

Modulating the Gut Microbiome in Cardiovascular Diseases: Mechanisms Microbial Metabolites and Therapeutic Perspectives

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ABSTRACT: The gut microbial community, composed of trillions microorganisms residing within the gastrointestinal route, is increasingly recognized as a vital regulator of host physiology. It plays a pivotal role in digestion, immune system modulation, and systemic metabolism. Emerging evidence has established strong links between gut microbiota composition with cardiovascular health, suggesting that microbial imbalances may contribute to the development and development of heart diseases. This review article aims to provide an integrated overview of the mechanistic metabolic and immunological links between the gut microbiome and cardiovascular diseases. Unlike previous reviews, it synthesizes current knowledge regarding the relationship between the gut microbiome and cardiovascular disease, with a specific focus on microbial metabolites like trimethylamine-N-oxide (TMAO) and short-chain fatty acids (SCFAs), which affect systemic inflammation, lipid metabolism, endothelial function, and thrombosis, causing central and cardiovascular disease pathogenesis. The methodology involves a comprehensive analysis of peer-reviewed literature from multiple scientific databases used in the primary research, as well as targeted and untargeted mass spectrometry for metabolite quantification. Mechanistic insights from both clinical trials and preclinical studies—particularly those involving germ-free and antibiotic-treated animal models—are examined to understand causal pathways. Furthermore, the review evaluates intervention strategies aimed at modulating the gut microbiota to improve cardiovascular outcomes. These include dietary approaches like probiotics and prebiotics, and fecal microbiota transplantation (FMT). It also highlights the microbiome role for further therapeutic approaches. By integrating molecular, clinical, and experimental evidence, the gut microbiome considered as novel and promising target of cardiovascular diseases prevention and treatment.



Keywords: Gut Microbiota, Cardiovascular Diseases, Trimethylamine N-oxide, Short Chain Fatty Acids, Inflammation

1. INTRODUCTION

1.1 OVERVIEW ON CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVDs) are considered the leading and main cause of mortality over the world. The traditional risk factors like hypertension, diabetes and hyperlipidemia are well-known; but recent researches have mentioned the gut microbiome could be the main factor in cardiovascular health prognosis. Dysbiosis, which means an imbalance in intestine microbial community, is significantly associated with many CVD risk factors, like atherosclerosis, hypertension and metabolic syndrome. If the mechanisms of gut microbiome influences are understood, cardiovascular health will help in preventing and treating multiple diseases strategies [1]. CVDs such as heart failure, coronary artery disease, in addition to hypertension— are known to be the leading agents of death worldwide, with the accounting of estimated 17.9 million cases of deaths yearly, or about 32% of all documented global deaths [2]. While

conventional risk factors like obesity, hypertension, diabetes mellitus, hyperlipidemia, sedentary lifestyles and smoking are very well studied. While the growing scale of evidences of gut microbiome to be as a modifiable and crucial factor that influence cardiovascular health still cryptic [3]. The gut microbiome contains of trillions microorganisms that including bacteria, fungi, archaea, and viruses—can strongly affect the human gastrointestinal route. These microbes are essential in both digestion besides nutrient absorption and regulation of the energy, balance, inflammatory responses and host immunity. Emerging research can suggest a strong bidirectional relationship of the gut microbiota besides the cardiovascular system that is mediated by the systemic inflammation, microbial metabolites and neurohormonal signaling pathways [4].

The most widely reported microbial metabolites in the gut is trimethylamine-N-oxide (or TMAO). The TMAO substances are produced through dietary precursors like choline, phosphatidylcholine, in addition to L-carnitine—abundant in foods like eggs and red meat—through gut microbial metabolism. These nutrients are first converted by intestinal bacteria into trimethylamine (TMA), which is subsequently absorbed and oxidized in the liver to TMAO by flavin-containing monooxygenases [5]. Increased circulating levels of TMAO have been strongly associated with a higher risk of atherosclerosis, thrombosis, and many serious adverse cardiovascular outcomes, highlighting the gut microbial important role in the progression of cardiovascular diseases via their metabolism. [6]; while mechanistic data from animal models suggest a contributory role of TMAO in atherogenesis definitive causal evidence in human populations remains limited and warrants further interventional investigation [7].

Moreover regarding TMAO role, dysbiosis—considered as the imbalance status of gut microbiome—that has been included in harmful development of many cardiovascular aspects. A dysbiosis gut microbes can often be characterized by the reduction of microbial diversity, with decreased beneficial species (e.g., *Faecalibacterium prausnitzii* and *Bifidobacterium* spp.), and increased pathogenic or pro-inflammatory taxa (e.g., *Enterobacteriaceae*) [8]. Gut microbiota dysbiosis may contribute to cardiovascular disease through immune and inflammatory mechanisms. Increased gut permeability allows the translocation of microbial components such as lipopolysaccharides (LPS) into the circulation leading to activation of inflammatory signaling pathways like in NF- κ B pathway. The resulting chronic low-grade inflammation is a recognized contributor to endothelial dysfunction and atherosclerosis. that is well-established contributor in atherogenesis and endothelial dysfunction [9].

Encouragingly, the intestinal microbiome is markedly modifiable. Dietary modes, particularly of rich people with no dietary fibers or plant-based kinds, may promote the growth of SCFA-producing bacteria, which itself improves the lipid metabolism, and reduces blood pressure, with attenuating of the inflammatory processes [10]. Similarly, using of probiotics, symbiotic and prebiotics or even fecal microbiota transplantation (FMT) are shown to be potential in early human and animal studies regarding modifying intestine microbial content in many ways which reduce cardiovascular incidence risks [11].

The current review aims to present a comprehensive examination about the mechanistic ties between the intestinal microbiome with cardiovascular disease, discussing recurrent and emerging strategies of therapeutic modulation of intestine microbiome, in addition to highlighting many clinical implications with the future research predictions in these rapidly evolving aspects.

1.2 MECHANISMS RELATING WITH GUT MICROBIOTA TO CARDIOVASCULAR INDIVIDUALS

1.2.1 METABOLITES PRODUCTION

Certain intestine bacteria can markedly metabolize dietary components for producing metabolites like influencing cardiovascular health status. For example, consuming the choline-rich foods results in the production of the trimethylamine (TMA) by intestine microbes, related to trimethylamine-N-oxide (TMAO) within the liver cells. Elevated level of TMAO is strongly associated with increased risks of atherosclerosis in as well as other cardiovascular events [12]. One of the most famous mechanisms regarding the gut microbiome relationship with cardiovascular disease (CVD) is that the microbial metabolism of dietary nutrients can be modified to bioactive metabolites, mainly trimethylamine N-oxide (TMAO). Dietary compounds like choline, phosphatidylcholine (which found in eggs, dairy and meat), in addition to L-carnitine, abundant in red meat, are all have been metabolized by gut microbiota towards trimethylamine (TMA) that is then absorbed and oxidized within the liver cells by flavin-containing monooxygenases enzyme (especially FMO3) to TMAO which is considered as a proatherogenic material [13]. Increased circulating levels of TMAO are strongly linked with the increased risks of huge adverse cardiovascular malfunctions, like stroke, myocardial infarction, and then death in many human retrospective studies [14].

Mechanistically, the compound of TMAO is contributing to atherosclerosis via many pathways as it can enhance cholesterol accumulation within macrophages, promote formation of foam cells, alter bile acid and cholesterol metabolism, and finally can affect responsiveness of platelets, so it will augment thrombosis risk. On the other hand, TMAO has been mentioned to impair the function of endothelium and promote the vascular inflammation status, which are both considered as key factors of atherogenesis [15].

Besides TMAO, other gut microbiota-derived materials are markedly recognized as crucial agents in cardiovascular cases. For example, Short-chain fatty acids (SCFAs), like butyrate, propionate or acetate are all metabolized formed through many dietary fiber's fermentation by microbes. Short-chain fatty acids (SCFAs) including

acetate propionate and butyrate are gut microbiota-derived metabolites that have been associated with beneficial cardiometabolic impact. Available evidence suggests that SCFAs may modulate inflammatory responses improve endothelial function and influence blood pressure regulation however, these effects appear to be context-dependent and influenced by host and microbial variability by G-protein coupled receptors (like GPR41 besides GPR43), with integrity maintaining of the intestine barrier. Contrarily, the phenylacetylglutamine (PAGln), which is another gut-derived kind of metabolites that is formed from phenylalanine, is also linked with enhancing platelets activity through thrombotic risk [16].

In addition to the metabolites production like SCFAs and TMAO, multiple molecular pathways are identified by which the intestine microbes can influence the cardiovascular health positively. One of the pathways that is involved is the inflammatory signaling cascades activation, like the kappa-light-chain-enhancer nuclear factor to activate B cells (NF- κ B). Moreover, Microbial components like lipopolysaccharides (LPS) are translocated to bloodstream in case of compromising the gut barrier, which engaging toll-like receptor 4 (TLR4) located onto surface of immune cells and endothelial cells. This activation can promote the adhesion molecules expression with pro-inflammatory cytokines, resulting in endothelial dysfunction—as a precursor in atherosclerosis process [17].

1.2.2 IMMUNE MODULATION AND INFLAMMATION

The gut microbiome takes an important part in regulation of systemic inflammation, as a key factor of CVDs development. Dysbiosis can result in increasing intestinal permeability, which allow the microbial products translocation like lipopolysaccharides (LPS) within bloodstream that triggers inflammatory response. Proinflammatory cytokines then promotes atherogenesis and endothelial dysfunction [18].

Such unique mechanism in which the intestinal microbiome can cause cardiovascular disease (CVD) is called modulating of systemic inflammation in addition to immune responses. In healthy conditions, the epithelium of gut with the immune system of gut can maintain a symbiotic relation with the commensal gut microbes, to ensure immune tolerance maintenance and to keep microbial homeostasis. On the other hand, intestinal dysbiosis which refers to imbalance microbial composition in gut can compromise whole integrity of gut barrier, causing increased gut permeability or the term “leaky gut.” This event allows microbial-derived components translocation like flagellin, lipopolysaccharides (LPS) and peptidoglycans to the bloodstream in which they altogether activate the receptor called pattern recognition (PRRs) such as Toll-like receptor 4 (TLR4) on surface of immune cells [19]. The cascade activation regarding NF- κ B signaling pathways can itself promotes producing proinflammatory cytokines, like tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) with interleukin-6 (IL-6) that are having direct roles in dysfunction of endothelium and vascular system; besides development of atherosclerotic plaques [20].

The chronic low-grade systemic inflammation can accelerate atherogenesis and subsequently leads to insulin resistance in addition to metabolic dysfunction; all are recognized as cardiovascular risk factors. For example, elevated circulating levels of LPS which is a term of metabolic endotoxemia condition—can be observed in obese and people with diabetes- type 2, in aspects of microbial inflammation presence in cardiometabolic cases [13]. Furthermore, a specific microbial taxa alteration, like reductions in short chain fatty acid (SCFA) of *Roseburia* spp and *Faecalibacterium prausnitzii* bacteria can be associated with many impaired immune phenomenon. SCFAs such as butyrate can normally support regulatory T cells (Tregs) function and integrity of mucosal barrier, which are considered essential functions to prevent massive immune activation [21].

1.3 ATTEMPTS OF MODULATING GUT MICROBIOTA IN CARDIOVASCULAR CASES

1.3.1 DIET MODIFICATION TRIALS

Diet is a direct and important modulator of the intestine microbiome. The diet which is rich with fibers is meant to be rich with prebiotics like β -glucan and inulin, which are promoters of the beneficial bacteria growth (For example: *Lactobacilli* and *Bifidobacteria*). These beneficial bacteria can produce materials like short chain fatty acids (SCFAs) such as butyrate, acetate and propionate. They all exert direct cardio-protective effect through reducing rate of inflammation, endothelial function improving, besides lipid metabolism enhancing [22]. Moreover, food rich with polyphenol, such as citrus fruits and walnuts, have favorable impacts in intestine microbiota function and composition. Walnuts, for example, contain hydrolysable tannins and fibers that can be metabolized by gut bacteria to produce urolithins, compounds that may confer cardiovascular benefits [23]. Dietary patterns of high fiber content such as plant-based foods or polyphenols can increase microbial diversity and abundance of beneficial gut bacteria, mainly the ones capable of generating short-chain fatty acids (SCFAs) like *Faecalibacterium prausnitzii*, *Bifidobacterium* spp and *Roseburia* spp. [24]. SCFAs—composed of acetate, butyrate with propionate are meant to be produced by microbial fermentation as non-digestible carbohydrates (prebiotics) that exert anti-inflammatory effects, antihypertensive impact, in addition to lipid lowering activity via immune cells modulating. Findings showed that they also improve integrity of gut barrier, and activate G-protein coupled receptors which influence the host metabolism [25]. Antibiotics significantly modulate the gut microbiota by reducing microbial diversity and altering community composition, which may disrupt metabolic and immune homeostasis and influence cardiovascular disease risk [26].

Attachment to dietary modes like in Mediterranean type of diet that is rich in fruits, nuts, whole grains, vegetables, nuts, legumes and olive oil are linked to the occurrence of cardiovascular diseases caused by shifts in intestine microbiota component. This kind of diet can strongly increase the abundant SCFA-producing bacteria then reduce pro-inflammatory kinds resulting in cardiovascular risks [27]. Additionally, food rich in polyphenol like red wine, walnuts, berries, and tea metabolized by intestine microbes to bioactive phenolic materials which enhance function of endothelium and can reduce the oxidative stress in it [28]. Contrarily, the western foods—that are high in red meat, saturated fats or processed foods—can highly promote the pathogenic and opportunistic bacterial growth then increase the production of microbes and pro-atherogenic metabolic compounds like trimethylamine (TMA), which is a precursor towards TMAO metabolite. The reduction of red meat consumption with increased plant-derived diet intake can markedly lower the amount of circulating TMAO metabolites, so cardiovascular risks will be reduced [13]. Figure (1) illustrates the gut microbiota relationship with cardiovascular health [29].

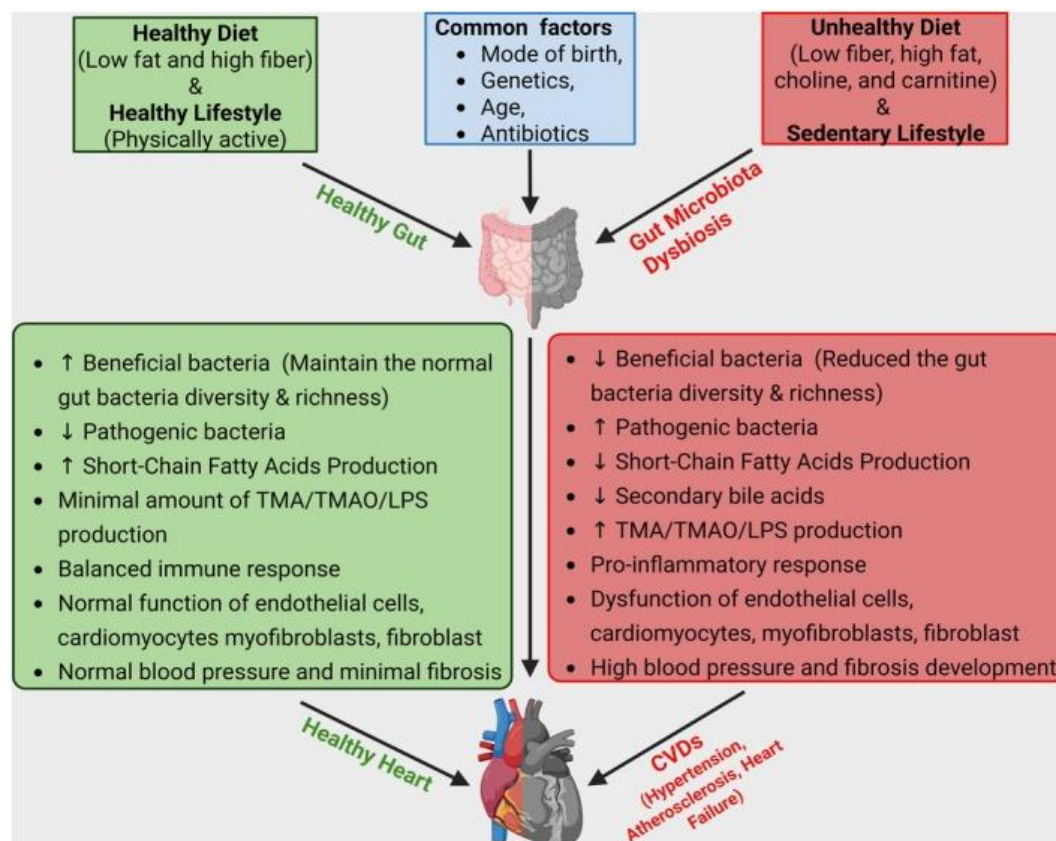


FIGURE 1. - Role of gut microbiota in cardiovascular health

1.3.2 PREBIOTICS AND PROBIOTICS

Probiotics is a term of living microorganisms which confer health advantages to host in time of administrating them in suitable amounts. The supplementation of probiotics such as *Lactobacillus plantarum* bacteria is meant to lower low-density lipoprotein cholesterol level (LDL-C) then the atherosclerotic plaque will be inhibited in hypercholesterolemia cases [30].

Prebiotics, which are non-digestible foods promote beneficial gut bacterial growth, can demonstrate cardiovascular positive effects. For example, supplementation of probiotics rich inulin-type diet has been recorded to increase SCFA-producing bacterial presence and to improve levels of lipid profiles [31].

Probiotics with prebiotics resemble promising therapeutic approaches as useful modulating of gut microbiome which reduce cardiovascular risks. Probiotics are termed to be tiny living organisms that can be administrated as adequate counts, to offer health advantages for host, such as setting microbial balance, enhancing barrier function, and immune responses modulating. Common probiotic strains like *Bifidobacterium* and *Lactobacillus* can demonstrate potential effects in minimizing serum cholesterol reduce systemic inflammation, besides improve endothelial function, so strengthening cardiovascular protection. For instance, clinical findings have recorded that the probiotic

administration may modestly decrease low density lipoprotein type of cholesterol (LDL-C) besides inflammatory markers minimizing like C-reactive protein (CRP), that are very important as cardiovascular predictors [32].

Prebiotics in turn are meant to be non-digestible diet components—specifically fermentable fibers such as inulin, galacto-oligosaccharides and fructo-oligosaccharides are selectively stimulators of beneficial gut bacteria growth and development. By promoting of SCFA-producing microbial proliferation, prebiotics can enhance butyrate and propionate production that together improve lipid and glucose body metabolism, and lower blood pressure, in addition to attenuate inflammatory processes associated with atherosclerosis trials [33].

1.3.3 FECAL MICROBIOTA TRANSPLANTATION (FMT)

The fecal microbiota content cultures were developed by transferring process of fecal matter from healthy donors to recipients to restore balanced gut microbiome in patients. Meanwhile, Fecal microbiota transplantation (FMT) procedures have shown promising metabolic effects in experimental and early clinical studies. However, their applications in cardiovascular diseases still need more investigation. Concerns regarding donor selection long-term safety protocol standardization and the potential transmission of pathogenic organisms currently limit its routine clinical use [34].

So, Fecal Microbiome Transplantation processes (FMT) are considered as emerging therapeutic strategy which involves transferring fecal amount from healthy persons to enhance gastrointestinal microbiota of recipients. Basically, this process was established as effective treatment approach for *Clostridioides difficile* recurrent infection. Nowadays, FMT is explored for its potent modulating role for systemic disorders, including cardiovascular disease in human (CVD) [30]. The FMT benefit in CVD is mainly based on transplanting microbes of healthy ones to correct metabolism associated with dysbiosis with inflammatory onsets in atherogenesis and heart failure patients [35].

Many preclinical studies demonstrated that the transferred FMT from healthy-metabolic donors to hypertensive or obese animals can improve insulin sensitivity, and can reduce systemic inflammation, then lower blood pressure—which are all factors tightly related to cardiovascular risks. Human experimental studies proved that FMT may transiently alter intestine microbial community and can also improve metabolic parameters like blood insulin sensitivity with peripheral inflammatory markers within patient's body of metabolic syndrome cases. Additionally, the FMT direct effects of cardiovascular cases is randomized and need more controlled investigation because the clinical administration of FMT in CVD patients depends on selecting suitable donor, protocol standardization with long-term safety, along with probable risk in transferring some pathogenic organisms with undesired microbial species [39]. However, FMT can represent promising therapy in cardiovascular targeting frontiers in gut-heart related axis via microbiome manipulation. Proceed next-generation microbiome-based curing, including specific defined microbial types called “synthetic FMT,” can improve safety and efficacy of future attempts [36].

1.4 FUTURE DIRECTIONS AND CHALLENGES

Although the promising potential of intestine microbiota manipulation in cardiovascular cases were studied and proved, several challenges remain ambiguous. The individual variability and complexity of human microbiome in gut necessitate unique approaches to interventions. Additionally, full safety with efficacy regarding long-term probiotic intake besides FMT require more investigation. Further research should highlight identification of specific microbial species along with their metabolites to confer cardiovascular advantages and to develop targeted treatment approaches [37].

Despite presence of numerical evidences that link the gut microbiota with cardiovascular health, but many challenges are remaining in these findings interpreting to medical applications. Majority of limitations are restricted with the difficulties of established trials; even though the high levels of microbial produced metabolites like trimethylamine-N-oxide (TMAO) were associated in large scale with elevated cardiovascular risks and some of them remain unclear; whether these were disease prior markers or causing agents of it. The huge inter-individual variation of gut microbiota kinds resulted from many factors like diet, genetics, medication and environment may have more complications on developing standardized study interventions. Besides, the complexity of human microbe interactions, which includes a scale of microbial functions and redundancy along with host immune response are all requiring serious approaches like multi-omics integration with machine learning for understanding mechanisms and pathways suggested [38]. Clinical picture is hindered mainly by limitations of the randomized trials to evaluate the efficacy regarding microbiome-manipulation therapeutic attempts as prebiotics, probiotics and fecal microbiota transfer (FMT), by which regulatory with safety concerns that surround these live microbiotic interventions can be resolved. Future tests should also highlight identifying precise microbial targets or metabolic pathways amenable to therapeutic modifications, like hepatic FMO3 inhibition for reducing TMAO production, and they should incorporate specific microbiome profile in order to have a unique dietary guide of probiotic interventions in patients or trials [39]. Longitudinal and multi-ethnic cohort studies, and the well-designed clinical experiments measuring both of microbiome with cardiovascular endpoints, considered so critical in establishing gut microbiota as potent and viable target within cardiovascular disease prevention or treatment fields.

2. DATA ACQUISITION

The current review was prepared to display recurrent evidence of the gut microbiome role among the pathogenesis, prevention, colonization and treatment of the cardiovascular diseases (CVDs) in human being. A comprehensive literature of searches was performed by global databases including PubMed, Web of Science Scopus, and, covering articles that are published from 2010 to 2026. The search strategy implicated very important terms like “hypertension”, “gut microbiota”, “cardiovascular diseases”, “TMAO”, “fecal microbiota transplantation”, “SCFAs”, “microbial metabolites”, “prebiotics”, “probiotics”, “atherosclerosis”, and “dietary intervention” will be mentioned below.

Findings were selected according to the following aspects: (1) original research articles with systematic reviews published into peer-reviewed scientific journals; (2) researches examining relationship of gut microbiota with cardiovascular outcomes of animal models and human being; (3) mechanistic studies that express and explore microbial metabolites (like., TMAO and SCFAs) in addition to their effects onto inflammatory, vascular and metabolic pathways; and finally (4) interventional documents assessing strategies of gut microprobes modulation. Exclusion criteria also including conference abstracts, non-English publications with studies that lacking cardiovascular relevance in their findings.

The extracted data were categorized into three thematic areas which include: (1) microbial metabolite pathways, (2) the host-microbiome interactions into cardiovascular physiology, besides (3) therapeutic modulation of human gut microbiota. Emphasis has been placed above studies employing rigorous methodologies like metagenomic sequencing, that are targeted the metabolomics, antibiotic-treated animal models, germ-free and randomized several clinical trials.

3. RESULTS

The cardiovascular diseases (CVD) still the main leading causes of global morbidity and mortality high rates as nearly 18 million death cases each year as in World Health Organization reports. Recently, the epidemiological findings showed that the diet type is considered the main factor to intestine microbiota misbalance and various heart progressions like atherosclerosis, heart failure and hypertension [40]. The gut microbial alteration in function and composition is increasingly related with cardiovascular risks by metabolites production like trimethylamine N-oxide material (TMAO) that is causing vascular damage and inflammation. People-based studies among diverse locations which include China, USA, Europe and Iran demonstrated consistent links between adverse cardiac outcomes and gut microbiota dysbiosis. Interventions targeting the intestine microbiome, like probiotic supplements, intake of food rich with fibers and transfer of fecal microbes may actively investigate to affect cardiovascular risks, to reflect the emerging epidemiological state of microbial ecology and heart health in human being [41]. The following findings strongly suggest the important effect of gastrointestinal microbiota modulation as a vital fighter in CVD patients, in addition to implications of both therapeutic management and prevention within different populations, as in table 1 below.

Table 1. - Recent Studies on Modulating the Gut Microbiome to Prevent or Treat Heart Diseases (2010–Present)

Study/Topic	Results	Reference	Country
Fecal microbiota transplantation improves insulin sensitivity	FMT from lean donors elevated insulin sensitivity with beneficial microbiome in metabolic syndrome patients	[42]	Netherlands
Gut microbiota metabolite TMAO and cardiovascular risk	Plasma TMAO elevated levels predict major adverse cardiovascular events; TMAO promotes atherosclerosis via foam cell formation and platelet activation	[43]	USA
Relation of gut microbiota with carnitine metabolism and atherosclerosis	Gut microbiome convert dietary carnitine to TMAO, promoting atherosclerosis; antibiotic suppression reduces TMAO and atherogenesis	[44]	USA
Impact of high-fiber diet on gut microbiome and cardiovascular	High-fiber diet increased SCFA-producing bacteria and reduced	[45]	Australia

biomarkers	inflammatory markers in healthy adults		
Gut dysbiosis linked to atrial fibrillation progression	Dysbiosis correlates with progression of atrial fibrillation, highlighting microbiome as a therapeutic target	[46]	Global (Systematic Review)
Microbial metabolites modulate myocardial infarction and endothelial function	Gut-heart axis metabolites influence myocardial infarction pathogenesis and vascular health	[47]	China
Oral-gut microbes transmission enhances diabetic related coronary heart disease	Oral <i>Fusobacterium nucleatum</i> translocated to gut, worsening myocardial injury in diabetic mice	[48]	China
SCFAs regulate blood pressure and inflammation in hypertensive mice	SCFAs like propionate reduce cardiac fibrosis, blood pressure, and inflammation through GPR41 receptor activation	[49]	Germany
Gut microbial metabolites and hypertension	SCFAs lower blood pressure via vasodilation; TMAO increases cardiovascular risk	[50]	Global (Review)
High-intensity interval training modifies gut microbiota post-PCI	HIIT enriched beneficial bacteria (<i>Coprococcus eutactus</i>), improved endothelial function and reduced inflammation in CHD patients	[51]	China

4. DISCUSSION

The current review consolidates obvious evidence that the gut microbiome take an important part in mechanistic cardiovascular diseases (CVD), as pathogenesis via inflammatory, metabolic, with immunological pathways. These findings can be summarized in present study that tightly supporting the **gut–heart axis** that microbially-derived metabolites can affect host–microbial community with interactions cardiovascular interactions.

One of the more important aspects that are involved in the pathogenesis is that **trimethylamine-N-oxide (TMAO) generated by microbes** are associated with increased risk of huge cardiovascular outcomes, like myocardial infarction, and stroke, in addition to mortality [52]. Mechanistically, the TMAO included in atherosclerosis through promoting cell formation, then impairing reverse cholesterol transport system, and enhancing platelet increased activity, inducing endothelial cells dysfunction. Current studies also suggest that the TMAO can activated by **adrenergic receptor signaling mechanisms**, to link microbial metabolism in a direct way for the regulation in cardiovascular system [53]. These results reinforce the earlier observations and providing more important and deep molecular insight within receptor-mediated host effects.

On the other hand, the **short-chain of fatty acids (SCFAs)** like acetate, butyrate and propionate can exert protective cardiovascular impacts. SCFAs significantly regulate the blood pressure via activating G-protein–coupled type of receptors (like GPR41, GPR43), which can improve endothelial cell function, and also suppress systematic inflammation. Clinical recent studies demonstrate that SCFAs can reduce cardiac hypertrophy, vascular stiffness, and inflammatory cytokine production, highlighting their therapeutic potential in hypertension and heart failure [54].

Extra critical sight of this study highlights **gut dysbiosis in systematic inflammation** as elevated intestinal permeability which allows microbial components translocation like lipopolysaccharides (LPS), trigger Toll-like receptors (TLR)-and mediate inflammatory pathways. The chronic decreased-grade of inflammation is said to be a key driver in atherogenesis with metabolic dysfunction. Moreover, emerging proves is that the microbiome-implemented in inflammation can not only be a consequence of this state but also might be a **direct contributor in cardiometabolic outcomes**, in relation with type 2 diabetes besides coronary artery human diseases [55].

Markedly, current evidences in **multi-omics genomic technologies** (like **metagenomics** transcriptomics and **metabolomics**) cause more comprehensive interpretation of the host–microbiome entire state. All approaches above revealed that the specific microbiome signatures is associated with CVD phenotypes that might identified novel metabolites like **phenylacetylglutamine (PAGln)** which modulate platelet function with thrombosis initiation [56]. Those discoveries could open more new avenues for biomarker and targeted therapeutic development.

The therapeutic modulation regarding the gut microbial community represents promising aspects for cardiovascular risk elimination and prevention. Dietary interactions—mainly **Mediterranean diet** in addition to **high-fiber diets**—are consistently demonstrated as beneficial ffactors via increasing the production of SCFA from gut bacteria then reducing pro-atherogenic mediators. Recent trials also document that the dietary fibers in diet can strongly improve host vascular function and reduce inflammation, with altering the gut microbial composition leading to cardioprotective situation [57].

In a similar way, **probiotics with prebiotics** are significant substances that can improve lipid profile in patients, balance inflammatory markers, besides inhance endothelial cell function, but their clinical efficacy should remain under monitoring like microbiome variability, strain specificity, dosage, and differences among individuals. So, standardized and large scale trials are requiring clinical clear guidelines [58].

Fecal microbial transplantation (FMT) process is a novel and significantly transformative potent approach. Whereas last studies reported that they are included in insulin sensitivity improvement and other metabolic parameters in blood, but their usage in cardiovascular diseases still remain ambiguous. The protocols included donor selection, safety in addition to the long-term effect of FMT materials. Future clinical use could be aided with **next-generation microbial therapeutics** (definition of microbial consortiabetides postbiotics) to overcome the reported care-requiring limitations and challenges [59].

Additionally, the heterogeneity of the host microbiome can be influenced by the geneticstate, environment, medications and diet that complicate identifying of universal standard therapeutic agents. Most current proves are extracted from long time retrospective researches. So, **longitudinal cohort findings of well-designed and controlled procedures** are very essential to validate transferred microbiome-based therapies [60].

Shortly, specific gut microbial community resembles a modifiable dynamic factor in cardiovascular outcomes. Integrating gut microbial profiling within clinical practice can enable **personalized medicine strategies**, with considering of diet type, fibers, probiotic, and pharmaceuticals that might interact with individuals, health. Future research should focus on translating mechanistic insights into clinically applicable strategies to reduce the global burden of cardiovascular diseases and enhancing general health through microbial composition.

5. CONCLUSION

Modulation of the gut microbiome represents a promising yet evolving therapeutic avenue for the preventive management regarding cardiovascular diseases. Although dietary interventions and microbiome-targeted strategies show potential further well-designed longitudinal and interventional studies required to establish causality safety withclinical efficacy prior to widespread implementation. Meanwhile prebiotic supplementation, probiotic, FMT and dietary interventions can offer potential therapeutic gut and body avenues. Furthermore, researches are so essential to establish human safety, body systems efficacy, and long-term health benefits. Integrating of above strategies towards clinical practices might provide a huge and holistic approach in cardiovascular health field, emphasizing the intricate connection which binds gut microbiota with heart function for large scale of alternative medicine applications.

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CONFLICTS OF INTEREST

No conflict of interest

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