initiate potential blood pressure regulatory mechanisms to decreasing blood pressure (56). However, the mechanism of antibiotic against hypotension has yet to be investigated.

The mechanisms by which gut microbiota affects hypertension are complex. Studies found that short chain fatty acids (SCFAs) produced by the gut microbiota regulate blood pressure through various receptors and pathways (57,58). Additional animal research conducted on rats indicated that the inhibition of intestinal sodium transporters might offer potential benefits in ameliorating cardiorenal damage associated with essential hypertension (59). Angiotensin-converting enzyme 2 (ACE2) plays a significant role in the pathophysiology of hypertension (60). It has been demonstrated that ACE2 serves

as a regulator of gut microbiota homeostasis, inflammation and genetic susceptibility to colitis (61,62).

Heart failure. A growing number of studies support the role of the gut in the pathogenesis of heart failure (63,64). Under normal circumstances, the gut microbiota maintains a balanced state and performs a crucial role in supporting the integrity and functionality of the intestinal barrier (65). However, in patients with heart failure, the intestinal tract function is altered and dysbiosis of the gut microbiota occurs due to factors such as congestion of the visceral circulation and immune deficiency of the host (66). It has been shown that patients with chronic heart failure may have excessive growth of pathogenic gut microbiota and increased intestinal permeability, which is related to the severity of heart failure (67).

In addition to the clear link between TMAO and risk of atherosclerotic cardiovascular disease, TMAO levels have recently been associated with the development and poor prognosis of patients with heart failure (35). Previous studies have shown that circulating TMAO levels are higher in patients with heart failure compared with age- and sex-matched subjects without heart failure (68,69). In addition, the study observed significantly strong adverse prognostic values associated with elevated plasma TMAO levels in a group of stable patients with heart failure, which were incremental to traditional risk factors, cardiac and renal indices and systemic inflammatory markers (68). However, the mechanisms explaining the elevated TMAO levels in patients with heart failure remain to be elucidated.

Cardiac infarction. Compared to normal subjects, patients with myocardial infarction have high levels of phosphatidylcholine metabolites, which are plasma choline, TMAO and betaine, and these three substances are significantly associated with the development of cardiovascular diseases (70). In both patients and mice, their metabolism, which involves the dietary phosphatidylcholine pathway, relies on the active participation of gut microbiota (71). In addition, an association between gut microbiota and myocardial infarct severity has been reported in rats (71-73). The use of broad-spectrum antibiotics has been shown to affect the levels of analytes produced during leptin and aromatic amino acid catabolism, which are associated with a reduction in myocardial infarct size. In addition, in rodent model studies, delivery of *Lactobacillus plantarum* was correlated with a significant infarct size reduction following myocardial infarction relief and improvement in left ventricular function. Another study showed that administration of *Lactobacillus rhamnosus* GR-1 attenuated left ventricular hypertrophy and heart failure after myocardial infarction in rats (74). These observations not only demonstrate the relationship between gut microbiota and myocardial infarction, but also suggest that altering the composition of the flora can be a potential therapeutic strategy.

4. Effects of gut microbiota on metabolites related to cardiovascular diseases

Cholesterol. The gut microbiota can influence the regulation of cholesterol metabolism in the liver (75,76) and plays a role in altering bile acids, which can affect systemic cholesterol levels (77). Bile acids, catalyzed by the rate-limiting enzyme cholesterol 7-α-hydroxylase (78), are the main metabolites of cholesterol in the liver and contribute to the absorption of fats and lipophilic vitamins (79), as well as to the regulation of lipid, glucose and energy metabolism (80,81). Primary bile acids are conjugated with the amino acids taurine or glycine to form bile salts, which are secreted into the bile and stored in the gallbladder until they are released into the small intestine, where they emulsify fats and form micelles that are absorbed by enterocytes (79). In the intestine, primary bile acids such as cholic acid and chenodeoxycholic acid (CDCA) are deconjugated by the gut microbiota and bile salt hydrolase to form secondary bile acids including deoxycholic acid, lithodeoxycholic acid and ursodeoxycholic acid (82). The ratio of primary to secondary bile acids may be associated with the development of hypercholesterolemia and cardiovascular diseases. For example, one study (83) found that patients with heart failure had reduced plasma primary bile acids and a higher ratio of secondary to primary bile acids. Bile acids may also play a role in cardiovascular function by modulating channel conductance and calcium dynamics in sinoatrial and ventricular cardiomyocytes and by regulating vascular tone to reduce heart rate (83). Furthermore, it has been proposed that an unbalanced and unhealthy gut microbiota, which regulates the bile acid ratio, may lead to a decrease in secondary bile acids, which may increase primary bile acids, such as CDCA, activating farnesoid X receptor and downregulating bile acid secretion, thereby increasing cholesterol and cardiovascular diseases development. Therefore, the gut microbiota and the underlying mechanisms involved require further study.

It has long been known that certain gut microbiota has the ability to convert absorbable cholesterol into coprostanols, which are reduced non-absorbable sterols that are excreted in the feces (84-86). Coprostanol production in humans begins at 6 months after birth (87) and is sex-dependent, with young women possessing a higher production compared with young men (88). Furthermore, the conversion of microbial cholesterol to coprostanol in human populations is currently considered to be bimodal, with high converters converting almost 100% cholesterol and low converters converting less than one-third of the fecal neutral sterol content (89,90). To date, isolated cholesterol-reducing strains have been limited to the genera *Eubacterium* (*E. coprostanoligenes*) and *Bacteroides* (*Bacteroides* sp. strain D8) (91,92), but a number of remain to be discovered. In rabbit models with diet-induced hypercholesterolemia, oral administration of coplanar alkanoic bacteria caused a significant decrease in plasma cholesterol levels that lasted for >34 days after the last bacterial feeding (93). Clinical studies have extensively investigated cholesterol metabolism in the intestine (87,89,91,94,95). These studies have indicated an inverse relationship between human serum cholesterol levels and the ratio of human fecal coprostanol to cholesterol (96,97). However, these studies used very small sample sizes, limited variation in sample populations and lack of diverse population backgrounds, which reduces the generalizability of the studies. Attempts to isolate the specific microbial strains responsible for copolymer/cholesterol conversion in these studies were also unsuccessful, making it difficult to continue the mechanistic studies that followed. In addition, the genes or enzymes

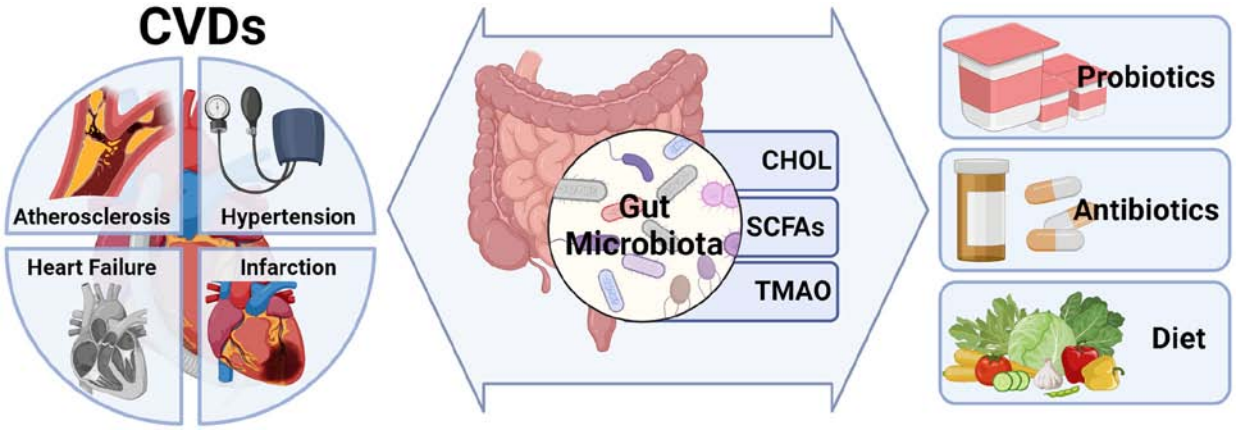

Figure 1. The association between the gut microbiome and cardiovascular diseases, along with potential interventions. Microbiome dysbiosis can cause an increase in opportunistic pathogens or a decrease in SCFA-producing bacteria, which may lead to an accumulation of CHOL and TMAO and a decrease in SCFA, all of which can aggravate the progression of CVDs. Conversely, during the progression of CVDs, microbiome dysbiosis can be induced or exacerbated by inflammation and altered gastrointestinal blood flow in the body. Interventions such as probiotics, antibiotic drugs and dietary modifications that modulate the gut microbiome offer indirect ways to influence the progression of CVDs. SCFA, short chain fatty acid; CHOL, cholesterol; TMAO, trimethylamine-N-oxide; CVDs, cardiovascular diseases.

involved in the conversion of cholesterol to coplanar alcohols in the intestine remain unknown (98).

Short chain fatty acids (SCFAs). SCFAs are metabolites derived from microbial activity during the fermentation of complex carbohydrates (99,100). These compounds exert influence on microbiota composition and gut motility, thereby affecting various host processes (101). The most abundant SCFAs are acetate, propionate and butyrate (100). Phylum Bacteroidetes members produce acetate and butyrate, while Phylum Siliques produces butyrate. SCFAs are also positively correlated with *Alistipes putredinis*, *Bacteroides* spp, *Roseburia*, *Eubacterium rectale* and *Faecal prausnitzii* (102). In addition, SCFAs play a pivotal role in preserving intestinal barrier integrity by modulating the expression of tight junction proteins (103). SCFAs can also reduce serum lipid levels by blocking cholesterol synthesis and transferring it to the liver. Therefore, they are considered as a protective factor in the progression of cardiovascular diseases. The presence of SCFA-producing bacteria is diminished due to the activation of G protein-coupled receptor 41 (104) observed in certain cases of cardiovascular diseases (30,105). This reduction is also apparent in the dysbiosis of the gut microbiota observed in hypertensive patients (106). Therefore, their role *in vivo* and their targets need to be further examined.

TMAO. TMAO is identified as a risk factor contributing to the development of cardiovascular diseases (71,75). This compound originates from various sources, including red meat, eggs, fish and vegetables (107). Compounds such as choline, betaine, phosphatidylcholine, lecithin and L-carnitine (71,108,109) found in the diet are implicated in the production of TMAO. A clinical study revealed that elevated levels of TMAO are linked to an increased risk of death, nonfatal myocardial infarction, or stroke (110). An *in vitro* study revealed the ability of the gut microbiota to produce choline through the enzyme phospholipase D (111). TMA molecules, produced by microbiota, can enter the circulation of the host and subsequently reach hepatocytes. Within these hepatocytes, they undergo metabolism to form TMAO through the action of flavin-containing monooxygenases (FMO) encoded by the FMO gene. These enzymatic reactions occur predominantly in the liver, kidneys and other tissues (109). Elevated production of TMAO has been shown to affect blood lipids (112) and is associated with an increasing risk of cardiovascular diseases (71,108,113). In situations involving heightened intestinal permeability, TMAO exhibits associations with C-reactive protein and endothelial dysfunction. In addition, increased serum levels of LPS endotoxin (114) are also linked to TMAO. Moreover, TMAO has been observed to induce calcium release and increase platelet hyperreactivity (115), potentially influencing the progression of cardiovascular diseases.

The gut microbiota markedly influences the production of TMAO. Healthy individuals have a large number of TMAO-producing microorganisms, with a 2:1 ratio of *Firmicutes* to *Bacteroidetes* (116). TMAO production was found in 102 genomes covering 36 species, including *Firmicutes*, *Aspergillus* and *Actinobacteria* (107). It has been shown that *Firmicutes* and *Proteobacter* are associated with the production of TMA (114). One study found that eight species from *Stachybotrys* and *Proteobacter* consumed >60% of the choline used for TMA production (117). *Acinetobacter*, *Sporotrichum*, *Prevotella* (107) and *Micrococcus* (118) are intestinal species capable of producing higher TMAO than other species and they are associated with atherosclerotic cardiovascular diseases. Therefore, metabolites including choline, TMAO and betaine can help predict the development of cardiovascular diseases. As a potential therapeutic pathway, probiotic or pharmacological interventions can be used to inhibit or block specific metabolic pathways and reduce TMAO-producing microbes (119).

5. Potential therapeutics

Probiotics. The role of lactobacilli with probiotic effects such as immunomodulation, absorption promotion and disease prevention in the intervention of hyperlipidemia and hypertension is of interest. Previous animal studies have identified a variety of lactobacilli with antihypertensive effects, the main

one being *Lactobacillus swiss* (120,121). Experiments in mice suggest that *Lactobacillus rhamnosus* can lower cholesterol and improve non-alcoholic fatty liver disease (122).

There have been reviews on the role of probiotics in regulating blood lipids (123,124). Entry of probiotic flora (mainly *Bifidobacterium*, *Lactobacillus* and *Propionibacterium*) into the intestine from dietary sources leads to an increase in SCFAs-producing flora and a decrease in the number of protein-producing flora, thus promoting an increase in the synthesis of SCFAs and butyrate and a decrease in protein synthesis, leading to changes in carbohydrate metabolism. Probiotics have been proven to regulate blood lipids, but their mechanism has not been determined yet. From a certain perspective, it is suggested that Lactobacillus and other probiotics facilitate the metabolism of cholesterol during their growth, consequently leading to a reduction in cholesterol levels (125). Additionally, the hypolipidemic effect attributed to lactic acid bacteria has been linked to the modulation of 3-hydroxy-3-methylglutaryl CoA reductase expression, which is the rate-limiting enzyme in cholesterol synthesis.

Probiotics and their fermented products (e.g., yogurt) have been shown in a number of studies to have significant antihypertensive effects. Khalesi *et al* (126) showed that blood pressure (both systolic and diastolic) was significantly lower in individuals whose intake was ≥1 billion probiotic colonies per day. This indirect evidence indicated that the gut microbiota plays a crucial role in maintaining stability in blood pressure. It suggests the mechanism underlying the hypotensive effect of probiotic products based on two primary aspects: i) The hypotensive effect of probiotic products is attributed to the hydrolysis of extracellular proteases and peptidases (such as carboxypeptidase and aminopeptidase). This process leads to the liberation of peptides from food proteins, such as milk protein, which exhibit hypotensive activity. These released peptides, such as ACE inhibitory peptide and opioid active peptide, contribute to the observed antihypertensive effects; ii) Certain probiotic organisms, particularly *Lactobacillus*, can transit to the intestinal tract as live bacteria. These organisms facilitate the intestinal absorption of specific minerals known to regulate blood pressure. Through this action, they demonstrate antihypertensive effects. Therefore, the application of probiotics to modify the composition of the gut microbiota is a potential therapeutic target for cardiovascular diseases.

Dietary intervention. Dietary interventions to correct intestinal dysbiosis could be a therapeutic strategy for cardiovascular disease. Indeed, a heart-healthy diet, abundant in vegetables and high in fiber, is regarded as advantageous for the cardiovascular system (127). Certainly, lifestyle can markedly impact bacterial transmission, particularly environmental sanitation practices and drinking water treatment methods. These aspects play a crucial role in influencing alterations observed in the gut microbiota. The Mediterranean diet is a combination of fish, beans, vegetables, fruits, nuts, olive oil and a moderate amount of red wine (128,129). This diet has become particularly popular in recent years and is considered to prevent cardiovascular disease and reduce cardiovascular mortality in both men and women (130,131). For most individuals, a Mediterranean-style diet is an effective and viable way to prevent heart disease and other health problems.

Antibiotics. The microbiota can be regulated with antibiotics and used to restore the microbiome and prevent cardiovascular disease. A study showed that oral vancomycin reduced infarct size and improved post-infarct cardiac function in rats (72). Furthermore, in an experimental mouse model, antibiotics reduced bacterial translocation, inflammation and myocardial injury (132). In one study, a 69-year-old patient with a long history (44 years) of hypertension and resistant hypertension showed reduced blood pressure after combination antibiotic therapy (133). Moreover, a two-month dietary intervention involving a broad-spectrum antibiotic cocktail successfully reversed vascular dysfunction induced by a Western diet in mice. This reversal represents a crucial preclinical step in preventing the progression of cardiovascular disease (134). In addition, a study on rats showed that vancomycin administration was associated with a reduction in myocardial infarct size and improved recovery of mechanical function after ischemia, while effectively reducing the total number and group of intestinal microbes (72).

Collectively, various clinical and animal studies have strongly indicated the involvement of gut microbiota composition in acute myocardial infarction. However, the specific direction of microbiota alterations and the potential metabolic or inflammatory pathways involved remain poorly understood.

6. Conclusions

The relevance of gut microbiota to disease is in its infancy and, similarly, the relevance to cardiovascular disease is still at an early stage and a number of key questions need to be explored. Increasing evidence indicates an association between the gut microbiome and the incidence of cardiovascular disease. Studies suggest that the microbiota interacts with the host through multiple pathways. Abnormal gut microbiota composition or microbial metabolites may be responsible for altered cardiovascular disease risk and its associated pathological changes (Fig. 1). Thus, the potential role of the gut microbiota could be utilized in the future to develop novel therapeutic strategies for the prevention and treatment of cardiovascular disease.

As a potential therapeutic strategy, the feasibility of gut microbiota transplantation has been demonstrated in short-term studies, but long-term trials are needed to evaluate the safety and efficacy. Modulation of gut microbiota as a potential therapeutic target for cardiovascular disease needs to be further evaluated and the therapeutic indications and specific strategies need to be further demonstrated.

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Availability of data and materials

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Authors' contributions

ZFN, LL, KQC and GLW conceived and supervised the present study. SWX, YC, YL and DWS prepared the first draft of the manuscript. XPY, ZWu, YLS, ZhiW, JL and ZFN reviewed the manuscript for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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