Review Article

Exploring the Role of Gut Microbiota in Cardiovascular Health and Disease Management

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ABSTRACT

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| The modulation of gut microbiota presents a promising therapeutic strategy for cardiovascular diseases (CVDs), leveraging the gut-heart axis to influence systemic inflammation and metabolic pathways. Emerging interventions such as prebiotics, probiotics, and fecal microbiota transplantation (FMT) aim to restore a healthy gut microbiome, potentially reducing CVD risks by impacting glycemic control, blood pressure, and lipid profiles. The gut microbiota produces metabolites like trimethylamine-N-oxide (TMAO), which is linked to atherosclerosis and endothelial dysfunction and short-chain fatty acids (SCFAs), which have protective effects against cardiac damage. FMT, initially successful in treating recurrent Clostridium difficile infections, is now being explored for its potential in modulating systemic inflammation and metabolic pathways critical to cardiovascular health. However, challenges such as individual variability in microbiome composition and the need for robust clinical trials remain. Additionally, gut permeability, or "leaky gut," contributes to heart failure progression by allowing harmful metabolites into the bloodstream, triggering systemic inflammation. Overall, targeting gut microbiota and its metabolites offers a novel approach to managing CVDs, though further research is needed to establish effective and personalized therapeutic strategies. |

**Key Words**: Gut Microbiota, Systemic Inflammation, Cardiovascular Diseases (CVDs), Trimethylamine-N-oxide (TMAO), Gut-Heart Axis

# Introduction

The gut microbiota, a complex ecosystem of microorganisms, plays a pivotal role in maintaining systemic health and influencing a wide array of physiological processes. This intricate community, primarily composed of viruses, bacteria, fungi, and other microorganisms, has co-evolved with humans, establishing a symbiotic relationship that is crucial for various bodily functions such as immune regulation, digestion, and nutrient synthesis 1,2. The gut microbiota's influence extends beyond the gastrointestinal tract, impacting metabolic, neurological, and cardiovascular health, and is implicated in the pathogenesis of numerous diseases, including obesity, diabetes, inflammatory bowel disease, and even neurodegenerative conditions like Parkinson's and Alzheimer's 3,4. Dysbiosis is linked with chronic inflammation and immune dysregulation, in the onset and progression of these diseases 3. Moreover, the gut microbiota interacts with genetic factors, influencing disease susceptibility and progression, and acts as a biomarker for various conditions. Recent developments in genomic methodologies and novel instruments such as organ-on-chip models are augmenting our comprehension of these intricate interactions, thereby facilitating the formulation of microbiome-oriented therapeutic strategies and personalized medical approaches. 3,5.

Cardiovascular diseases (CVDs) represent a significant global health burden, with projections indicating a 90% increase in prevalence and a 73.4% rise in crude mortality by 2050, driven largely by an aging population and atherosclerotic diseases 6. The multifactorial nature of CVDs encompasses genetic predispositions, lifestyle factors, and socioeconomic influences. Lifestyle choices such as smoking, excessive alcohol consumption, poor diet, and physical inactivity are major modifiable risk factors that significantly impact CVD incidence and outcomes 7. Despite advancements in medical care reducing age-standardized mortality rates, the global burden remains substantial, particularly in low- and middle-income countries where 80% of CVD-related deaths occur 8. The burden is further exacerbated by transnational inequities, with higher societal development levels correlating with increased CVD burden, highlighting the need for equitable healthcare strategies 9. Physical activity emerges as a critical preventive measure, with guidelines advocating moderate to vigorous exercise to mitigate CVD risk and mortality 10. Addressing these multifactorial elements through comprehensive public health policies and individual behavior changes is essential to reducing the global CVD burden. This includes implementing national tobacco control programs, ensuring access to CVD medications, and promoting physical activity as a low-cost, effective intervention 8,10.

The gut microbiota, residing in the human digestive tract, maintains health and influences disease states 11,12. This diverse microbial community is integral to various physiological processes, such as immune regulation, metabolism, and inflammation control 13,14. A balanced gut microbiota is essential for immune system development and homeostasis, as it shapes immune responses and protects against pathogens through mechanisms like cytokine production and regulatory T-cell induction 15. Dysbiosis is linked to numerous diseases, including metabolic disorders, inflammatory bowel disease, and neurological conditions, often accompanied by chronic inflammation and dysregulated immune responses 12–14. The gut microbiota also influences metabolism by modulating bile acid homeostasis and interacting with the host's metabolic system, impacting conditions such as obesity and diabetes 11,12. Recent research underscores the potential of the gut microbiota as a therapeutic target, with interventions like probiotics and fecal transplants showing promise in restoring microbial balance and ameliorating disease states 14,15.

The gut microbiome as a modifiable risk factor for heart diseases, suggesting that interventions targeting gut health could influence cardiovascular outcomes. The gut-heart axis is a communication network where gut health impacts cardiovascular health through various mechanisms, like systemic inflammation and metabolic processes. Disruptions in this axis, such as gut dysbiosis, can lead to increased levels of harmful metabolites like TMAO and lipopolysaccharides (LPSs), which exacerbate conditions like myocardial infarction (MI) and other CVDs16,17. Conversely, beneficial metabolites such as SCFAs produced by a balanced gut microbiota can protect against cardiac damage 16. The gut microbiota's influence extends to modulating blood pressure, glycemic control, and lipid profiles, with dietary patterns playing a crucial role in shaping its composition 18. Emerging therapeutic strategies, including prebiotics, probiotics, and FMT, aim to restore a healthy gut microbiota, potentially reducing CVD risks 18. Moreover, gut-heart axis is implicated in the pathogenesis of various cardiovascular conditions, including hypertension and atherosclerosis, through its impact on systemic inflammation and neurohumoral pathways. Despite promising findings, challenges such as individual variability in composition of microbiome and the need for robust clinical trials remain, underscoring the importance of further research to establish causality and develop personalized therapeutic approaches 17,18.

# Mechanistic Links Between Gut Microbiota and Cardiovascular Diseases

Gut dysbiosis, in the intestinal microbiota, increases intestinal permeability, allowing lipopolysaccharides (LPS) from gram-negative bacteria to translocate into the bloodstream, thereby triggering systemic inflammation. This process begins with the disruption of intestinal epithelial barrier, often exacerbated by factors such as antibiotic use or alcohol consumption, which further promotes dysbiosis and barrier dysfunction19,20. Once the barrier is compromised, LPS enters the portal circulation and can reach the liver, where it interacts with Toll-like receptor 4 (TLR4) on hepatocytes and Kupffer cells, inducing hepatic inflammation and contributing to conditions like nonalcoholic fatty liver disease (NAFLD) 20,21. The systemic circulation of LPS also primes platelets, enhancing their response to agonists and promoting a prothrombotic state, which is implicated in liver inflammation and thrombosis 21. Furthermore, LPS can localize in atherosclerotic plaques, associating with activated macrophages and contributing to vascular inflammation and atherosclerosis progression. This low-grade endotoxemia, resulting from gut dysbiosis, thus plays a critical role in the pathophysiology of liver and cardiovascular diseases, highlighting the importance of maintaining gut barrier integrity and microbiome homeostasis to mitigate systemic inflammation and its associated health risks 21.

Chronic inflammation is intricately linked to atherosclerosis and endothelial dysfunction, forming a vicious cycle that exacerbates cardiovascular diseases. Atherosclerosis is essentially characterized as a chronic inflammatory pathology in which the immune system assumes a pivotal role in its advancement and exacerbation. The dysfunction of endothelial cells induced by inflammation enhances vascular permeability, facilitating the subendothelial accumulation of lipoproteins, which in turn recruits leukocytes and activates platelets. 22. This dysfunction is characterized by an imbalance in vasoconstriction and vasodilation, reduced nitric oxide bioavailability and elevated reactive oxygen species all of which are exacerbated by inflammatory cytokines such as IL-1β, IL-6, and TNF-α 23. The endothelial dysfunction further promotes oxidative stress and inflammation, creating a feedback loop that perpetuates vascular damage and atherosclerosis 24. Chronic inflammation also impacts the vascular endothelium by activating inflammatory cells and releasing cytokines, which increase endothelial permeability and contribute to cardiovascular dysfunction 25. In the context of aging, chronic inflammation and endothelial dysfunction are pivotal in the pathophysiology of vascular diseases, as they accelerate the decline of organ function and promote disease progression 26. Anti-inflammatory interventions targeting these pathways have shown potential in reducing cardiovascular events, although they may increase infection risks 22.

TMAO is a metabolite produced by gut microbiota through trimethylamine (TMA) oxidation, which is derived from dietary choline and carnitine. This process involves the gut microbial enzyme trimethylamine lyase, which cleaves choline to form TMA, subsequently oxidized to TMAO by hepatic flavin-containing monooxygenase-3 (FMO3) 27,28. TMAO has been implicated in the pathogenesis of atherosclerosis by promoting oxidative stress and inflammation in endothelial cells, leading to vascular dysfunction and the formation of atherosclerotic plaques27,29. It enhances the formation and vulnerability of these plaques by upregulating cytokines, adhesion molecules, and reactive oxygen species (ROS), contributing to endothelial dysfunction and platelet hyperreactivity 29. TMAO is associated with abdominal aortic aneurysm formation by inducing vascular inflammation and smooth muscle cell phenotypic switching, primarily through the activation of the NF-κB signaling pathway 28,30. Therapeutic strategies targeting TMAO production, such as the use of inhibitors like 3,3-dimethyl-1-butanol (DMB) and fluoromethylcholine, have shown promise in reducing TMAO levels and stabilizing atherosclerotic plaques, offering potential avenues for cardiovascular disease prevention 27,28.

SCFAs, primarily propionate, acetate, and butyrate, are metabolites produced during the fermentation of dietary fibers by gut bacteria and have significant anti-inflammatory and vasodilatory effects. SCFAs exert their anti-inflammatory effects through mechanisms such as inhibition and activation of histone deacetylase and G-protein coupled receptors respectively, which help regulate immune responses and maintain intestinal and systemic health 31. These fatty acids also play a crucial role in vascular health by improving endothelial function and reducing arterial stiffness, as demonstrated in studies where acetate supplementation ameliorated age-related arterial dysfunction in mice 32. Furthermore, SCFAs have been shown to prevent vascular dysfunction and hypertension in systemic lupus erythematosus (SLE) models by reducing oxidative stress and modulating immune cell activity 33. The vasodilatory effects of SCFAs are also linked to their ability to enhance aortic relaxation and mitigate vascular oxidative stress, which are critical in preventing conditions like atherosclerosis33,34 . Reduced SCFA production, often due to an imbalance in gut microbiota, can lead to increased inflammation and vascular dysfunction, contributing to the development of CVDs (atherosclerosis and hypertension) 34,35. Therefore, maintaining adequate SCFA levels is essential for vascular health, highlighting their potential as therapeutic agents in managing inflammatory and cardiovascular diseases. Table 1 comprises the summary of Gut Microbiota Metabolites and Their Effects on Cardiovascular Diseases

As highlighted in recent research, gut bacteria significantly modulate immune responses that influence cardiovascular health through various mechanisms. The gut microbiota, impacts cardiovascular health by influencing host metabolism, immune responses, and lipid processing, which are crucial in the development and progression of cardiovascular diseases (CVDs) such as atherosclerosis 36. Key metabolites produced by gut bacteria (TMAO and SCFAs), play pivotal roles in modulating lipid metabolism, inflammation, and blood pressure regulation, thereby affecting vascular function and contributing to CVDs 37,38. The gut microbiota influences immune homeostasis through pathways such as tryptophan metabolism, which converges on the Aryl hydrocarbon Receptor (AhR), a critical regulator of immune responses, further impacting cardiovascular health 39. In heart failure, gut microbiota-derived metabolites act as signaling molecules that influence immune processes and cardiac remodeling, highlighting the complex interplay between gut bacteria and immune mechanisms in cardiovascular conditions 40. Dysbiosis, is linked to increased inflammation and altered immune responses, exacerbating cardiovascular risk. Interventions targeting gut microbiota, including prebiotics, probiotics, and dietary modifications, have shown promise in restoring microbial balance and reducing cardiovascular risk factors, underscoring the potential of microbiota-targeted therapies in managing CVDs 36,38. The gut microbiota's modulation of immune responses is a critical factor in cardiovascular health, offering novel insights and therapeutic opportunities for CVD management.

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| **Metabolite** | **Mechanism of Action** | **Cardiovascular Outcome** | **Associated Condition** | **Therapeutic Implication** | **Reference** |
| **Trimethylamine N-oxide (TMAO)** | Promotes oxidative stress, inflammation (via NF-κB pathway), platelet hyperreactivity, and pyroptosis of endothelial cells | Accelerates plaque formation, increases plaque vulnerability, endothelial dysfunction | Atherosclerosis, abdominal aortic aneurysm | Inhibitors (e.g., DMB, fluoromethylcholine) to reduce TMAO levels | (27, 28, 41, 42) |
| **TMAO** | Increases systemic inflammation, alters bile acid and cholesterol metabolism | Contributes to cardiac remodeling, fibrosis | Heart failure (HFpEF) | FMT to modulate gut microbiota composition | (52, 53) |
| **Short-Chain Fatty Acids (SCFAs)** (propionate, acetate, butyrate) | Anti-inflammatory (via histone deacetylase inhibition, GPCR activation), vasodilatory, reduces oxidative stress | Lowers blood pressure, improves endothelial function, reduces arterial stiffness | Hypertension | Prebiotics (e.g., inulin, FOS) to boost SCFA production | (31, 32, 46) |
| **SCFAs** | Reduces inflammation, modulates immune responses (e.g., TH17 axis) | Protects against cardiac damage, reduces fibrosis | Heart failure | Dietary fiber supplementation | (38, 50) |
| **Lipopolysaccharides (LPS)** | Increases gut permeability, triggers systemic inflammation via TLR4 activation | Promotes vascular inflammation, prothrombotic state | Atherosclerosis, heart failure | Probiotics to restore gut barrier integrity | (19, 21, 50) |

Table 1: Summary of Gut Microbiota Metabolites and Their Effects on Cardiovascular Diseases

# Gut Microbiota and Specific Cardiovascular Diseases

Microbial byproducts, particularly trimethylamine N-oxide (TMAO), significantly accelerate plaque formation and destabilization, contributing to atherosclerotic progression. TMAO, a metabolite produced by gut microbiota from dietary precursors like phosphatidylcholine and L-carnitine, is recognized as an independent risk factor for atherosclerosis and cardiovascular diseases 41,42. Elevated TMAO levels are associated with proatherogenic effects, including alterations in bile acid and cholesterol metabolism, platelet hyperactivation, and induction of inflammatory processes and oxidative stress, which collectively contribute to endothelial dysfunction and endoplasmic reticulum stress 41. Studies have demonstrated that TMAO can induce pyroptosis of vascular endothelial cells, further exacerbating atherosclerosis in animal models 42. Additionally, research using fecal microbiota transplantation in mice has shown that gut microbiota from patients with acute coronary syndrome can transmit characteristics of plaque instability, such as increased necrotic core size and fibrous cap thinning, which are linked to specific bacterial genera 43. This suggests that the gut microbiota composition significantly influences plaque vulnerability, highlighting the potential for therapeutic interventions targeting microbial metabolites like TMAO to modulate atherosclerotic plaque composition and stability 43,44. Consequently, strategies to regulate gut microbiota or inhibit TMAO production are being explored as promising avenues for preventing and treating atherosclerosis 45.

Gut bacteria regulating blood pressure through producing SCFAs, modulation of vascular tone, and influence on the renin-angiotensin system. SCFAs, produced by the fermentation of dietary fibers by gut microbiota, have been shown to lower blood pressure by modulating immune responses and reducing inflammation 38,46. These metabolites also affect vascular tone by influencing nitric oxide synthesis, essential for maintaining vascular health 46. Furthermore, the gut microbiota can modulate the renin-angiotensin system, a critical regulator of blood pressure, by producing bioactive molecules that influence systemic inflammation and immune activation 47. Gut dysbiosis contributes to salt-sensitive hypertension (SSH), where blood pressure increases in response to high salt intake. Dysbiosis affects the host's immune system and metabolic functions, contributing to the development of SSH by altering the TH17 axis and immune cell activity 48. The imbalance in microbial composition, particularly the ratio of Firmicutes to Bacteroidetes, is associated with hypertension, highlighting the potential for targeted interventions to restore microbial balance and improve cardiovascular health 49.

The relationship between gut permeability, microbial translocation, and heart failure progression is increasingly recognized as a significant factor in cardiac health. Gut permeability, often referred to as "leaky gut," allows for the translocation of microbial metabolites (LPS and peptidoglycan (PGN)) into the bloodstream, which can trigger systemic inflammation and contribute to heart failure progression50,51 . In models of heart failure, such as those involving DSS-induced colitis in mice, increased gut permeability was associated with elevated levels of PGN, which activated inflammatory pathways in cardiac tissue, leading to cardiac dysfunction and fibrosis 50(Ranjan et al., 2024). Similarly, in ZSF1 rats, an impaired intestinal barrier was linked to increased levels of TMAO, a metabolite associated with heart failure with preserved ejection fraction (HFpEF), indicating that microbial metabolites play a role in cardiac remodeling and fibrosis 52. Furthermore, alterations in gut microbiota composition, such as decreased diversity and changes in specific bacterial families, have been associated with heart failure and its comorbidities, including obesity and metabolic syndrome 51,53. These microbial changes can lead to an imbalance in metabolites that influence cardiac health, such as increased TMAO and other lipid metabolites, which have been linked to myocardial fibrosis and hypertensive heart disease 53,54. Table 2 comprises the summary of Therapeutic Strategies Targeting Gut Microbiota for Cardiovascular Health. The interplay between gut permeability, microbial translocation, and microbial metabolites underscores a complex relationship contributing to cardiac remodeling and fibrosis, highlighting the potential for therapeutic strategies targeting the gut-heart axis.

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Table 2: Summary of Therapeutic Strategies Targeting Gut Microbiota for Cardiovascular Health

# Therapeutic Potential of Modulating Gut Microbiota

Probiotic strains, particularly Lactobacillus and Bifidobacterium, have shown promising effects in reducing CVD risk factors such as cholesterol, inflammation, and blood pressure. These probiotics can modulate lipid metabolism, thereby reducing low-density lipoprotein (LDL) cholesterol and increasing high-density lipoprotein (HDL) cholesterol, which are critical in managing hypercholesterolemia and atherosclerosis 55,56. Clinical trials and meta-analyses have demonstrated that probiotics, when used alongside conventional medications for coronary artery disease (CAD), significantly reduce LDL cholesterol, fasting glucose, and hypersensitive C-reactive protein (hs-CRP), while increasing HDL cholesterol and nitric oxide levels. However, they do not significantly affect triglyceride levels or blood pressure 57. The anti-inflammatory properties of these probiotics are also notable, as they help reduce oxidative stress and inflammation, which are key contributors to atherosclerosis 56,58. Furthermore, probiotics can alter gut microbiota composition, decreasing gut permeability and levels of harmful metabolites like trimethylamine N-oxide (TMAO), associated with cardiovascular risks 58,59. Despite these benefits, the exact strains and dosages for optimal health effects remain unclear, necessitating further research to understand the mechanisms and individual variability in response to probiotic interventions 55,59.

Prebiotics such as fructooligosaccharides (FOS) and inulin promote the beneficial gut bacteria, which can indirectly improve cardiovascular health. Inulin, a type of fructan, is not digestible by human enzymes but is fermented by gut microbiota, particularly favoring the growth of SCFA-producing bacteria like Anaerostipes and Bifidobacterium. These SCFAs play a crucial role in enhancing glucose metabolism, reducing hepatic lipogenesis, and decreasing inflammation, which are key factors in managing cardiovascular health 60. Inulin has been shown to improve lipid metabolism and reduce inflammation, which are critical in alleviating atherosclerosis, a major contributor to cardiovascular diseases. Studies on ApoE-knockout mice demonstrated that inulin, especially in its short-chain form, significantly reduced atherosclerotic plaque formation and improved lipid profiles 13. Furthermore, a systematic review and meta-analysis of randomized controlled trials indicated that inulin-type fructans (ITF) can reduce low-density lipoprotein cholesterol (LDL-C), triglycerides, and body weight, which are important cardiovascular risk factors 61. The consumption of fructans like inulin and FOS has also been associated with improved glycemic control and immune function, further supporting cardiovascular health 62. The potential of prebiotics in modulating gut microbiota to produce beneficial metabolic effects that extend beyond the gut, contributing to improved cardiovascular outcomes 60,63.

FMT is an innovative therapeutic approach to restore gut microbial balance by transferring fecal material from healthy donors to recipients suffering from dysbiosis-related conditions. Initially recognized for its high efficacy in treating recurrent Clostridium difficile infections (CDI), with success rates up to 90% 64, FMT has expanded its potential applications to include a variety of gastrointestinal and systemic diseases, such as metabolic disorders, inflammatory bowel diseases (IBD) and even neuropsychiatric conditions 64–66. The underlying mechanism of FMT involves re-establishing a healthy gut microbiome, which plays a crucial role in host metabolism, immunity, and disease resistance 65. This therapeutic strategy is particularly promising for heart disease, as emerging research suggests that gut microbiota imbalances may contribute to cardiovascular conditions through mechanisms like inflammation and metabolic dysregulation 67,68. Although FMT is generally safe, with mild side effects such as transient diarrhea, rare severe complications necessitate rigorous donor screening and standardized protocols 64,69. The potential of FMT in heart disease lies in its ability to modulate systemic inflammation and metabolic pathways, which are critical factors in cardiovascular health 68,70.

Bioactive compounds derived from gut bacteria, such as SCFAs like butyrate and acetate, have shown potential in mitigating cardiovascular risk factors. These compounds are produced through the fermentation of dietary fibers by the gut microbiota and play significant roles in maintaining cardiovascular health. Butyrate, for instance, is known for its anti-inflammatory properties and ability to reduce oxidative stress, which can help lower the risk of CVDs71. It also influences the gut-brain axis by crossing the blood-brain barrier, potentially impacting systemic inflammation and neurohumoral pathways that are critical in CVD pathogenesis 17. Acetate supplementation has been shown to ameliorate age-related arterial dysfunction in mice, improving endothelial function and reducing systemic inflammation, which are key factors in cardiovascular health 32. The gut microbiota's role in producing these SCFAs for maintaining a balanced microbial community, as dysbiosis can lead to increased CVD risk through mechanisms such as hypertension and atherosclerosis 17. Therapeutic strategies, including prebiotics, probiotics and dietary modifications, aim to enhance the production of beneficial metabolites like SCFAs, thereby offering a promising approach to reducing cardiovascular risk factors 72. Despite these promising findings, challenges like individual variability in microbiome composition and the need for robust clinical trials remain, necessitating further research to harness the cardioprotective potential of gut-derived bioactive compounds fully.

# Pharmacological Strategies Addressing the Gut-Heart Connection

Emerging drugs targeting gut microbiota, particularly those inhibiting TMAO synthesis and mimicking short-chain fatty acids (SCFAs), represent a promising frontier in treating metabolic and cardiovascular diseases. TMAO, a metabolite derived from gut microbial metabolism of nutrients like choline, has been implicated in obesity, diabetes, and cardiovascular diseases due to its role in promoting inflammation and atherothrombosis 73,74. Inhibitors targeting the microbial enzymes CutC and CutD, responsible for TMA production, have shown efficacy in reducing TMAO levels, thereby mitigating thrombosis potential and metabolic disturbances without affecting the viability of commensal bacteria 75,76. By selectively accumulating in intestinal microbes, these inhibitors offer a nonlethal approach to modulate gut microbiota and reduce systemic exposure, highlighting their potential as safe therapeutic agents 76. Additionally, the manipulation of flavin-containing monooxygenase (FMO3) involved in TMAO production is being explored to understand further and develop rational drug design strategies 73. The development of these drugs is part of a broader trend in drug discovery that leverages synthetic biology and conventional approaches to target gut microbiota and their metabolites, aiming to address the underlying mechanisms of metabolic disorders and cardiovascular diseases 77. This innovative approach underscores the potential of gut microbiota-targeted therapies in reshaping treatment paradigms for complex diseases linked to metabolic dysregulation.

Integrating probiotics and prebiotics with traditional cardiovascular drugs, such as statins and ACE inhibitors, presents a promising strategy to enhance therapeutic outcomes for cardiovascular diseases (CVDs). Probiotics and prebiotics have been shown to influence cholesterol levels, inflammation, and endothelial function, which are critical factors in CVD management 78,79. Probiotics, particularly strains like Lactobacilli and Bifidobacteria, have demonstrated potential in reducing inflammation and improving endothelial health, which could complement the cholesterol-lowering effects of statins 72. The microbiota of gut helps in drug metabolism and response, potentially modulating the efficacy and side effects of statins 80. This interaction suggests that probiotics could enhance the therapeutic effects of statins by optimizing gut microbiota composition, thereby improving lipid metabolism and reducing inflammation 72,80. Furthermore, prebiotics exhibit anti-inflammatory properties and may aid in managing hypertension and hypercholesterolemia, conditions often targeted by ACE inhibitors 72. The synergy between probiotics, prebiotics, and cardiovascular drugs could also be mediated through the modulation of gut microbiota-derived metabolites, such as tryptophan derivatives, which influence immune and inflammatory pathways crucial in CVDs 39. Despite these promising insights, further well-designed clinical trials are necessary to fully understand the long-term effects and potential benefits of combining these dietary components with traditional drug therapies in CVD prevention and treatment 78.

# Future directions

Microbiome profiling is increasingly advocated for designing individualized therapies tailored to a patient's gut microbiota composition, as it holds significant potential in advancing personalized medicine. The gut microbiota in modulating metabolic and immune functions, impacting disease susceptibility and overall health, which underscores the importance of personalized nutrition strategies based on individual microbiota compositions 81. Progress in next-generation sequencing and metabolomic analysis have permitted the high-fidelity characterization of microbiome ecosystems, thereby promoting the formulation of specific therapeutic interventions for ailments such as IBD by means of the modulation of the gut microbiome through dietary alterations or the utilization of engineered probiotics82. Furthermore, gut microbiota's influence on the efficacy and side effect profile of biological therapies for autoimmune diseases highlights its potential in optimizing treatment outcomes and minimizing adverse events, suggesting that microbiota assessments could enhance personalized treatment strategies 83. Personalized medicine approaches, such as FMT and use of probiotics and prebiotics, are emerging as effective tools to restore microbiome balance and improve health outcomes 84. The concept of the human gut metacommunity, which emphasizes the metabolic interplay within microbiomes, supports the development of precision medicine by addressing functional dysbioses and providing tailored therapeutic interventions 85.

The clinical translation of probiotics faces several challenges, including variability in gut microbiota across populations, strain-specific effects, and long-term safety concerns. The gut microbiome's inherent variability among individuals complicates the standardization of probiotic treatments, as different populations may respond differently to the same probiotic strains due to distinct microbiome compositions 82. This variability is further compounded by the strain-specific effects of probiotics, where certain strains may be beneficial for specific conditions like IBD, but not others, necessitating precise strain selection for effective treatment 86. Moreover, the long-term safety of probiotics remains a significant concern, particularly as their use expands into vulnerable populations. The potential for adverse events, including the transfer of virulence or antibiotic resistance genes, underscores the need for rigorous safety assessments and whole genome sequencing to ensure strain identity and safety 87. Additionally, the lack of global harmonization in probiotic regulation poses challenges in ensuring product quality and safety, as different countries have varying standards for evaluating and approving probiotic products 88. These challenges highlight the need for integrated research and regulatory frameworks to advance the safe and effective clinical application of probiotics, considering both individual microbiome variability and the specific characteristics of probiotic strains.

The exploration of the gut-heart connection necessitates a collaborative approach involving microbiologists, cardiologists, and pharmacologists due to complex interplay between cardiovascular health and gut microbiota. The gut-heart axis influences CVD pathogenesis through mechanisms such as systemic inflammation and metabolic regulation, mediated by gut-derived metabolites like SCFAs and TMAO 16,17. Dysbiosis, linked to various cardiovascular conditions, such as myocardial infarction, atherosclerosis and hypertension, highlighting the need for interdisciplinary research to develop effective therapeutic strategies 16,17,59. Pharmacologists play a crucial role in understanding how gut microbiota affects the metabolism of cardiotropic drugs, which can lead to variability in drug efficacy and safety among patients 89.

# Conclusion

The gut-heart axis plays a pivotal role in cardiovascular health by influencing systemic inflammation and metabolic processes, with disruptions in this axis leading to increased levels of harmful metabolites like TMAO and LPSs, which exacerbate cardiovascular diseases such as myocardial infarction. Beneficial metabolites like SCFAs, produced by a balanced gut microbiota, can protect against cardiac damage and influence blood pressure, glycemic control, and lipid profiles. Despite these promising findings, challenges such as individual variability in microbiome composition and the need for robust clinical trials remain, highlighting the importance of further research to establish causality and develop personalized therapeutic approaches. Understanding and modulating the gut microbiota could revolutionize cardiovascular disease prevention and treatment by offering novel insights and therapeutic opportunities, with strategies like prebiotics, probiotics, and dietary modifications aiming to enhance the production of beneficial metabolites.

# Declarations

# DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

**ETHICAL APPROVAL**

It is not applicable.

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