Gut Microbiome Modulation: A Frontier in Cardiovascular Diseases (CVDs) Prevention

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Abstract

Trillions of microorganisms, mainly bacteria, live in the gut microbiome and are essential to the host's physiological and metabolic health. In this regard, research has revealed a direct relationship between the gut microbiota and the development, course, and management of cardiovascular diseases (CVDs). Dietary habits influence the gut microbiota through various metabolic pathways. Eating a balanced diet supports gut microbiota whereas high consumption of red meat and fats leads to unfavorable microbial shift which can produce harmful metabolites. Consequently, these metabolic products can negatively influence the different body cells and lead to gut microbiota-driven heart failure, hypertension, atherosclerosis, myocardial infarction, myocardial fibrosis, and coronary artery disease (CAD). To improve both the development of treatments and the prevention of CVDs, this review primarily focuses on investigating the role of gut microbiota-associated metabolites and their therapeutic potential in CVDs. It's quite possible that shortly, gut microorganisms used for the clinical treatments of CVDs.

Keywords

Gut microbiota, Gut-Heart axis, Dysbiosis, Metabolites, Cardiovascular Diseases, atherosclerosis, hypertension

Introduction

The human halobiont is a unique functional unit composed of a much-diversified assembly of microbial species. In the digestive tract, there is a diverse colony of around 100 trillion microbial cells, and they have an impact on human physiology, metabolic processes, nutrition, and immunological function (Wang et al., 2022). Colonizing trillions of bacteria in the anaerobic and nutrient-rich gut environment develops a healthy intestinal physiological ecology. These communities are known as "gut microbiota," and "gut microbiomes", the collective term for all the microorganism genomes found in the gut, including the sequences of their DNA and other genetic data (Masenga et al., 2022). A term used to describe changes in the microbiota's composition and its metabolites is called dysbiosis. It has been involved in the spread of metabolic and inflammatory diseases. These include cancer, inflammatory bowel disease, cardiovascular disease (CVD),

hypertension, obesity, heart disease, atherosclerosis, renal disease, and type 2 diabetes mellitus. One of the root causes of mortality in the whole world is cardiovascular disease or CVD for short CVD. A lot of factors have been associated with an increased risk of CVD. These include smoking, obesity, a sedentary lifestyle, diabetes mellitus, hypertension, lipidemia, and dysfunctional lipid metabolism (Rajendiran, Ramadass, & Ramprasath, 2021). To a great degree, the gut microbiota is composed of Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria. In healthy individuals, the composition of the gut microbiota is relatively consistent. But it is not balanced in patients with several disorders or cardiovascular diseases (CVDs). In the large intestine, round about 90% of the gut microbiota includes that of Firmicutes and Bacteroidetes. This ratio is a vital health parameter that exposes the health condition and is related to the occurrence of CVDs. To create an energetic and stable microbial system, the gut microbiota maintains a symbiotic or hostile relation with its host (Masenga et al., 2022). Various metabolic pathways might regulate the dangerous effects of a modified microbiota. These include bile acid and trimethylamine (TMA/TMAO) pathways. TMAOs have been associated with a greater risk of CVD. The recent reviews have caused an upsurge in research initiatives to clarify the link between gut bacteria and CVD. This shows that gut microbiome plays a vital role in the development of CVD risks (Rajendran et al., 2021). This review provides a detailed and in-depth outline of the last decade's worth of published research. Furthermore, this involves mechanisms, ongoing developments, diagnostic strategies, and therapeutic implications of the gut microbiota's role in CVD (Rashid et al., 2024; Wang et al., 2022).

Gut Microbiome

The human gastrointestinal system has a complex and varied component called the gut microbiome. This balanced composition of microbiome varies from person to person. Firmicutes and Bacteroidetes are the two major dominant phyla. Whereas Actinobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia are the less prominent groups. Greater than 90% of the Firmicutes and Bacteroidetes species are present in a healthy gut microbiome. The abundance ratio of these species can be influenced by a lot of factors. This includes gender, age, dietary patterns, BMI, physical workouts, geography, socioeconomic backgrounds, indoor pets, use of antibiotics, and illnesses. The gut microbiota profiles of Westernized humans have developed parallel to their dietary habits. Most of the our ancestors' diet were plant-based, mostly consisting of indigestible fiber and complex carbohydrates. Short-chain fatty acids (SCFAs) can be produced from indigestible macromolecules and have a variety of advantageous psychological impacts on the host. Certain gut microorganisms can use SCFAs generated by other microbes, which lowers cytokine levels and gives the human host energy. Like propionate, acetate, and butyrate, SCFAs enter the bloodstream through passive absorption by intestinal enterocytes. In addition to controlling physiological processes such as gastrointestinal barrier integrity, epithelial cell proliferation, and the activity of histone deacetylase inhibition, they also control the inflammatory process and biological responses. Through interactions with epithelial cells, the gut microbiome strengthens the gut barrier by stimulating immune cells and initiating signaling cascades. By changing the bile acid composition and transforming escaping primary beta-amylases (BAs) into secondary BAs, which enter circulation and function as signaling molecules to regulate host

metabolism and inflammation, the gut microbiota also impacts host metabolism (Luqman et al., 2024; Rajendiran et al., 2021).

The Role of Host's Gut Microbiota

The microbiota that exists in the body is live with their host to thrive. Utilizing proteolytic and saccharolytic pathways, the main anaerobic microbiota colonizes the colon of the gastrointestinal tract (GIT) and breaks down nutrients. Together with the host, the gut microbiota stimulates digestion and regulates the function of gut mucosal layers. It supplies tissue for immunity and lessens the pathogenicity of microbes. The immune system's defense against infections is influenced by the gut microbiota when certain conditions are met. It has been demonstrated to positively impact lipid metabolism by lowering adipocyte lipoprotein lipase activity. It has been demonstrated that Bacteroides thetaiotaomicron increases the synthesis of a colipase required for pancreatic lipase to digest lipids, therefore improves the efficiency of lipid hydrolysis. Polyphenols, which are found in fruits, vegetables, tea, chocolate, and wine, and which are absorbed through diet, are broken down by the human gut bacteria. For optimal homeostasis, a healthy microbiota in the gut is necessary because it must accept helpful commensals while inhibiting pathogen expansion. Antimicrobial defense is mostly based on a two-tiered mucosal layer, especially in the large intestine. The gut microbiota stimulates host Paneth cells to manufacture antimicrobial proteins (AMP) such C-type lectins, cathelicidins, and (pro) defensins through a PRR-based pathway. Additionally involved in gut immunomodulation, the gut microbiota stimulates intestinal dendritic cells (DCs) to produce IgA (sIgA) (Rahman et al., 2022).

The gut microbiota is an intricate web of bacteria that inhabits different parts of the gut, including intestinal Bacteroidetes. The growth of Firmicutes and Bacteroidetes is influenced by more than 90% of these bacteria, and in people with cardiovascular disease (CVD), the Firmicutes/Bacteroidetes (F/B) ratio does not change. Children who have diabetes and obesity, two conditions that increase the risk of CVDs, may benefit from this ratio. As a carrier, the gut microbiota interacts with the host to maintain intestinal integrity. The gut bacteria convert TMAO, a chemical produced during the digestion of meals high in choline, lecithin, and L-carnitine, into TMA and g-butyrobetaine. Higher levels of TMAO in the bloodstream are linked with a higher risk of CVDs and death. This association is mediated by inflammatory pathways and modifications in the metabolism of bile and cholesterol. Increased TMAO levels in the arteries are linked to type 2 diabetes, metabolic syndrome, atherosclerosis, and the advancement of renal disease (Martins et al., 2024; Rahman et al., 2022).

Microbiota Dysbiosis and CVDs

An imbalance in the interactions between host and microbe is known as microbiota dysbiosis. Modifications in the makeup of microorganisms or community-derived elements (such as genotoxins or metabolites) may be linked, either directly or indirectly, to increase health risk. These microbiome-based factors could activate signaling pathways, which could result in the pathophysiological disorders associated with CVDs. Furthermore, it is possible to target these components for medicinal uses (Jin et al., 2021). A dysbiosis gut is characterized by an increase in proinflammatory species and a decrease in microbial diversity. With over a million

microorganisms, the colon is where it is mainly located. A lot of factors might impact the gut microbiome. This involves nutrition, xenobiotics, genetics, behavior, deep seated illnesses, immunological issues, and lifestyle habits. All of these chemicals and microbes combine with food particles to yield metabolites, which govern the body's overall metabolism. The vital functions of the cardiovascular system, lungs, brain, liver, and pancreas to function biologically depend on the gut bacteria of a healthy person. A disorder in the gut microbiome results in a depletion in the bacterial diversity or the production of the metabolites. This may influence signaling pathways and human function. Ultimately, this may result in the generation of toxins and degenerative effects (Dosh et al., 2024; Singh et al., 2023).

We discussed above that Firmicutes and Bacteroidetes make up the bulk of the gut population in healthy adults. So, this ratio indicates the overall health of intestinal microbiota. The composition of microbes, however, varies among people. This is continuously sensitive to host characteristics and environmental factors. Cardiovascular diseases (CVDs) risk has been linked to an increased rate of host opportunistic infections and a decreased bacterial load that produces short-chain fatty acids (SCFAs). The probability of developing CVDs may differ based on the relative abundance of these two kinds of bacteria. Bacterial genome analyses, which use 16S rDNA sequencing and metagenomic sequencing to evaluate microbial compositions and relative abundances, have changed studies of microorganisms. By detecting every organism's full genome, shotgun metagenomics increases sensitivity to both known and unknown bacteria (Jin et al., 2021).

Blood is now thought to have a blood microbiome, despite historically being thought of as a sterile environment. Most bacteria in the body's microbiota of healthy people are proteobacteria, whereas Firmicutes and Bacteroidetes predominate in the gut microbiota. Through prenatal migration or translocation, microbes get into the circulation. Atherosclerotic plaques may get colonized by circulating microorganisms, which can cause inflammation and cardiovascular illnesses (CVDs). Proteobacteria and Pseudomonadaceae populations are greater in CVD patients' bloodstreams, but Firmicutes, Gamma proteobacteria, Bacillales, and *Staphylococci* populations are less common. Increased blood levels of *Staphylococcus* species are associated with inflammatory reactions and chronic infections, which can result in CVDs (Cheemala et al., 2024; Jin et al., 2021).

Variations in the Metabolites of Microbes

The gut contains a variety of gastrointestinal microbial metabolites, including hormones, vitamins, SCFAs, derivatives of amino acids, and antioxidants. These metabolites may move to distant organs by directly entering the circulation of the host and absorbing them. Alternatively, they could be converted into signaling molecules by the host's enzymes. In healthy people, most metabolites produced by microbes can have synergistic effects (Jin et al., 2021).

Short chain fatty acids (SCFA)

Saturated fatty acids (SCFAs) can be produced when the human gut bacteria ferments complex carbohydrates. Three SCFA i.e.: acetate, butyrate, and propionate are critical for lipid metabolic pathways, anti-inflammatory reactions, and gluconeogenesis. They also act as substrates for energy for the intestinal epithelial cells. Systemic circulation SCFAs can modify the impact of the microbiome on cardiovascular diseases (CVDs). Additionally, they maintain the immune system

and attenuate oxidative stress through immunomodulatory actions. It has been demonstrated that 1% butyrate dietary supplements improve plaque stability and decrease the course of atherosclerosis. SCFA propionate guards against cardiac hypertrophy, vascular dysfunction, fibrosis, and hypertension in a way that is dependent on T cells (Jin et al., 2021; Mousavi Ghahfarrokhi et al., 2024).

Trimethylamine N-oxide (TMAO)

Trimethylamine or TMAO is a hepatic oxidation byproduct of trimethylamine (TMA) which has a major impact on cardiovascular diseases (CVDs). Studies have shown a positive association between increased plasma TMAO levels and an increased risk of cardiovascular disease. Higher plasma TMAO levels may indicate an increased risk for myocardial infarction, heart failure, peripheral arterial disease, stroke, and chronic coronary artery disease. Broad spectrum antibiotic users have significantly lower TMAO levels and a less diverse gut microbiota. To reduce the risk of CVD, foods high in lecithin, choline, and carnitine should be taken in moderation. Several choline analogues, including more powerful TMA lyase inhibitor like fluromethylcholine (FMC), bro methylthionine, iodomethylcholine (IMC) chloromethyl choline, and naturally occurring substances like 3,3-dimethyl-1-butanol (DMB), have been shown to lower TMAO levels in the bloodstream (Dinakis, O'Donnell, & Marques, 2024; Hemmati et al., 2023; Jin et al., 2021).

Additional metabolites

Tryptophan (Trp), phenylalanine (Phe), and tyrosine (Tyr) are examples of aromatic amino acids that can influence neurological, metabolic, and immune responses. Tyr acts as a neurotransmitter that can transform into adrenaline and norepinephrine. Phe is a precursor for Tyr whereas serotonin's precursor is called Trp. Plasma levels of a certain Trp metabolite generated by microbes are decreased among individuals with advanced atherosclerosis. According to a study, the degree of myocardial infarction (MI) may be correlated with the gut microbiota metabolites of Tyr and Phe. When phenylacetic acid (PAGln) is formed from phenylacetylglutamine (Phe), it has been linked to adverse outcomes and cardiovascular disorders (Jin et al., 2021).

Influence of Dietary Choices on Gut Microbiota and CVD

By balancing harmful and helpful bacteria or microbial products, diet may have an impact on the gut microbiota. Animal-protein-rich diets, such as those high in animal-protein, Bacteroides enterotype, and other species associated with proatherogenic chemicals and CVDs are fostered by vegetarian diets, which increase the favorable microbiota composition through the increase of Prevotella enterotype. The liver enzyme flavin monooxygenase 3 oxidizes TMA to create the proatherogenic metabolite TMAO, which has been connected to peripheral artery disease, coronary plaques, and consequences from CVD. TMAO-mediated actions that cause atherosclerosis are facilitated by common dietary components containing a TMA moiety, including phosphatidylcholine, L carnitine, and choline (Mao et al., 2024; Tang & Hazen, 2024).

Whole grains and other high-fiber diets raise the Bifidobacteria that produce acetate, which in turn lowers blood pressure, improves sensitivity of insulin, and reduces fibrosis and heart hypertrophy. Plant-based beverage polyphenols have been demonstrated to enhance cardiovascular health by

acting as antiplatelets, anti-inflammatory agents, and by encouraging the production of nitric oxide in blood vessels. Quercetin reduces the risk of diet-induced obesity and enhances cellular energy homeostasis, oxidation of fatty acids, and nitric oxide availability by increasing the number of *Bacteroides vulgatus* and *Akkermansia muciniphila* (Addissouky et al., 2024; Panyod et al., 2023). Immune activation may result from diet-induced changes in the makeup of gut microbes. Immune cells known as regulatory T cells (Tregs) are necessary to preserve immunologic self-tolerance. In the colon, SCFAs, particularly butyrate, cause peripherally derived Tregs to differentiate, reducing the activation of inflammation. By lowering SCFA-forming bacteria, a lower intake of soluble dietary fibers may lower the number of colonic Tregs and elevates the risk of chronic inflammatory conditions. Increased salt intake has been connected to hypertension by altering the gut microbiota's makeup and function. Overconsumption of salt in the diet modifies the gut microbiota. This can activate dendritic cells and increase synthesis of interferon-gamma (IFN-γ), interleukin 17 (IL-17), and tumor necrosis factor alpha (TNF-α). All these together results in hypertension. In addition, a diet rich in salt may destroy the intestinal barrier. This causes insulin resistance, systemic inflammation, and rise in blood pressure (Wang et al., 2022).

Fermentable oligo-, di-, and monosaccharide's along with polyols contains short-chain sugars and sugar alcohols. Because of osmotic activities, these are readily digested by intestinal bacteria but have little absorption in the small intestine. Studies have suggested that they could have potential therapeutic advantages in illnesses. These are linked with high intestinal permeability, such as non-celiac gluten intolerance and irritable bowel syndrome. Although, more scientific studies are necessary, but these results indicate possible involvement in dyslipidemias and atherosclerosis. (Novakovic et al., 2020; Ross et al., 2024).

It is confirmed that the Mediterranean diet effectively improves and blocks cardiovascular disease. Extra virgin olive oil (EVOO) is a popular fat source in the Mediterranean diet. It has significant nutritional value due to its biologically effective make up. Oleic acid is a main constituent, and it makes up as much as 70%–80% of EVOO. Furthermore, it involves more than 30 phenolic compounds, like HT, that is vital for preventing cardiovascular disease. Extra virgin olive oil (EVOO) is suggested as a best functional food. It has many benefits in improving levels of cholesterol, reducing inflammation, improving sensitivity to insulin, endothelial function, preventing thrombosis, and reducing atherosclerosis. All these beneficial effects are due to the bioactive elements of EVOO such as polyphenol and mono- and polyunsaturated fatty acids. (Abrignani, Salvo, Pacinella, & Tuttolomondo, 2024; Lu et al., 2024).

Several studies were conducted on the effects of several types of maize flour on gut flora and heart health. The duration of study was sixteen weeks and included a randomized crossover design. The study analyzed three types of corn flour. These were refined, whole grain, and a blend of refined corn flour and bran. Findings revealed that people who are not a high-risk benefit from utilizing refined corn flour enriched with bran in their daily meals. This in turns prevents their CVDs and low-density lipoproteins (LDLs). Further, the study found that at genus level a rise in alpha diversity was linked with a higher dietary fiber intake. This shows that consuming bran-enriched maize flour into diet can improve heart health and gut microbiota (Harris, 2024).

Microbiome Interventions

The human gut flora is one major potential focus for intervention in people with CVDs for better therapeutic outcomes. The recent therapeutic approaches focus on enhancing the gut flora and intestinal barrier restoration. Here, we have covered how supplements and food affect the gut microbiota as well as the possible benefits of various therapies to further reduce CVDs (Novakovic et al., 2020).

Probiotic and Prebiotic Therapy

Microorganisms' aka probiotics have a beneficial impact on the intestinal system and the host's microecological balance. They are often taken as a supplement to control obesity and lipid metabolism. Bacteroides species help to facilitate the degradation of branch-chain amino acids (BCAAs). Probiotics have the ability to control blood pressure, generate SCFAs, and modify lipid metabolism. It has been recently found that *Bifidobacterium breve* and *Lactobacillus fermentum* helps a lot in cases of hereditary hypertension. This can further prevent endothelial dysfunction and high blood pressures. Probiotics are currently explored in relation to atherosclerosis prevention and treatment. *Lactobacillus*, for example, regulates the gut microbiota makeup and enhances lipid metabolism and TMAO plasma levels. Probiotics may also lower the extent and enhance the future likelihood of heart failure following myocardial infarction. This which would be further beneficial for treating heart failure (Masenga et al., 2022; Ordovás, 2024).

On the other side, Prebiotics are non-digestible carbohydrates that modify the microbiome's composition and functions. They are abundant in resistant starches, dietary fibers, and oligo- and polysaccharides. Prebiotics aid in weight loss, obesity, and glucose tolerance by controlling plasma lipid profiles and glycemic conditions. Prebiotics and antibiotics have been demonstrated in studies to counteract the features of the microbial population linked to diabetes mellitus, as well as to enhance intestinal permeability, reduce metabolic endotoxemia, reduce inflammation, and encourage sugar intolerance. In conclusion, by focusing on gut flora, food may be an effective treatment for cardiovascular disorders (Rahman et al., 2022; Shah et al., 2024).

Drugs

Antibiotics

Antibiotics have been shown to enhance the prognosis of cardiovascular diseases (CVDs), decrease toxic bacteria, and modulate metabolites of the gut microbiota. They can improve the progression of atherosclerosis by lowering the levels of TMAO in plasma and preventing the production of macrophage foam cells. On the other hand, prolonged usage of antibiotics stands alone as a risk factor for atherosclerosis events. Antibiotic-induced atherosclerosis is exacerbated by the reduction of gut diversity and bacterial metabolic activity. Currently, antibiotics are used to treat CAD based on the gut microbiome, to eradicate disease-causing microbiota to change the course of the disease. Antibiotic therapy has a mixed record when it comes to lowering adverse cardiac incidents in CAD patients. It has been discovered that certain antibiotics, such as macrolides and quinolones, negatively impact cardiac prognosis when used in clinics for secondary prophylaxis. Antibiotics have been linked to CVDs, according to the available data, although prolonged antibiotic use can also lead to drug resistance. Extended usage of antibiotics can upset the dynamic equilibrium of microorganisms in the intestine. To fully understand the relationship

between antibiotics, CVDs and gut microbiota more preclinical and clinical research is required. Patients with CVDs ought to be given special consideration when using antibiotics (Rahman et al., 2022).

Transplantation of Fecal Microbiota

To restore a patient's gastrointestinal system to normal, a therapeutic procedure called fecal microbiota transplantation (FMT) involves inserting donor fecal samples into the depleted patient's digestive tract. Fecal materials from a healthy donor, or allogeneic FMT, and patient-supplied autologous FMT, on the other hand, are the two types of FMT. Among these, allogenic FMT is the most widely applied. Four techniques can be used in a laboratory to prepare FMT: purification, microfiltration plus centrifugation (MPC), filtration plus centrifugation (FPC), and rough filtration. The upper, middle, and lower gastrointestinal tracts are the delivery routes for FMT. FMT has demonstrated superiority over antibiotic therapy in the treatment of persistent *Clostridium difficile* bacterial infection and has been effective in the management of intestinal disorders such as inflammatory bowel diseases. Individuals with cardiometabolic problems have also benefited from its application; obese individuals, after initially receiving intestinal bacteria from lean donors, demonstrated increased insulin sensitivity. But there are several ethical problems with FMT, such as adjusting the balance between beneficial and harmful bacteria, getting representative donor samples, possibly transferring infectious agents or endotoxins, and setting up safeguards to keep an eye on the process and keep patients and donors safe. These procedures will discourage misuse and encourage more study on FMT (Jin et al., 2021).

One significant use of the gut microbiota is the development of new diagnostic and treatment methods for preventive and curative effects in human health, which is a newer area of research focus (Rahman et al., 2022). This review presents a connection between the occurrence of CVD and the gut microbiome. It has been discussed that there are several ways in which the gut microbiota interacts with the host. Alterations in the risk of CVD and the associated pathological alterations may be brought about by abnormalities in the composition of the microbial metabolites or gut microbiota. Consequently, by utilizing the potential of gut microbiota, new therapeutic targets and approaches for the treatment and prevention of CVD have been established. The potential application of microbiota in cardiovascular diseases along with other illnesses in humans in general is being actively pursued. To begin with, identifying certain microbe strains as opposed to a broad bacterial population could help clarify the roles played by different microorganisms in the development of a particular disease (Ezenabor, Adeyemi, & Adeyemi, 2024; Jin et al., 2021).

Conclusion

With several pathways, dysbiosis raises the risk for numerous CVDs. It is linked to the translocation of microorganisms from the GI tract into the interstitial and perivascular tissues, which can lead to hypertension, atherosclerosis, irregularities in the metabolism of fat and glucose, and systemic inflammation. The Western diet and eating schedule alter the gut flora, which raises the risk of CVD. Consuming a lot of salt in the diet raises the chance of developing hypertension, dysbiosis, and other CVDs. One of the risk factors for CVD emerging is sex-dependent microbial makeup. Still, there is not much of information on this topic, therefore more research is necessary.

The aging process is linked to a decrease in microorganisms that promote health and an increase in the metabolic pathways that cause heart disease.

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