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Review Article

Dysbiosis—An Etiological Factor for Cardiovascular Diseases and the Therapeutic Benefits of Gut Microflora

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The human gut is colonized by a variety of microorganisms especially bacteria. There are multiple evidences that gut microflora dysbiosis is a novel risk factor for development of various intestine-related diseases such as irritable bowel syndrome and inflammatory bowel disease as well as nonintestinal diseases including obesity, type II diabetes, and cardiovascular diseases. A mutual relationship among the host's immune system and the metabolites produced by the gut microflora, including trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids, is present. Alterations in the host-microbial interaction lead to impaired homeostasis and thus contribute towards the activation of several pathways that causes progression of cardiovascular diseases. This review summarizes the role of gut microflora dysbiosis in the development and progression of atherosclerosis, coronary artery disease, and hypertension. Dysbiosis has been implicated in the pathogenesis of atherosclerosis by TLR activation, intracellular Ca^{2+} release, FXR-induced signalling, and decreased removal of cholesterol from peripheral macrophages, while in hypertension the mechanism involved is prolonged haemodynamic effects of angiotensin-II and oxLDL-induced hypertension. In fact, CVDs are the leading cause of mortality across the globe; thus, targeting the gut microflora in the treatment of these diseases along with the conventional therapy can markedly reduce the cardiovascular disease burden. The gut microbiota-targeted treatment including prebiotics, probiotics, and postbiotics can be therapeutically beneficial. In future, the heart-gut axis can be presented as a novel and clinically relevant area for research.

1. Introduction

The human body acts as a host for trillions of the microbes leading to the development of an ecosystem that forms a link within and without the human body. These microbes are known as microflora. Bacteria are the most prominent among the microflora. The microflora of the gastrointestinal system is referred as gut microflora and most of which resides in the terminal part of the gut, i.e., the colon. These microbes play a vital role in the nutrition as well as the maturation of the immune system and maintaining the immunity of the body [1]. The bacteria of the gut microflora are diverse in nature with most of the bacteria from the Bacteroidetes and Firmicutes phyla [2]. The ratio of the bacterial cells to the human cells is estimated to be 1 : 1 [3]. In normal physiology, the gut microflora remains in symbiosis with the body. Certain conditions including irrational use of antibiotics, alcohol intake, nonvegetarian diet, accidental chemical consumption, and poor dental hygiene lead to dysbiosis which is found to be linked with the development and exacerbation of various neuronal disorders such as schizophrenia, inflammatory conditions such as inflammatory bowel disease, and metabolic disorders including type I diabetes mellitus [4, 5]. It is the alteration in the composition of the human gut microflora caused by factors such as stress, diet, illness, lifestyle patterns, antibiotic use, toxins, and pathogens [6]. Recent studies have proved the link of gut microflora dysbiosis with certain cardiovascular diseases especially atherosclerosis, coronary artery disease, and chronic heart failure via heart-gut axis [7–9]. The metabolites produced by the gut microflora serve a crucial role in predicting, enhancing, and alleviating cardiovascular diseases. Trimethylamine-N-oxide (TMAO) and short-chain fatty acids (SCFAs) are the major metabolites produced by the gut microflora [10–12]. High dietary intake

of L-carnitine, choline, and phosphatidylcholine leads to their conversion into TMA [13]. The TMA is then transported to the liver where it is converted to TMAO by the hepatic FMO3 [14, 15]. TMA is reduced by enzyme TMAO reductase present in *Vibrio* and *Shewanella* spp. TMAO induces platelet aggregation which serves as a critical pathological feature in the atherosclerotic event as depicted in Figure 1 [13, 16]. SCFAs are the end products when gut microflora metabolizes the dietary fibre. Chemically, these are carboxylic acids including acetate, propionate, and butyrate [17]. They have been found to enter into bloodstream through portal vein and alter physiological processes via binding to G-protein-coupled receptors. SCFAs have diverse range of physiological actions as they maintain the integrity of the small and large intestines. They are found to reduce blood pressure and lower the blood cholesterol levels and are therefore proven to mitigate the risk of cardiovascular disease [18, 19].

2. Composition and Development of Gut Microflora

Human gut microflora consists a wide range of bacteria, archaea, and eukarya as listed in Table 1 [20]. On an average, it is estimated that 1000-1150 microbial species reside in the human gut. A study has been conducted on the stool sample of 124 healthy, overweight, obese, and patients of inflammatory bowel disease (IBD) to identify the gene database of gut microflora by the international metagenomics of human intestinal tract project and reported 3.3 million nonredundant microbial genes which were derived from 576.7 gigabases of sequence [2, 21]. The data from MetaHit and the Human Microbiome Project estimated that 2172 species reside in human gut microflora which was broadly categorized into 12 phyla. Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes are the predominant. Others include Cyanobacteria, Fusobacteria, and Verrucomicrobia [22, 23]. The gut microflora begins to develop before birth. After birth, the gastrointestinal tract begins to colonize [24]. Maternal flora, mode of delivery, breast-feeding, age, diet, illness, and exposure to antibiotics are the factors that tend to have an impact on the development of gut microflora [20]. Mode of delivery greatly affects the composition of gut microflora. Infants delivered by normal vaginal delivery possess lactobacilli in abundance during the first few days, and later on, colonization of *Prevotella* and *Atopobium* occurs. Infants delivered by C-section consist of the colonization of the *Bacteroides* genus [25–28].

Diversity of gut microflora tends to increase during the 1st year of birth and resembles to that of an adult gut microflora composition by the age of 2.5 years [24, 29, 30]. By age, the composition of gut microflora also alters as in the case of individuals above 65 years of age, where Bacteroidetes and *Clostridium* cluster IV are predominant, whereas in individuals of young age, *Clostridium* cluster XIVa is in abundance [2, 31]. Diet also serves as a critical factor in the colonization of various species in the human gut. For example, a study conducted on rural children in Burkina Faso in Africa stated the abundance of bifidobacteria which helps in the digestion of a plant-rich diet among these children [32, 33].

3. Gut Microflora Dysbiosis

The gut microflora is important in the stabilization of the homeostatic functions of host via maintaining digestion, metabolism, and immune system. It also helps in maintaining the integrity of the gut. Therefore, dysbiosis leads to abnormalities in the host's homeostasis and plays a role in the pathophysiology of various diseases. Dysbiosis of gut microflora is linked to the development and progression of cardiovascular diseases. A brief correlation between gut microflora dysbiosis and the development of cardiovascular disease is described in Figure 2. Dysbiosis does not develop a cause-and-effect relationship but states that microflora dysbiosis is the major contributor in various ailments [34]. On an average, cardiovascular diseases (CVDs) are responsible for 31% of deaths across the globe [35]. In animal models with dysbiosis, the most commonly observed cardiovascular disease was hypertension [36, 37] followed by endothelial dysfunction [38] and ventricular hypertrophy [9, 39].

4. Role of Gut Microflora in Atherosclerosis and Coronary Artery Disease

In recent times, a correlation among the gut microflora and pathophysiology of atherosclerosis and coronary artery disease has been developed. Jonsson and Backhed detected the gut bacterial DNA in the atherosclerotic plaques [40]. The proposed mechanisms of the link of gut microflora with atherosclerosis include

(1) Systemic inflammation

(2) Production of harmful metabolites

(3) Imbalance in the lipid metabolism

(4) Infection

The gut microflora has been found to play a vital role in the metabolic processes of the body including uric acid metabolism, cholesterol metabolism, and oxidative stress which can lead to the formation of plaques in the blood vessels. In patients with coronary heart disease, significant alterations in the composition of gut microbiota have been observed. A study was conducted in 2016 to determine the differences in the bacterial composition of the gut between coronary heart disease patients and normal volunteers using terminal restrictive fragment length polymorphism and 16S rRNA which revealed a significant rise in the number of mature lactobacilli and decline in the number of *Bifidobacterium* and *Prevotella* [41]. The metabolites which are thought to be involved in the abovementioned mechanisms are TMAO, SCFAs, toll-like receptors (TLR), lipopolysaccharides, and bile acids. A study conducted on 1876 stable subjects revealed the positive correlation among the plasma level of TMAO and the size of atherosclerotic plaque. TMAO increases the expression of CD36 receptor and scavenger receptor A and leads to the accumulation of cholesterol. TMAO has also been found to reduce the expression of Cyp7al, which is the major enzyme for bile synthesis,

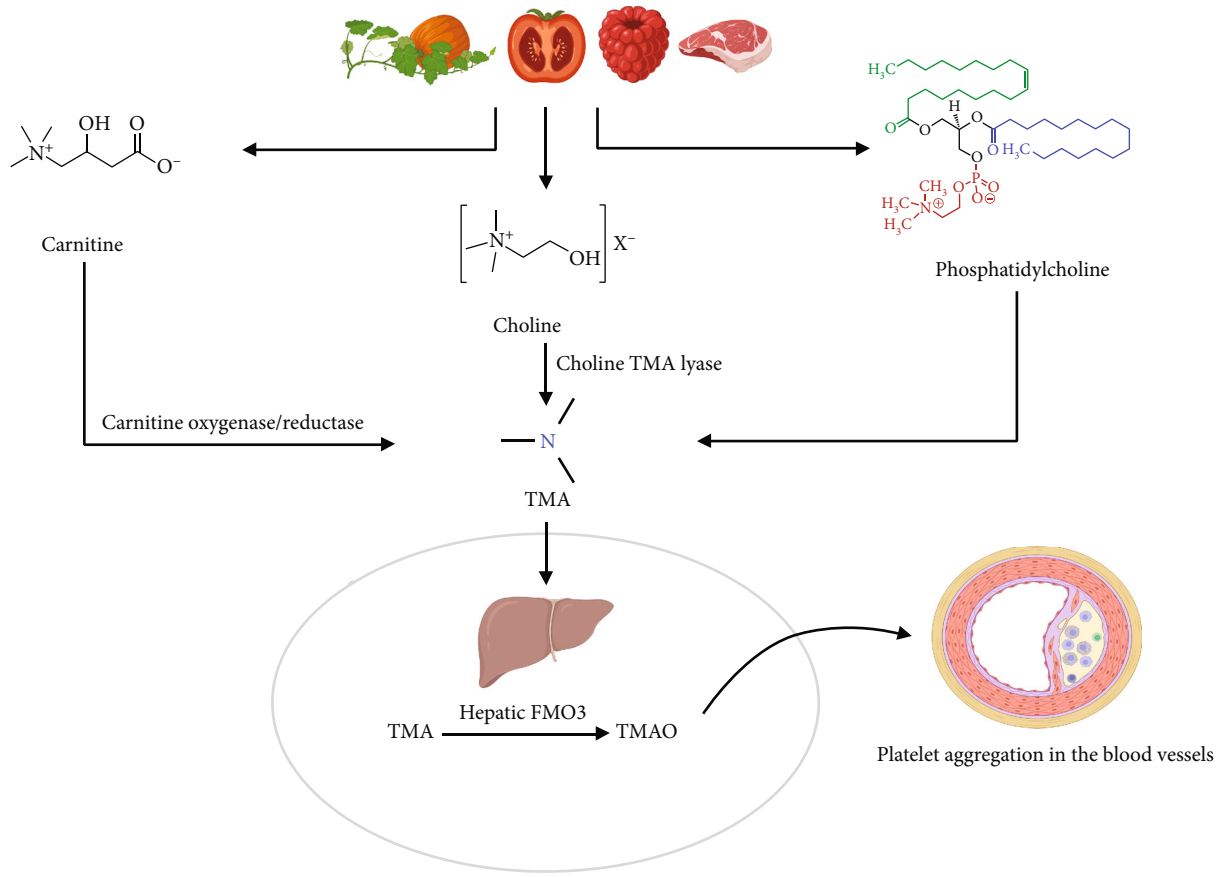

Figure 1: Platelet aggregation mediated by TMAO produced by dietary intake of carnitine, choline, and phosphatidylcholine.

leading to the inhibition of cholesterol transport, and cause the accumulation of cholesterol and formation of foam cells [42]. The inhibition of reverse cholesterol transport by TMAO results in the decreased removal of cholesterol from peripheral macrophages and alters the atheroprotective properties of high-density lipoproteins which in turn lead to the development of atherosclerotic plaques. A positive correlation was demonstrated among the serum TMAO levels and atherosclerotic plaques. Induction of atherosclerosis via increased cell formation is also seen as TMAO has potential role in the inhibition of reverse cholesterol transport system and the accumulation of macrophage cholesterol by inducing the expression of scavenger receptor, namely, differentiation 36 and scavenger receptor A [43]. The role of bile acids in the progression of atherosclerosis and coronary artery disease is not yet clearly understood. Direct and indirect mechanisms have been proposed as key factors in the development of atherosclerosis by bile acids. In the direct mechanism, bile acids are thought to interact with myocytes and affect the contractility and excitability of heart muscles. In the indirect mechanism, bile acids are thought to alter the metabolic pathways via FXR-induced signalling [7]. The primary bile acids are produced from cholesterol, and gut microbiota catalyze their deconjugation via bile salt hydrolase (BSH) to synthesize secondary bile acids as mentioned in Table 2. The secondary bile acids have a significant atheroprotective activity. The dysbiosis of gut microflora leads to decreased BSH activity leading to variations in the atheroprotective activity of bile acids and thus promoting the formation of atherosclerotic plaques [44]. The mechanism of infection involving as a link between atherosclerosis and gut microflora dysbiosis can be classified into the following two categories:

4.1. Direct Infection. It has been estimated that more than 50 different species of bacterial DNA have been observed in the plaques [45]. The Proteobacterium phylum was found to be most common. Other bacteria include Lactobacillales, *Collinsella*, Enterobacteriaceae, and *Streptococcus* spp. Various bacteria such as *Clostridium* and Lactobacillales can be used as a diagnostic marker for the detection and diagnosis of coronary artery disease [46].

4.2. Indirect Infection. Microorganisms contribute to the development of atherosclerotic plaques via the production of inflammatory cytokines. An alteration in the gut microflora in murine models by using antibiotics results in imbalance of lipid metabolism [2]. Uric acid is found to be another independent risk factor for the development of atherosclerosis [47]. Increased levels of uric acid are related with oxidative stress, vascular endothelium dysfunction, inflammatory reactions, and the development of atherosclerosis. Increased levels of serum uric acid in coronary heart disease patients are related with the gut microbiota

Table 1: Microorganisms associated with cardiovascular diseases.

Microorganisms associated with cardiovascular diseases
(1) *C. pneumoniae*
(2) *P. gingivalis*
(3) *Enterobacteriaceae*
(4) Human immunodeficiency virus
(5) SR1
(6) Lactobacillales
(7) *Streptococcus parasanguinis*
(8) *Collinsella*
(9) *Veillonella*
(10) *Aggregatibacter*
(11) Firmicutes
(12) Bacteroidetes
(13) Actinobacteria
(14) Fusobacteria
(15) Proteobacteria
(16) Spirochaetes
(17) Chloroflexi
(18) Gemmatimonadetes
(19) *Neisseria polysaccharea*
(20) *Neisseria subflava*
(21) *Waddlia chondrophila*
(22) *Prevotella*
(23) *Beggiatoa* sp. P5
(24) *Alloprevotella rava*
(25) *Megasphaera micronuciformis*
(26) *Acidovorax* sp. CF316
(27) *Atopobium parvulum*
(28) *Solobacterium moorei*
(29) *Clostridium difficile*
(30) Influenza A
(31) Cytomegalovirus
(32) Candidte division TM7 single-cell isolate TM7c
(33) Tenericutes
(34) *H. pylori*
(35) Deinococcus-Thermus

dysbiosis. Levels of uric acid are inversely related to circulating carotenoids. A study has demonstrated that gut microflora in atherosclerosis patient was rich in genes that encode peptidoglycan biosynthesis, whereas in healthy volunteers, the gut microflora was rich in genes that encode carotenoids. Thus, gut microflora dysbiosis decreases the bacteria that encode for carotenoids and thus increase the oxidative stress which ultimately promotes the development of atherosclerosis [41].

5. Role of Gut Microflora in Hypertension

Hypertension is considered to be a modifiable risk factor for various cardiovascular diseases [14]. It is the leading cause of disability and mortality in the developed countries and affected 1.13 billion individuals across the globe in 2015 [48, 49]. The findings form faecal microbiota transplantation experiments have developed a potential link between the gut microflora dysbiosis and hypertension [50]. As mentioned in Table 3, in prehypertensive and hypertensive patients, the lower gene richness and α-diversity had been observed as compared to normotensive individuals. The higher percentage of *Prevotella* had also been reported. SCFAs are produced by the Bacteroidetes and Firmicutes bacteria. In a study of hypertensive animal models, it has been reported that Firmicutes/Bacteroidetes (F/B) ratio is found to be elevated [51–54]. The salt intake is also a factor for the development of hypertension. The gut microflora is also linked with salt sensitivity as the absorption of the sodium mainly occurs in the intestine. In the animal models with high salt-induced hypertension, the bacteria of the *Erwinia* genus and the Corynebacteriaceae family were found to be increased [48]. In the hypertension, the TMAO does not directly affect the levels of the blood pressure, whereas it prolongs the haemodynamic effects of the angiotensin-II [14]. Specifically, the gut microflora dysbiosis is found to be linked with the hypertension via oxLDL-induced vasoconstriction [55, 56]. The abrupt imbalance between the vasoconstriction and vasodilation is the crucial pathophysiological factor in promoting the hypertension, as it has been stated earlier that the gut microflora dysbiosis creates the oxidative stress via proinflammatory cytokines expression. This oxidative stress leads to the oxidation of LDL. Increased levels of oxLDL result in the decreased generation of vasodilators and stimulated production of vasoconstriction which in turn leads to hypertension. Nitric oxide (NO) is a potential endogenous vasodilator produced from L-arginine by NO synthase enzyme in the body via oxidation reaction [57]. The increased levels of oxLDL result in the inhibition of the activity of the NO synthase enzyme leading to the underproduction of NO which ultimately leads to less vasodilation and therefore causes hypertension. oxLDL also upregulates the endothelin-1 expression. The higher levels of endothelin-1 act on endothelin receptor A (ET_A) present on the vascular smooth muscle cells and induce vasoconstriction and ultimately result in hypertension [44, 58].

6. Emerging Role of Gut Microflora in the Treatment of Cardiovascular Diseases

As a clear role of gut microflora dysbiosis has been developed by numerous studies, therefore the gut microflora emerges out to be a potential target for the novel therapy of cardiovascular diseases for the improved therapeutic outcomes.

6.1. Dietary Interventions. Targeting the gut microflora via dietary interventions is a key point in improving the health status of patient with cardiovascular disease. Intake of the whole grains in the diet reduces the mortality from cardiovascular diseases [60]. Zinc is a cofactor for various commensal bacterial proteins playing a role in the metabolism [61]. Deficiency of zinc leads to higher β-diversity [62].

6.2. Prebiotics. These are the oligosaccharides which are selectively fermented with bacteria such as lactobacilli and bifidobacteria [2, 63]. Gan et al. reported the reduction in the infarct size and improved cardiovascular functioning after administration of *Lactobacillus rhamnosus* GR-1 [64]. Some studies demonstrated that prebiotics also regulate the

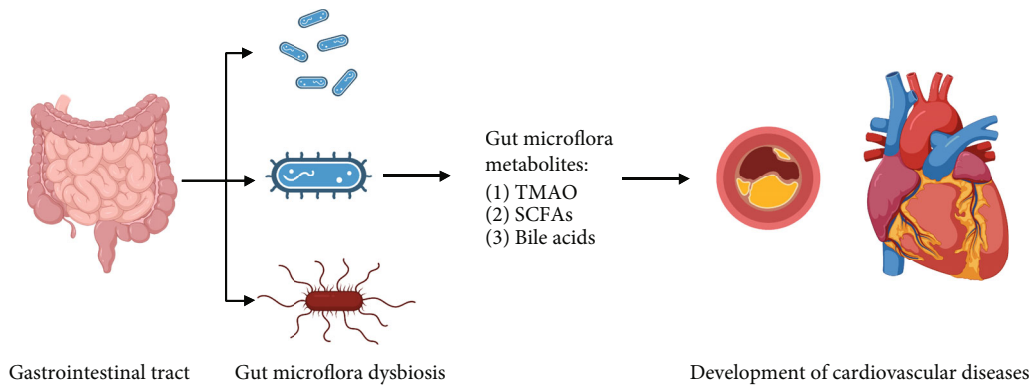

Figure 2: Depiction of dysbiosis correlation with the development of cardiovascular disease.

Table 2: Overview of the association of gut microflora dysbiosis with atherosclerosis.

Gut bacteria involved in atherosclerosis	(1) *Streptococcus* (2) Enterobacteriaceae (3) Lactobacillales (4) *Bacteroides* [48]
Metabolites involved in atherosclerosis	(1) TMAO (2) SCFAs such as acetate, propionate, and butyrate (3) Bile acids [48]
Mechanisms involved in atherosclerosis	(1) TLR activation (2) Intracellular Ca^{2+} release (3) FXR-induced signalling (4) Increased expression of CD36 receptor and scavenger receptor A [42] (5) Decreased removal of cholesterol from peripheral macrophages (6) Imbalanced uric acid metabolism

Table 3: Overview of the association of gut microflora dysbiosis with hypertension.

Gut microflora involved in hypertension	(1) Decreases α-diversity (2) *Prevotella* (3) *Erwinia* (4) Corynebacteriaceae (5) Increased Firmicutes/Bacteroidetes (F/B) ratio [48]
Metabolites involved in hypertension	(1) SCFA (direct) (2) TMAO (indirect)
Mechanisms involved in hypertension	(1) oxLDL-induced hypertension [44] (2) Prolonged haemodynamic effects of angiotensin-II [59]

metabolism of lipids to maintain the well-being. Other commonly administered bacteria as prebiotics are *Bifidobacterium*, *Enterococcus*, and *Streptococcus* [48].

6.3. Probiotics. These are the live microorganisms that are helpful in maintaining the gut microflora [65]. A study conducted on 36 active smokers who were administered with probiotic containing the *Lactobacillus plantarum* reported reduced adhesion of isolated monocytes and reduction in the levels of blood pressure as well as proinflammatory cytokines which demonstrated its role in preventing atherosclerosis [2, 66]. The atherosclerotic lesions have been diminished by *Akkermansia muciniphila* via the amelioration of metabolic endotoxin-induced inflammation by recovery of gut barrier in $ApoE^{-/-}$ mice being treated by oral gavage for eight weeks on a daily basis [67, 68].

6.4. Postbiotics. These are the metabolic products produced by microorganisms and have shown a positive effect on the well-being of an individual. They include SCFAs, exopolysaccharides, enzymes, and cell wall fragments. SCFAs are widely studied and being used for cardiovascular disease treatment [69]. Decrease in blood pressure is shown by an acute bolus of SCFA [70]. As compared to probiotics, postbiotics have

an advantage as they are the bacterial metabolites which are simple to control compared with live cells [68].

6.5. Antibiotic-Like Substance. These are derived from food, plants, or herbs and possess antimicrobial activity. Predominantly, they include herbs and spices [71]. Garlic has been used in food from ancient times. It contains allicin which has been confirmed to alter the gut microflora, and it reduces TMAO generation [72]. The colonization of *Faecalibacterium prausnitzii* and *Akkermansia* spp. is found to be promoted by administering raw garlic juice [68]. Resveratrol is found to promote the colonization of *Lactobacillus* and *Bifidobacterium* spp. [73].

6.6. Faecal Microbiota Transplantation (FMT). It is a technique of transferring the bacteria from healthy individual to the gut of patients [74]. It is generally done by the administration of faecal solution of a healthy individual to patient. In an animal model of autoimmune myocarditis, FMT is found to be effective by counteracting the dysbiosis [75]. It has been listed as a part of the guidelines for treatment of recurrent *Clostridium difficile*. The major drawback of FMT is that the disease-causing pathogen may also get transferred which may lead to further complications [48].

7. Conclusion

Gut microflora is an explorable area for evaluating its role in diseases. The gut microflora dysbiosis is a well-established risk factor for the development of cardiovascular diseases. Studies have proven that metabolites produced from the gut microflora are critical contributing factors in the development of cardiovascular diseases; therefore, targeting the gut microflora during the treatment is a novel approach in the therapy. Despite of the previous studies, further studies must be conducted to verify that the pathways linking the gut microflora dysbiosis and cardiovascular diseases are casual, correlational, or consequential. The agents such as prebiotics, probiotics, and postbiotics have proven beneficial effects in the gut microflora-induced cardiovascular diseases. A further exploration is needed on the long-term effects of the postbiotics. In the future, research must be conducted for the better understanding of the molecular mechanisms involved in the cardiovascular diseases caused by gut microflora dysbiosis. In conclusion, the gut microflora dysbiosis is a key factor in the pathogenesis of various cardiovascular diseases, and targeting of gut microflora in the treatment is the emerging strategy of treatment.

Conflicts of Interest

The authors have declared that no competing interests exist.

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