Review

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Role of gut microbiota in cardiovascular diseases – a comprehensive review

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Abstract

The connection between cardiovascular illnesses and the gut microbiota has drawn more and more attention in recent years. According to research, there are intricate relationships between dietary elements, gut bacteria, and their metabolites that affect cardiovascular health. In this study, the role of gut microbiota in cardiovascular disorders is examined, with an emphasis on the cardiac consequences brought on by changes in gut microbiota. This essay discusses the gut-heart axis in depth and in detail. It talks about clinical research looking at how soy consumption, probiotic supplements, and dietary changes affected gut microbiota and cardiovascular risk variables. Our goal is to clarify the possible pathways that connect gut microbiota to cardiovascular health and the implications for upcoming treatment approaches. The authors examine the composition, roles, and effects of the gut microbiota on cardiovascular health, including their contributions to hypertension, atherosclerosis, lipid metabolism, and heart failure. Endotoxemia, inflammation, immunological dysfunction, and host lipid metabolism are some of the potential processes investigated for how the gut microbiota affects cardiac outcomes. The research emphasizes the need for larger interventional studies and personalized medicine strategies to completely understand the complexity of the gut-heart axis and its implications for the management of cardiovascular disease. The development of novel treatment strategies and cutting-edge diagnostic technologies in cardiovascular medicine may be facilitated by a better understanding of this axis.

Keywords: cardiac outcomes, cardiovascular diseases, gut microbiota

Introduction

The association between an unhealthy diet and cardiovascular disease (CVD) morbidity has long been recognized as a significant factor. It was initially established based on determinants of metabolic stress and overweight, such as adiposity and visceral fat presence[1]. However, recent research has highlighted the intricate interactions between dietary components, gut microbiota, and their metabolites, influencing cardiovascular health. Consequently, there is increasing interest in investigating the potential benefits of probiotics in mitigating atherosclerosis and other CVD forms, driven by a growing understanding of the gut microbiota's role in CVD[2,3]. While a relationship between coronary heart disease and atherosclerosis has been established, our knowledge about the microbiome composition changes linked to these conditions remains limited[4,5].

HIGHLIGHTS

- The paper highlights the increasing attention given to the relationship between cardiovascular illnesses and the gut microbiota. Research suggests that intricate connections exist between dietary elements, gut bacteria, and their metabolites, which collectively influence cardiovascular health.
- The study examines the role of gut microbiota in cardiovascular disorders, with a specific focus on the cardiac consequences resulting from changes in gut microbiota composition. The paper delves into the concept of the 'gut-heart axis' and thoroughly discusses its implications.
- The paper presents clinical research findings on the effects of soy consumption, probiotic supplements, and dietary changes on both gut microbiota and cardiovascular risk factors. It explores the potential pathways connecting gut microbiota to cardiovascular health, including influences on hypertension, atherosclerosis, lipid metabolism, heart failure, endotoxemia, inflammation, immunological dysfunction, and host lipid metabolism.

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CVD, encompassing hypertension, atherosclerosis, and heart failure (HF), remains a leading global cause of mortality[6]. Studies have revealed diverse interactions between the gut microbiota and its metabolic products with the host, influencing the development and occurrence of CVD. Trimethylamine-N-oxide (TMAO), bile acids, and short-chain fatty acids (SCFAs) are among the gut microbiota's metabolic byproducts associated with CVD[7,8]. Early studies suggested a potential link between the microbiota and atherosclerosis, as human atherosclerotic plaques contained bacterial DNA. However, it was uncertain whether the DNA originated from live bacteria within the artery wall[51]. The first studies that provided insight into a potential cause-and-effect relationship between the gut microbiome and CVD focused on TMAO, a metabolite formed after consuming dietary nutrients abundant in a Western diet[9].

Rationale for exploring the gut-heart axis and cardiac outcomes

Understanding the gut-heart axis offers new possibilities for preventive and therapeutic interventions in cardiovascular medicine. Researchers and clinicians are exploring the gut microbiota and its metabolites to identify strategies that can reduce cardiovascular risks, improve treatment outcomes, and enhance overall heart health.

While research in the gut-heart axis is still emerging, promising results from preclinical studies and early human research have generated considerable interest in this field. By unraveling the intricate mechanisms linking gut microbiota to cardiac outcomes, we may pave the way for novel therapeutic approaches and personalized interventions for CVDs in the future. However, further research is needed to fully comprehend the complexities of this relationship and translate these findings into effective clinical applications. In this paper, we delve into the gut-heart axis and explore various aspects of it.

Gut microbiota and cardiovascular health

Composition and functions of the gut microbiota

The gut microbiota is a diverse community of microorganisms, comprising bacteria, yeast, and viruses. Bacteria are classified into various hierarchical levels, including phyla, classes, orders, families, genera, and species[9]. Over 160 species have been identified, with a majority belonging to dominant phyla[9]. The primary gut microbial phyla are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with Firmicutes and Bacteroidetes making up around 90% of the gut microbiota[10]. The Firmicutes phylum encompasses over 200 genera, such as Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus, with the Clostridium genera being particularly abundant[10]. Bacteroidetes is mainly composed of notable genera like Bacteroides and Prevotella, while the less abundant Actinobacteria phylum is primarily represented by the Bifidobacterium genus[10,11]. The gut microbiota serves various vital functions within the human body, including protection against pathogens through colonization of mucosal surfaces and the production of antimicrobial substances, which contributes to enhancing the immune system[12]. Additionally, the gut microbiota plays essential roles in digestion, metabolism, epithelial cell proliferation and differentiation, as well as influencing insulin resistance and secretion[13–15]. Moreover, the gut microbiota plays a significant role in brain-gut communication, impacting the mental and neurological functions of the host[16]. Hence, the gut microbiota's role within the human body is evident and multifaceted[17].

Gut microbiota-host interactions and their influence on cardiovascular health

The gut microbiota plays a significant role in food digestion through two main catabolic pathways known as saccharolytic and proteolytic pathways[18]. In the saccharolytic pathway, the gut microbiota break down sugars and produce the majority of SCFAs. On the other hand, the proteolytic pathway involves protein fermentation, leading to SCFA production along with other co-metabolites such as ammonia, various amines, thiols, phenols, and indoles. Some of these metabolites can be toxic, and their accumulation, primarily cleared by the kidneys, are referred to as microbial uremic toxins[19]. Besides their role in food digestion, the gut microbiota performs multiple functions and interacts with the host in various ways. It contributes to the formation and regulation of the intestinal mucosal barriers, controls nutrient uptake and metabolism, aids in the maturation of immunological tissues, and prevents the proliferation of pathogenic microorganisms[20–24]. Under normal conditions, the gut microbiota continues to stimulate the immune system, serving as a rapid and effective defense mechanism against pathogens[25]. Overall, the microbiota have a fundamental impact on systemic immunity and metabolism, and a healthy gut microbiota is crucial for the overall health of the host[3,26].

A small study demonstrated that hypertensive patients had lower microbial community diversity and distinct clustering compared to normotensive individuals[27]. Both prehypertensive and hypertensive patients exhibited lower gene richness and α-diversity than healthy controls, along with a higher percentage of bacteria from the genus Prevotella[28]. Recent research has connected the gut microbiota with CVD by reporting cases of bacterial translocation from the gut to the heart[29] and detecting gut bacterial DNA in atherosclerotic plaques[2]. These findings suggest that the intestine may act as a potential reservoir of pathogenic microorganisms, and the gut microbiota may play a role in atherosclerosis development. Metagenomic analysis revealed differences in the gut microbiome between atherosclerotic cardiovascular patients and healthy individuals, with elevated levels of Streptococcus and Enterobacteriaceae species in patients[30]. Another study, using the terminal restriction fragment length polymorphism method, found altered gut microbiota profiles in patients with coronary artery diseases (CADs), with an increase in Lactobacillales and Clostridium subcluster XIVa, and a reduction in Bacteroides in fecal samples[31]. Extensive evidence supports the involvement of the gut microbiota in HF development and progression, leading to the proposal of the 'gut hypothesis'. This hypothesis suggests that reduced cardiac output-induced intestinal hypoperfusion and congestion may lead to bowel wall edema and impaired barrier function, resulting in increased bacterial translocation-related inflammatory responses and changes in the gut microbiota that can further exacerbate HF[32–34]. HF patients with lower intestinal blood flow were found to have higher anti-LPS IgA serum levels, associated with increased growth of bacteria from colonic mucosa biopsies[35]. A comparison of fecal bacteria in HF patients and healthy

individuals revealed higher colonization of pathogenic bacteria, including Campylobacter, Shigella, Salmonella, and Yersinia enterocolitica, in chronic HF patients[36]. Furthermore, species such as Candida, Campylobacter, and Shigella were positively correlated with HF severity[37,38].

Clinical trials

In the study conducted by Malik *et al*., the researchers investigated the impact of supplementing patients with stable CAD with Lactobacillus plantarum 299v probiotics. The 6-week intervention resulted in improved endothelial function, but other vascular parameters remained unchanged. Probiotic supplementation also led to reduced levels of inflammatory cytokines and plasma leptin, and specific changes were observed in the gut microbiome composition, with an enrichment of Lactobacillus and Bacillus species. However, there was no significant change in the plasma TMAO concentration. The findings suggest that Lactobacillus plantarum 299v supplementation may have a positive effect on vascular function and certain plasma biomarkers in patients with CAD. Nevertheless, further research is needed to gain a comprehensive understanding of its impact on cardiovascular health[39].

In a randomized, controlled crossover trial, Wang *et al*. investigated the effects of different dietary interventions on gut microbiota composition and cardiovascular risk factors. The participants followed either a healthy lacto-ovo vegetarian diet (VD) or the same diet supplemented with cooked unprocessed or processed lean red meat for three weeks each, with washout periods in between. While specific changes were observed in certain gut microbiota genera and operational taxonomic units in response to the diets, the overall gut microbiota structure remained unaffected. The healthy dietary pattern led to improvements in blood lipid profiles, resulting in reduced total cholesterol and low-density lipoprotein cholesterol levels, regardless of red meat consumption. Additionally, certain gut bacteria were found to be associated with cholesterol levels. The study emphasizes the potential advantages of adopting a healthy dietary pattern for gut microbiota and cardiovascular health, with individual responses varying among participants[40].

Shah *et al*. conducted a research study to investigate the links between dietary soy intake, gut microbiota, and metabolites in healthy individuals. The study identified two distinct gut enterotypes (Enterotype 1 and Enterotype 2) based on the composition of the gut microbiome. The association between soy intake and plasma and stool metabolites varied significantly between these enterotypes. Moreover, specific gut microbiota taxa were found to be connected to blood pressure, with Prevotella associated with increased blood pressure and Dialister linked to decreased blood pressure. Notably, the presence of Prevotella without the protective co-occurrence of Dialister was associated with higher blood pressure and unfavorable cardiometabolic risk markers. The research suggests that the gut microbiome plays a crucial role in influencing the effects of soy intake on metabolites and blood pressure, independent of dietary sodium intake, highlighting the intricate interactions between diet, gut microbiota, and cardiovascular health. More research is needed to fully comprehend the underlying mechanisms and implications for human health[41].

Djekic *et al*. conducted a clinical trial to compare the effects of a VD and a meat-based diet (MD) on patients with ischemic heart disease (IHD) receiving optimal medical therapy. The VD group exhibited lower levels of plasma oxidized LDL-C, total cholesterol, LDL-C, body weight, and BMI compared to the MD group. Although the overall composition of the gut microbiota remained similar between the diets, specific microbial genera differed. The VD induced changes in plasma metabolites, including acylcarnitine metabolites and phospholipids. Plasma concentrations of TMAO and l-carnitine were reduced after VD, while choline levels increased. Individual responses varied, with some participants experiencing greater benefits from VD, resulting in reduced oxidized LDL-C and BMI. The study suggests that VD may have favorable effects on cardiovascular risk markers, possibly attributed to alterations in gut microbiota and plasma metabolites, in patients with IHD[42].

Gut microbiota and specific CVDs

Gut microbiota in hypertension and blood pressure regulation

The gut microbiota, with Firmicutes and Bacteroidetes as dominant phyla, plays a vital role in regulating various aspects of cardiovascular health[43]. It can adapt to lifestyle modifications, including diet and exercise, and influences about 10% of the host's transcriptome, impacting immunity, cell proliferation, and metabolism[44]. The gut microbiota's role in CVD, particularly arteriosclerosis and hypertension, has been studied extensively. Elevated levels of TMAO and toxic metabolites like p-cresol and indoxyl sulfate, derived from the fermentation of protein by gut microbes, are associated with CVD[45]. SCFA, produced by the gut microbiota, influence blood pressure through the activation of specific receptors, GPR41, GPR43, and Olfr78[46]. Chronic low-grade inflammation and alterations in microbial gene richness are linked to hypertension[47]. Probiotic consumption has been shown to modestly decrease blood pressure in humans[48]. The impact of specific gut microbial species on blood pressure regulation is complex and influenced by genetic factors[49]. Further research is needed to better understand the specific role of different gut microbial species in cardiovascular health.

Gut-heart axis in atherosclerosis and lipid metabolism

Recent studies have revealed the presence of bacterial DNA in atherosclerotic plaques, suggesting a potential role of the gut microbiota in the development of CVD[50]. Patients with atherosclerosis have shown distinct differences in gut microbiota compared to those without[51]. Some studies found that patients with coronary heart disease or high IMT values, a marker of subclinical atherosclerosis, had a greater Firmicutes/Bacteroidetes ratio, while others reported enrichment of the phyla Escherichia in patients with subclinical carotid atherosclerosis and CAD[52]. Atherosclerotic plaques exhibit dominance of the phylum Proteobacteria and also contain the gut-dominant phylum Firmicutes. However, the role of the gut microbiota in atherosclerosis development remains inconclusive. Some studies suggest significant differences in gut microbiota between patients with stable and unstable plaques, while others found no major distinctions[53]. Bacterial DNA in plaques may trigger macrophages and activate the innate immune system through Toll-like receptor 2 (TLR2) and TLR4, which could be linked to plaque stability[54].

Gut microbiota modulation and its impact on HF

The 'gut hypothesis' in HF proposes a significant connection between the gut microbiota, its metabolites, and HF pathogenesis[33]. Evidence suggests that bacterial translocation in HF results from various mechanisms leading to structural and functional changes in the gastrointestinal tract, including splanchnic congestion and alterations in the host's immune defense system[55]. The gut microbiota, as essential components of the intestinal micro-ecosystem, play a crucial role in HF, influencing inflammation and intestinal permeability. Studies have shown increased pathogenic bacteria and yeasts in stable chronic HF patients, with levels correlating with HF severity[37]. The presence of the Escherichia/Shigella genus is also increased during the decompensated phase of HF compared to the compensated phase[56]. This pathogen overgrowth raises the risk of gastrointestinal infections in HF patients, leading to a worse in-hospital prognosis, especially when combined with antibiotic treatment[57].

Potential mechanisms underlying gut microbiota-cardiac connections

The gut microbiota's function is closely linked to the risk of CVDs. Gut microbiota dysbiosis can lead to impaired mucosal barrier, overactivated inflammation, and immune dysfunction, which are crucial steps in CVD development. Gram-negative bacteria, particularly LPS, play a key role in endotoxemia and impaired intestinal mucosal barrier function[58]. Metabolic endotoxemia, is often associated with the negative effects of gut microbiota-derived LPSs on inflammation, dysglycemia, and metabolic dysfunction. Different types of LPS from various bacteria influence gut barrier function, inflammation, hormones, and blood glucose levels. The interaction between LPS and other bacterial components further affects host metabolism. Interestingly, certain types of LPS can promote a metabolically beneficial endotoxemia, countering the detrimental effects of others. This suggests that the metabolic outcome is influenced by the synergy between different LPS types and other bacterial components[58]. LPS has been implicated in the development of cardiometabolic diseases[59]. Studies have shown that a high-fat diet (HFD) reduces levels of beneficial gram-positive Bifidobacteria and increases LPS-containing gut microbiota, contributing to obesity, a major CVD risk factor[60]. The gut microbiota is described as a key player in regulating energy balance. Changes in its composition due to environmental factors can disrupt this balance, potentially contributing to obesity. Alterations in the gut microbiota can impact the production and release of fat molecules, influencing energy storage. The gut microbiota aids in breaking down dietary polysaccharides, leading to increased fat production in the liver. It also influences the expression of genes related to fat cell accumulation. The gut microbiota can affect the expression of genes involved in fat storage and metabolism. Changes in the structure of the gut microbiota can lead to reduced adenosine monophosphate–activated protein kinase (AMPK) activity, potentially contributing to fat accumulation[60]. Continuous subcutaneous LPS infusion mimics the effects of a HFD on glucose metabolism and weight gain[61]. Overall, gut dysbiosis and altered metabolites disrupt nutrient metabolism, promote insulin resistance, and increase adipose tissue storage, heightening the risk of cardiovascular risk factors such as obesity and diabetes.

CVD patients, especially those with HF or hypertension, often show dysfunctional intestinal barriers and increased levels of the systemic microbial component LPS, leading to inflammation[62]. In HF patients, the intestinal barrier, maintained by factors like tight junctions, mucus, and immunity, is often compromised. This leads to bowel wall swelling and impaired function, known as 'leaky gut'. This allows bacterial products to enter the bloodstream, causing inflammation. Studies link intestinal changes in HF patients to elevated proinflammatory cytokines, worse symptoms, and outcomes[62]. Factors like fluid overload, sympathetic activation, and low cardiac output worsen bowel edema and reduce mucosal blood flow, increasing permeability and bacterial biofilm formation. A compromised gut barrier lets lipopolysaccharides (LPS) from Gram-negative bacteria enter the bloodstream, activating immune receptors (TLRs) and releasing proinflammatory cytokines, promoting inflammation in the host[62]. Long-term consumption of a HFD induces microbial dysbiosis, with an increased proportion of Gram-negative bacteria like Alistipes and Bacteroides, along with higher levels of genes involved in LPS biosynthesis[63]. Dietary fats can impair the intestinal barrier by activating the secretion of proinflammatory cytokines (e.g. TNF-α, IFNγ, and IL-1β)[64]. Gut microbes also play a role in CVD through host lipid metabolism. Studies suggest that the gut microbiota is implicated in lipid metabolism disorders like dyslipidemia or hyperlipidemia, which are major CVD risk factors[51]. TMAO (trimethylamine-N-oxide), a gut microbial cometabolite derived from dietary nutrients, has been linked to CVD risk[65]. Diets high in choline or carnitine can increase circulating TMAO levels, leading to enhanced macrophage foam cell formation and aortic atherosclerotic plaque development, directly connecting diet-microbiota-related TMAO to CVD progression[66].

Results

Table 1.

Table 1

The results of this paper are summarized in this table

Rationale for exploring the gut-heart axis	Understanding the gut-heart axis offers new possibilities for preventive and therapeutic interventions in cardiovascular medicine
Composition and functions of gut microbiota	The gut microbiota is a diverse community of microorganisms, including bacteria, yeast, and viruses. It plays vital roles in various bodily functions
Gut microbiota-host interactions and health	The gut microbiota influences digestion, metabolism, immunity, and brain-gut communication. Disruptions in gut microbiota can impact health outcomes
Clinical trials	Various clinical trials have explored the effects of interventions on gut microbiota and cardiovascular health
Gut microbiota in specific cardiovascular diseases	The gut microbiota has been studied in relation to hypertension, atherosclerosis, lipid metabolism, and heart failure
Potential mechanisms underlying connections	Gut microbiota dysbiosis can lead to impaired mucosal barrier, inflammation, and immune dysfunction, contributing to CVD development

Figure 1. Provides a schematic overview of the mechanisms in which gut microbiota and cardiovascular issues interact.

Challenges and future directions

The limitations of the study pertain mainly to the small sample size of the studies which have been evaluated. The complex nature of gut microbiota may hinder a complete grasp of the gut-heart axis and its implications for cardiovascular outcomes, as many studies rely on observational data, making it difficult to establish definitive causality between gut microbiota and CVDs.

Moreover, the gut microbiome is hyper-specific, influenced by various lifestyle, genetic, and diet factors. While valuable associations between gut microbiota and cardiovascular health have been found in existing studies, most of them focus on correlations

rather than causation. Therefore, further interventional studies are needed to unveil the relationship between gut microbiota and CVDs. To address these challenges, translational research becomes crucial as it can bridge the gap between basic scientific discoveries and clinical applications. A deeper understanding of the gut-heart axis can lead to innovative diagnostic tools and novel therapeutic approaches for managing CVDs.

Furthermore, interventions such as probiotics, prebiotics, or fecal microbiota transplantation could be explored to deliberately modulate the gut microbiota and potentially improve cardiovascular outcomes. As the gut microbiota varies from person to person, personalized medicine approaches hold promise in tailoring specific interventions for more effective CVD management. By combining these research approaches, we can gain a better understanding of the complex gut-heart axis and its significance in cardiovascular health. Which may lead to more targeted and personalized strategies for preventing and managing CVDs.

Conclusion

By understanding the mechanisms through which the gut microbiota influences cardiovascular health, researchers aim to identify strategies that can mitigate cardiovascular risks, enhance treatment outcomes, and improve overall heart health. Research into the gut-heart axis has shown promising findings, sparking significant interest in this field. These findings suggest that understanding the complex relationship between gut microbiota and cardiac outcomes may lead to therapeutic approaches and personalized interventions for CVDs in the future. However, it is essential to recognize that further research is needed to fully grasp the complexities of this relationship (Fig. 1).

Ethical approval

Ethics approval was not required for this Review Article.

Consent

Informed consent was not required for this Review Article.

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Authors' contributions

S.R. and A.I.S.: designed the study and conceived the idea; M.S.A., A.A., B.A., and T.W.: wrote the first draft; R.A., K.M., and V.K.: wrote the second draft; U.T. and S.K.: worked on the revisions.

Conflicts of interest disclosure

No conflicts of interest declared.

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