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The Role of Gut Microbiota and Probiotics-Prebiotics in the Treatment of Cardiovascular Diseases

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ABSTRACT

Cardiovascular diseases (CVD), a major cause of morbidity and mortality worldwide, are among the most well-known and extensively studied diseases. The onset and progression of CVD are associated with multiple risk factors, among which the gut microbiota has gained significant attention over the past two decades. The microbial community colonizing the gut, referred to as the gut microbiota, plays a crucial role in human health. In particular, gut dysbiosis is directly linked to various acute and chronic dysfunctions of the host's cardiovascular system. Previous studies have demonstrated a strong association between CVD pathogenesis, gut microbiota imbalance, and inflammatory responses. Probiotics and prebiotics, which provide various health benefits to the host, have emerged as promising therapeutic interventions for many diseases. These two types of dietary supplements have the potential to reduce cardiovascular disease risks by improving the levels of cardiovascular markers such as total and low-density lipoprotein (LDL) cholesterol, high-sensitivity C-reactive protein (hs-CRP), and specific cytokines related to the inflammatory response. This review discusses the protective effects of probiotics and prebiotics in balancing structural and functional changes in the gut microbiota and maintaining immune homeostasis.

Keywords: CVD, Probiotics, Prebiotics, Gut Microbiota, Immune Homeostasis.

INTRODUCTION

In recent years, cardiovascular diseases (CVD) have emerged as one of the leading causes of early mortality and morbidity in developing countries, particularly in low- and middle-income populations. In developed countries, more than half of the deaths in the middle-aged population and approximately one-third of deaths in the elderly population are associated with CVD (1). Unhealthy lifestyle factors such as an unbalanced diet, alcohol consumption, smoking, and physical inactivity play a significant role in the etiology of CVD and markedly increase disease risk. The beneficial effects of probiotics and prebiotics on host health have been extensively studied. The term "probiotic" originates from Greek and means "for life." The definition of probiotics, established by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in 2014 and endorsed by the International Scientific Association for Probiotics and Prebiotics (ISAPP), describes them as "carefully selected strains of live microorganisms that, when administered in adequate amounts, confer health benefits to the host" (2). The term "prebiotics" was first proposed by Gibson and Roberfroid in 1995 and was updated in 2004 as "non-digestible food components that allow specificity in microbial changes within the intestinal system." These components have been reported to exert beneficial effects on host health (3). Probiotics and prebiotics have beneficial effects on human health and have long been recognized as potential nutritional supplements for preventing the development of various intestinal diseases, such as diarrhea and inflammatory bowel disease (IBD). In addition to their effects on the intestinal system, increasing evidence supports their ability to exert direct functions. Moreover, both probiotics and prebiotics are believed to improve metabolic disorders, including obesity, diabetes, and CVD (4). Thanks to high-throughput techniques developed for sequencing the gut microbiota, the role of the gut microbiota in human health and well-being has been extensively investigated. A growing body of evidence suggests that alterations in the gut microbiota are associated with various diseases, including CVD (5).

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A growing body of evidence suggests that alterations in the gut microbiota are associated with various diseases, including CVD. Imbalances in the gut microbiota have been linked to conditions such as heart failure, thrombosis, atherogenesis, and arterial hypertension (6,7). The beneficial effects of probiotics and prebiotics in altering the microbial and metabolic composition of the gut microbiota can be considered a potential therapeutic strategy for CVD. Furthermore, the protective effects of probiotic and prebiotic treatments on CVD can also be explained by the modulation of the host's immune system. The effects of probiotics and prebiotics are associated with changes in dendritic cells, epithelial cells, regulatory T cells, effector lymphocytes, natural killer T cells, and B cells. As in many chronic diseases, low-grade inflammation plays a significant role in CVD. The plasma levels of pro-inflammatory factors, such as IL-1, IL-6, and TNF-α, which are activated by both innate and adaptive immune cells, are often found to be elevated in CVD (8).

Cardiovascular Disease: Risk Factors and Development Mechanisms

CVD encompass conditions affecting the heart and blood vessels, such as coronary artery disease, stroke, hypertensive heart disease, cardiomyopathy, venous thrombosis, arrhythmias, and thromboembolic diseases. CVD has become an increasingly significant global health issue. It has been shown that CVDs can develop due to lesions in the coronary, cerebral, or peripheral arteries. Atherosclerosis, thrombosis, and coagulation are frequently involved in the pathophysiology of these diseases. The onset and progression of atherosclerosis are regulated by various immune responses (9).

Atherosclerosis is characterized by the formation and progressive growth of atherosclerotic plaques (primarily lipid-rich) in the arterial walls. The lipids in these plaques primarily originate from cholesterol derived from circulating LDL particles. Lipoproteins pass through the arterial subendothelial space, activating endothelial cells. Meanwhile, monocytes in the vascular wall take up lipoproteins and differentiate into macrophages, transforming into foam cells, which are a characteristic feature of the atherosclerotic plaque. Therefore, atherosclerosis is a lipid-focused, chronic inflammatory disease and a key predisposing factor for heart disease and stroke. The second most common pathophysiology of CVD involves coagulation, initially produced in an inactive form as a precursor or zymogen, which is then activated by a proteolytic reaction cascade (10). Among the factors that influence the risk of developing cardiovascular diseases are genetics and unhealthy lifestyle choices (lack of physical activity, poor diet, smoking, and alcohol consumption). Hypertension is considered the most common modifiable risk factor for cardiovascular diseases. High blood pressure is often associated with metabolic imbalances, which, similar to the effects of type 2 diabetes, can damage blood vessels and lead to high blood cholesterol levels, promoting the development of atherosclerosis. The reciprocal interaction between hypertension and hypercholesterolemia, and their effects on the development of atherosclerosis, involve the renin-angiotensin-aldosterone system and endothelial dysfunction (11,12).

Gut Microbiota and Cardiovascular Diseases

The gut microbiota refers to a community of microorganisms that inhabit our intestines, including bacteria, archaea, viruses, and unicellular eukaryotes. Among these microbial interactions, bacteria have been the most extensively studied to understand their roles in human health. It is estimated that the number of bacterial cells in the gastrointestinal tract (GIT) is approximately 3.8×1013, which is similar to the total number of human cells in the body. However, the total mass of the gut microbiota in a healthy individual accounts for only about 0.3% of the total body weight (13). Surprisingly, the 9 million unique genes observed in the GIT through metagenomic studies are 450 times greater than the entire human genome (14). Increasing evidence links the gut microbiota to the development of various cardio-metabolic diseases, including diabetes mellitus, obesity, hypertension, and CVD (15). Certain unique bacterial species found in the gastrointestinal system have been reported to play critical roles in human health. Recently, although Akkermansia muciniphila has not been included in the list of traditional probiotics, it has been suggested to have the potential to be a next-generation probiotic. It has been demonstrated that the relative abundance of this bacterium is higher in healthy individuals compared to patients with obesity and diabetes (16). In stool samples from patients with CVD, a significant presence of pathogens such as Shigella, Campylobacter, Yersinia, Streptococcus spp., Enterobacteriaceae, and Candida has been observed. Additionally, it has been determined that the gut microbiota and its metabolites are strongly associated with the progression of CVD (17).

Metagenomic and metabolomic analyses of stool and plasma samples from healthy individuals and chronic heart failure (CHF) patients have revealed significant differences in the composition of the gut microbiota and its metabolites. In this study, the abundance of Faecalibacterium prausnitzii was found to be lower in CHF patients, while Ruminococcus gnavus was higher compared to controls. Additionally, increased levels of butyrate and decreased levels of trimethylamine N-oxide (TMAO) were observed in CHF. TMAO, one of the well-studied metabolites produced by the gut microbiota, shows a positive correlation with early-stage atherosclerosis (18). This metabolite increases the size of atherosclerotic plaques, triggers prothrombotic platelet function, and supports arterial thrombus growth. Another study revealed that high levels of TMAO produced through choline metabolism by the gut microbiota in female C57BL/6J ApoE-/- mice fed a choline diet promoted the development of atherosclerosis. Additionally, lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, can negatively affect cardiovascular function and increase the risk of cardiovascular disease. Studies in animal models have shown that low-dose LPS intake leads to vascular inflammation and the development of atherosclerosis (19,20).

The Potential Effects of Probiotics and Prebiotics in Cardiovascular Diseases

Probiotics;

Fermented products such as yogurt, kefir, sauerkraut, tempeh, and kimchi have long been a part of the diet in various cultures as sources of probiotic strains. According to current information, probiotics include both bacterial species (Lactobacillus, Lactococcus, Leuconostoc, Pediococcus, Propionibacterium, Bifidobacterium, Bacillus, some Streptococcus, Enterococcus, Escherichia coli species) and yeast species (Saccharomyces) (21). The efficacy of probiotics is influenced by various factors, including their interactions with the host and microbiota. To exhibit a positive effect, probiotics must inhibit the growth of pathogenic bacteria (e.g., Enterococcus faecalis, Salmonella enterica subsp. enterica serotype Enteritidis, Listeria monocytogenes, Staphylococcus aureus, and Escherichia coli) through chemical or physical means and exert regulatory effects via immune, hormonal, and neuronal mechanisms. Additionally, it is important that they support the proliferation of beneficial microorganisms (22). According to the World Health Organisation, the number of viable cells in probiotic foods for human consumption should not be less than 106 cells per 1ml or 1g of product. In addition, the therapeutic dose should be 108-109 cells per 1ml or 1g of product. An important point is that the microorganisms it contains must be resistant to the effects of gastric juice and 6 of the 15 bile salts. After passing this chemical barrier, probiotics can adhere to the intestinal surface and exert their health-promoting functions (23).

Probiotic products are known to enhance non-specific cellular immune responses by activating natural killer cells and macrophages, and inducing the release of various cytokines. Additionally, they can improve intestinal mucosal immunity by increasing the number of IgA (+) cells. Furthermore, probiotics can aid the digestion process by assisting in the breakdown of lactose, enhancing the absorption of minerals, and stimulating the synthesis of several vitamins, such as thiamine, riboflavin, niacin, pantothenic acid, and vitamin K. They play an important role in the treatment of various conditions, including liver disease, diarrhea, and gastroenteritis. Moreover, they have been shown to exhibit antiproliferative, pro-apoptotic, and antioxidative properties (24).

Prebiotics;

Prebiotics are the most commonly used substances to maintain a normal gut microbiota and restore balance when homeostasis is affected. Prebiotics contain substances that stimulate the growth of microorganisms but do not contain bacteria in their composition. These substances can be derived from various sources such as soybeans and raw oats. However, plant oligosaccharides are the most popular prebiotics. Among the indigestible carbohydrates with prebiotic properties are polysaccharides (resistant starch, pectin, and dextrin), fructo-oligosaccharides, galacto-oligosaccharides, xylooligosaccharides, isomaltooligosaccharides, mannanoligosaccharides, raffinose oligosaccharides, arabinoxylan oligosaccharides, lactulose, and inulin. Prebiotics have the potential to improve human health by regulating the balance of the gut microbiome (25,26).

Prebiotics fermented by gut bacteria produce short-chain fatty acids such as propionate, butyrate, and acetate. The production of short-chain fatty acids has positive effects, including improving gut barrier integrity, enhancing mineral absorption, lowering glycemic levels and body weight, strengthening immunity, and modulating metabolic, cardiovascular, and inflammatory biomarkers. Additionally, the intake of prebiotics promotes the growth of beneficial bacteria, such as Lactobacillus and Bifidobacterium, which inhibit the proliferation of harmful bacteria. Due to the health benefits they provide, prebiotics are increasingly being used as functional ingredients in the food industry. These compounds can be utilized in the production of whole wheat bread, cereal bars, chocolate, dairy products, infant formulas, and meat products. In addition to natural sources, microorganisms and enzymes can also be used for the synthesis of prebiotic compounds (27,28).

The Effect of Probiotics and Prebiotics on the Mechanisms Leading to Cardiovascular Diseases

Oxidative Stress;

Oxidative stress plays a major role in the course of cardiovascular diseases. This important, high levels of intracellular oxygen radicals have detrimental effects on lipids, proteins and DNA. Reactive oxygen species (ROS) include highly active free radicals such as superoxide anion radicals, hydroxyl radicals and hydrogen peroxide. Most organisms use enzymatic defences (superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase (CAT) and non-enzymatic antioxidant defences (glutathione (GSH), thioredoxin, vitamin C, vitamin E) to protect against oxidative stress. Furthermore, organisms have repair systems to neutralise these radicals. However, these natural antioxidant systems may often be insufficient to prevent oxidative damage in organisms. Many studies have demonstrated that probiotic bacteria exhibit significant antioxidant capacities in both in vivo and in vitro environments. ROS can be generated from both endogenous and exogenous sources. These highly reactive molecules have the potential to modify other oxygen species, DNA, proteins, or lipids. Excessive ROS production is believed to lead to genomic instability, contributing to the development of chronic diseases such as atherosclerosis and cardiovascular diseases. ROS are produced through various enzymatic reactions and chemical processes, with the NADPH oxidase (NOX) complex recognized as the primary source of ROS production. NOX complex is considered the primary source of ROS production. In humans, there are seven NOX homologs that intentionally produce ROS for host defense and signaling functions. Recently, Gómez-Guzmán and colleagues suggested that the combination of probiotics Lactobacillus fermentum CECT5716, Lactobacillus coryniformis CECT5711 (K8), and Lactobacillus gasseri CECT5714 (LC9) (1:1) could reduce NOX activity and the mRNA expression of NOX-1 and NOX-4 in spontaneously hypertensive rats.

Many studies have focused on the antioxidant properties of probiotics. It has been determined that the culture supernatant, intact cells, and intracellular extracts of Bifidobacterium animalis 01 eliminate hydroxyl radicals and superoxide anions in in vitro environments. Furthermore, oxidative stress in patients with type 2 diabetes has been observed to be reduced by various probiotics. Lactic acid bacteria (LAB) have been extensively studied in both animals and humans, and it has been demonstrated that LAB may exhibit resistance against reactive oxygen species such as peroxide radicals, superoxide anions, and hydroxyl radicals. Rats fed high-fat diets supplemented with Lactobacillus plantarum P-8 exhibited high antioxidant capacity by reducing hepatic lipid accumulation and maintaining healthy liver function. In humans, Lactobacillus rhamnosus has shown strong antioxidant activity under conditions of high physical stress. As a result, recent studies have demonstrated that probiotic bacterial strains may possess antioxidant capacity in various forms (29,30).

Inflammation;

Subclinical inflammation forms the basis of many diseases. This inflammation increases with aging and becomes particularly common in older individuals. It is also an important risk factor for cardiovascular diseases. In these cases, it is often observed that plasma levels of pro-inflammatory mediators such as TNF-α, IL-1, and IL-6 are elevated. Inflammation is commonly associated with increased intestinal permeability. This condition increases the passage of bacterial-derived pro-inflammatory mediators, such as lipopolysaccharide (LPS), from the intestine to the bloodstream. An increase in lipopolysaccharide-binding protein (LBP) levels has previously been reported to be associated with an

increased cumulative incidence of cardiovascular diseases. LPS and other bacterial cell membrane components are recognized by certain receptors on endothelial cells. The binding of LPS to endothelial cells leads to the direct activation of adhesion molecules such as ICAM-1 and P-selectin, which play a crucial role in interactions with leukocytes. These data emphasize the critical role of the gut microbiota in controlling intestinal permeability and endotoxemia, highlighting its significant contribution to the development of chronic low-grade inflammation and the increased risk of cardiovascular diseases. It also increases interest in intervention strategies targeting the microbiota, as reducing low-grade inflammation is seen as a potential way to prevent cardiovascular diseases. Therefore, food components such as probiotics and prebiotics are considered promising tools for the dietary management of cardiovascular disease risk.

Tenorio-Jiménez and colleagues reported that the administration of L. reuteri V3401 for 12 weeks not only reduced the risk of CVD but also decreased the levels of inflammation biomarkers such as TNF-α, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in obese adults aged 18 to 65 with metabolic syndrome. However, although some studies have shown that probiotics can reduce the production of proinflammatory cytokines, the underlying mechanisms of these effects are still not well understood. In recent years, numerous studies have been conducted on the use of dietary fibers and prebiotics, as most of these polysaccharides are metabolized by the gut microbiota, leading to the production of short-chain fatty acids. The fermentation of prebiotics produces these metabolites, which exhibit anti-inflammatory and immunomodulatory properties (33).

Hypercholesterolemia and Hypertension;

It is suggested that probiotics may reduce cholesterol levels through various mechanisms. Most species of Bifidobacterium exhibit higher coliglycine hydrolase activity compared to other microorganisms. This enzyme hydrolyzes the amide bonds conjugated with taurine or glycine in bile acids, facilitating the release of primary bile acids. These acids easily precipitate at low pH and are excreted from the gastrointestinal system. Since they are not reabsorbed from the intestines, they must be replaced by newly synthesized bile acids, which are derived from blood cholesterol in the liver. Probiotics may have cholesterol-lowering effects through the action of bile salt hydrolase enzyme (a probiotic enzyme that hydrolyzes bile salts into amino acid residues and free bile acids). These beneficial effects have been demonstrated in both animal models and clinical studies. Furthermore, the relationship between the gut microbiota, probiotics, and lipid metabolism disorders has been thoroughly elucidated. In a randomized, single-blind, controlled clinical study, 70 pregnant women in their third trimester were given a daily supplement of 200 g probiotic yogurt for nine weeks. This probiotic yogurt, containing Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus acidophilus LA-5, and Bifidobacterium animalis BB12, resulted in a significant decrease in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) levels, and serum triglyceride concentrations (34). In a study conducted by Hoppu and colleagues, 256 pregnant women were divided into three groups—probiotic diet counseling (with L. rhamnosus GG and B. lactis), placebo diet counseling, and no counseling (control group) and followed from the first trimester of pregnancy to 12 months postpartum. Similar lipid serum levels were observed during pregnancy across the groups.

Other studies have observed the beneficial effects of probiotic supplementation in dyslipidemia through small-scale, double-blind, placebo-controlled trials. It has been stated that probiotic supplementation reduces blood lipid concentrations (35). Lew and colleagues, who identified L. plantarum DR7 with cholesterol-lowering properties through AMPK phosphorylation, reported that another research group suggested probiotic L. plantarum PH40 may also have cholesterol-lowering properties. Probiotics play an important role in the treatment of various diseases, such as liver disease, diarrhea, and gastroenteritis. Additionally, it has been shown that probiotics possess antioxidant, antiplatelet, and anti-inflammatory properties, and they also lower cholesterol levels (Figure 3) (36).

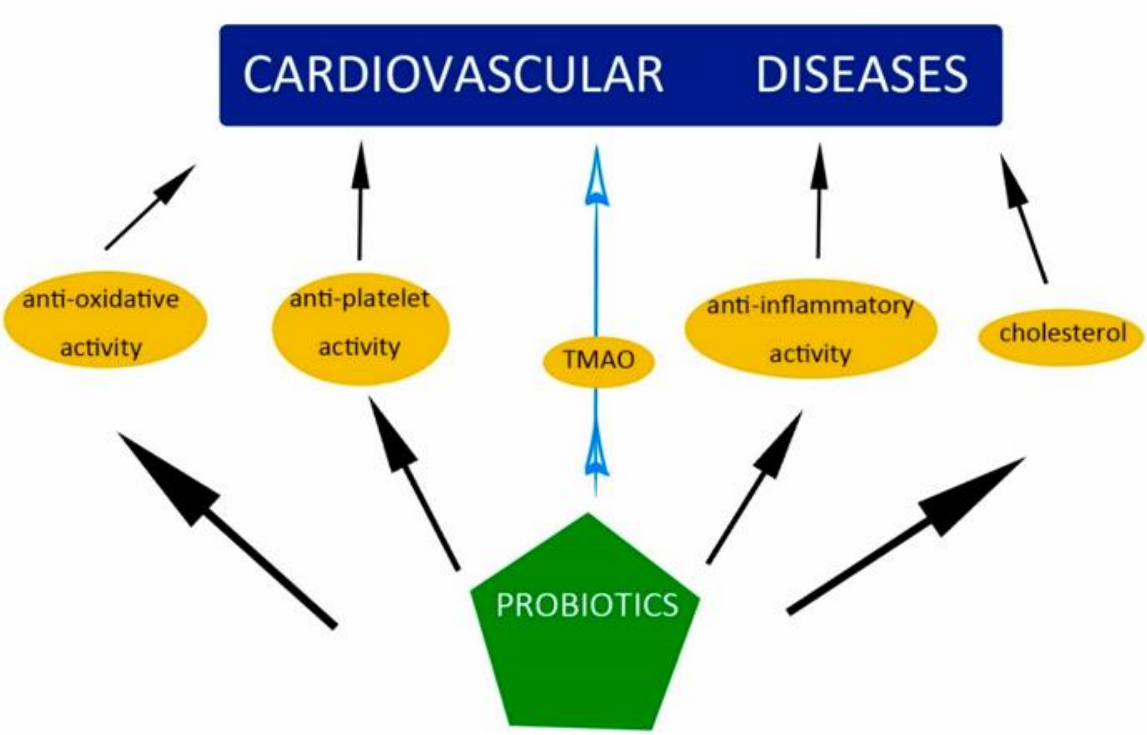

Figure 3. The effect of probiotics on cardiovascular disease (36).

Prebiotics also reduce cholesterol levels. Parnell and Reiner reported that prebiotic intake reduced total serum cholesterol in a hypercholesterolemic rat model. Prebiotics also lower cholesterol levels. Parnell and Reiner reported that prebiotic intake reduced total serum cholesterol in a hypercholesterolemic rat model. In this study, rats were fed three different diets containing 0%, 10%, or 20% prebiotic fiber for 10 weeks. Both doses of prebiotic fiber reduced serum cholesterol levels by approximately 25%. Additionally, this change has been associated with an increase in cecal digesta (a mixture of digested food and fluids from the small intestine directed to the large intestine) and the upregulation of genes related to cholesterol biosynthesis and bile production. In addition, obese rats receiving 10% prebiotic supplementation showed approximately a 40% reduction in hepatic triacylglycerol accumulation. Obesity is commonly associated with the progression of cardiovascular diseases, and both probiotic and prebiotic intake have been reported to exhibit anti-obesogenic effects in various clinical studies (37).

CONCLUSION

CVD, recognized as one of the leading causes of morbidity and mortality worldwide, have recently emerged as a prominent research focus in the context of their relationship with the gut microbiota. Traditionally associated solely with digestive health, the gut microbiota is now recognized as a crucial factor directly influencing cardiovascular health through key mechanisms such as inflammation regulation, lipid metabolism control, immune system modulation, and the maintenance of endothelial function. In this context, probiotics and prebiotics, which have the potential to maintain and improve gut microbiota balance, are gaining increasing importance in the prevention and treatment of CVD. Research highlights the beneficial effects of probiotics, particularly in the management of dyslipidemia, and suggests that certain probiotic strains may reduce the risk of atherosclerosis. For instance, specific bacterial strains such as Lactobacillus plantarum, Lactobacillus rhamnosus, and Bifidobacterium bifidum have been shown to exert beneficial effects on lipid profiles by lowering serum cholesterol levels. These bacteria modify bile salt metabolism, thereby reducing cholesterol absorption and contributing to systemic lipid homeostasis. Clinical studies further support the significant effects of probiotic supplementation in lowering LDL cholesterol levels, increasing HDL cholesterol, and balancing total cholesterol levels.

On the other hand, the gut microbiota plays a key role in regulating inflammatory processes. Chronic inflammation is known to be a central factor in the pathophysiology of CVD and is directly linked to

conditions such as atherosclerosis, hypertension, and myocardial infarction. Disruption of microbial balance can trigger inflammatory responses, negatively impacting vascular functions. Probiotics enhance the anti-inflammatory response by increasing microbial diversity in the gut and reducing levels of inflammatory cytokines (IL-6, TNF-α). The increase of bacteria known for their anti-inflammatory properties, such as Faecalibacterium prausnitzii, in the gut microbiota may contribute to the improvement of endothelial function.

The mechanism known as the gut-brain-heart axis reveals that the gut microbiota is not only limited to the digestive system but also affects the neuroendocrine and cardiovascular systems. Microbial metabolites, particularly short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, play a crucial role in regulating vascular tone and blood pressure, while also reducing systemic inflammation by protecting intestinal epithelial cells. Clinical data suggest that probiotic supplementation can lower blood pressure, indicating that probiotics may be considered as a complementary agent in the treatment of hypertension.

Recent advancements in innovative probiotic and prebiotic formulations aim to maximize their positive effects on cardiovascular health. Symbiotics, which capitalize on the synergistic effects of probiotics and prebiotics, along with postbiotics that enhance biological activity, have the potential to make therapeutic approaches more effective. Moreover, advanced biotechnological methods such as genetic engineering and CRISPR enable the design of probiotics with more specific and targeted effects, paving the way for the development of personalized treatment strategies. In particular, the development of Lactobacillus species that can regulate cholesterol metabolism more effectively through specific genetic modifications could play a crucial role in future personalized cardiovascular treatment approaches.

The role of gut microbiota and probiotics is gaining more attention in cardiovascular surgery. Ischemic damage to the intestinal mucosa may occur during cardiopulmonary bypass (CPB), which can increase the risk of bacterial translocation and potentially trigger the development of systemic inflammatory response syndrome (SIRS). Research indicates that probiotics may help reduce bacterial translocation by enhancing intestinal barrier functions, thereby preventing postoperative complications. Furthermore, the antioxidant effects of metabolites derived from the gut microbiota, along with their properties that support endothelial function, have the potential to accelerate the recovery process following cardiovascular surgery. Ultimately, the gut microbiota is emerging as a prominent research focus in the prevention and treatment of CVD. Probiotics and prebiotics can play a crucial role in cardiovascular health by regulating inflammation, improving lipid metabolism, maintaining intestinal barrier integrity, and enhancing microbial diversity through various mechanisms. However, to better understand these effects and integrate them into clinical practice, large-scale randomized controlled trials are required. In the future, the development of personalized probiotic and prebiotic treatment strategies targeting the gut microbiota could represent a groundbreaking step in the prevention and management of CVD. With technological advancements, it is anticipated that microbiota-based therapies will become more widespread in cardiovascular health management.

DESCRIPTIONS

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