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Use of Probiotics and Prebiotics in the Management and Intervention of Cardiovascular Diseases

Rabbya Rayan Shah[1], Ambreen Talib[2], Manahil Shafiq[3], Areesha Naveed[4], Iram Shahzadi[5], Uzma Bilal[6], Saleha Afzal[7], Fatima Hameed[8], Abia Muazzam[9], Ayesha Nadeem[10*]

[1, 2, 4, 8, 10] Department of Pathobiology and Biomedical Sciences Muhammad Nawaz Shareef University of Agriculture, 25000, Multan, Pakistan

[3, 6] Department of Zoology, the Woman University, Multan, Pakistan

[5] Department of Biotechnology, University of Health Sciences, Lahore, 54600, Pakistan

[7] Department of Microbiology and Molecular Genetics, Bahuddin Zakariya University, Multan, 60800, Pakistan

[9] Department of Biochemistry and Biotechnology Muhammad Nawaz Shareef University of Agriculture, 25000, Multan, Pakistan

[1] rabbiyarayanshah@gmail.com , [2]ambreentalib212@gmail.com , [3]manahilshafiq723@gmail.com ,[4]areesha.naveed237@gmail.com , [5]iramshahzadi5670@gmail.com , [6]uzmabilal31@gmail.com , [7]salehaafzal136@gmail.com , [8]fatimahameed838@gmail.com , [9]abiamuazzam@gmail.com , [10]ayeshanadeem5200@gmail.com

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Corresponding Author:

Ayesha Nadeem

Email:

ayeshanadeem5200@gmail.com

Abstract

Cardiovascular disease is one of the leading causes of illness and death worldwide. The following are risk factors for cardiovascular disease: smoking, dyslipidemia, diabetes, obesity, inflammation, and hypertension. From the immediate effects of the gut microbiota on energy metabolism and obesity to the adjacent interaction between periodontal illness, heart attack, and stroke, microorganisms have a major effect on cardiovascular health. The probability of affecting or determining microorganisms is associated with probiotic and prebiotic applications. Probiotics are referred to as "live microorganisms that, when used in sufficient amounts, provide major advantageous effects for the host." The effectiveness of probiotics can be determined by the relationship between probiotic bacteria and the host's microbiome. Many of these fermented strains of probiotic bacteria are obtained from foods. Prebiotics are not microbes; they're just chemical substances that help microorganisms grow. Prebiotics can be observed in various foods, such as unprocessed grains, soybeans, and human milk; however, one of the most common forms is organic oligosaccharide. Probiotics and prebiotics are involved in the treatment of a variety of immune system diseases, such as type 2 diabetes, obesity, and cancer, according to an increasing number of recent studies. Yet, little is known about the potential use of these supplements as essential dietary components in the prevention or treatment of cardiovascular disease. The goal of this review is to discuss the function of probiotics, prebiotics, and gut microbiota in the treatment and prevention of cardiovascular diseases.

Key words

Cardiovascular disease, probiotic, prebiotic, microorganisms, gut microbiota.

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Introduction

A variety of diseases collectively referred to as "cardiovascular disease" include ischemic heart disease, hereditary and chronic heart disease, peripheral artery disease, and venous thromboembolism. A long-term, continuous cardiovascular disease usually causes arterial thrombosis, myocardial infarction, stroke, and other unfavorable medical consequences. The permanent damage to circulatory tissues is known as atherosclerosis [1]. High blood cholesterol (hypercholesterolemia) is one known risk factor for cardiovascular disease. The accumulation of plaque carried by LDL-C cholesterol deposits in the artery walls is one of the major causes of atherosclerosis [2]. Due to its increasing severity, cardiovascular disease has become the world's leading cause of mortality in recent decades [3]. It has particular significance in high- and intermediate-income countries. However, the multiple causes of cardiovascular illness inhibited progress, and different preventive methods were delayed by our insufficient knowledge of the supporting systems [4].

It has been proven that a poor diet greatly increases the risk of cardiovascular disease. The factors that determine metabolic stress and overweight, such as visceral fat and adiposity, have been linked to dietary patterns and cardiovascular events. Environmental factors are considered to have a major and unreliable effect [5]. Genetic variation contributes to individual differences in obesity, even though it has a major effect on body mass index and the overall distribution of body fat [2]. Multiple interactions among dietary ingredients, gut microbes, and the chemical compounds they produce during meals have recently been associated with cardiovascular health [7]. The increasing role of gut microbiota in cardiovascular disease has piqued the interest of researchers to explore the potential use of probiotics as a research topic, including the prevention of atherosclerosis and other cardiovascular disorders [8]. Beneficial foods can assist in lowering several risk factors associated with cardiovascular disease [9]. Probiotics and prebiotics serve as essential food elements in the prevention and treatment of cardiovascular disease. Some of their roles are discussed in this context.

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Therefore, the purpose of this review is to examine the role of gut microbiota and probiotic supplements in the treatment and prevention of cardiovascular disease based on currently available studies [10].

Cardiovascular Disease: Prevalence, Pathogenesis, and Risk Factors

Arrhythmia, thromboembolic sickness, ischemic heart disease, heart failure, pulmonary embolism, and coronary artery disease are the most commonly recognized heart-related disorders. Cardiovascular diseases affect the heart or vessels that carry blood [11]. Cardiovascular diseases are a major health issue rising all over the world. 18 million deaths occurred due to cardiovascular diseases in 2015, resulting in thirty percent of deaths and a 12.5% increase from 2005. According to the prediction of the American Heart Association, approximately 92.1 million individuals in the US have cardiovascular disease nowadays, and by 2030, 43.9% of the country's population is predicted to have this disease [12].

Atherosclerosis is a chronic inflammatory disease caused by lipids that is characterized by the development and continuing growth of plaques characterized by atherosclerosis in the walls of arteries. It has been found that cerebral, coronary, or peripheral artery abnormalities can cause cardiovascular diseases. These disorders share a common pathogenesis that involves thrombosis, coagulation, and atherosclerosis [13]. There is a suggestion that different immune responses control the onset and course of atherosclerosis [14]. The appearance and progressive development of atherosclerotic plaques, primarily made of fat, in the artery walls are what define atherosclerosis [15]. The primary lipid in such plaques is cholesterol, derived from circulating low-density lipoproteins [16]. Endothelial cells in arteries are activated by lipoproteins that penetrate the sub-endothelial region. Similar to this, monocytes in the artery wall develop into macrophages, which then ingest lipoproteins and become the typical foam-like cells found in plaque associated with atherosclerosis. Consequently, a major risk factor for cardiovascular illness and cardiac arrest is plaque accumulation, an ongoing autoimmune condition caused by lipids [17].

Blood coagulation, which exists in an inert state, an early or cytoplasmic stage, and then depends on several enzymatic processes, is another major cause of cardiovascular disease [18].

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One of the main risk factors for heart attacks and strokes is atherosclerosis. The development and course of the disease are linked to several immune-mediated pathways [19]. The retention of lipoproteins in the artery's sub-endothelium and the activation of endothelial cells are the first events that lead to atherogenesis [20]. Once inside the vascular wall, monocytes undergo tissue macrophage differentiation. After consuming lipoproteins, the macrophages transform into foam cells. Extracellular matrix proteins are released by a collection of artificial vascular smooth muscle cells, which make up atheroma. Collagen and smooth muscle cells are key aspects of the cellulose covering that surrounds the plaque formed by atherosclerosis [21].

Genetics and a poor lifestyle (insufficient exercise, poor food, smoking, and alcohol consumption) are aspects that impact the chance of rising cardiac illnesses. The most prevalent adaptable hazard factor for CVD is hypertension [22]. Metabolic dysregulation, which raises blood cholesterol levels and damages blood vessels through atherosclerosis, is frequently linked to high blood pressure. Type 2 diabetes also raises blood cholesterol levels. Endothelial dysfunction and the renin-angiotensin-aldosterone system are two factors that interact between high blood pressure and high cholesterol to affect the development of arterial disease [23].

Function of Gut Microbiota in Cardiovascular Diseases

The group of bacteria referred to as the gut microbiota, which inhabits our digestive tract, is made up of bacteria, viruses, and unicellular eukaryotes [24]. The most extensively researched member of this microbial community to ascertain how it influences human health is bacteria.

It is estimated that there are roughly 3.8×10^{13} bacterial compartments in the intestinal tract (GIT), which is comparable to the total number of human cells in the body. However, a healthy person's overall gut microbiota mass is merely 0.3% of their body weight [25]. Interestingly, metagenomic investigations have found that the GIT has 9 million distinct genes, which exceeds the entire genetic material of the human body by 450 times [26].

A growing quantity of evidence indicates that the gut microbiota may contribute to the development of certain cardio-metabolic disorders, such as obesity, diabetes mellitus, elevated blood pressure, and heart failure [27]. It is now known that some diseases result in morphological

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abnormalities of the gut microbiota. For instance, it is commonly seen that the aforementioned diseases have decreased gut microbiota evenness, richness, and diversity, as well as the F/B ratio, which measures the proportion of Firmicutes to Bacteroidetes [28]. Furthermore, several other bacterial species that are present in the gastrointestinal tract are significant for human health. Akkermansia muciniphila is a promising candidate that has lately been indicated as a viable contender that could be the modern probiotic, even though it is not on the list of traditional probiotics. In contrast to people with diabetes and obesity, there is a positive correlation between a healthy state and the prevalence of Akkermansia muciniphil [29]. However, it is known that certain growing microbes found in the intestinal tract can lead to illnesses; Shigella species, Salmonella, Escherichia coli, and Campylobacter are a few examples of these bacterial pathogens that induce diarrhea [30].

Adenosine triphosphates, deoxycholic acids, and lithocholic acids are functional metabolites or microbial products that can be produced by the gut microbiota, which is also thought of as "bioreactors" [31]. Therefore, the gut microbiota's structural and functional alterations are crucial for preserving host health.

The progression of CVD is closely linked to the gut microbiota and its metabolites [32]. Stool samples from CVD patients were found to include high concentrations of pathogens, such as Candida, Yersinia, Campylobacter, Shigella, and Enterobacteriaceae [33]. Additionally, significant differences within the structure and compounds of the gut microbiota between healthy individuals and patients with chronic heart failure (CHF) were found by genetic and metabolomic studies of the blood and stool specimens, respectively. In this study, there is a higher number of Ruminococcin gnavus in chronic heart failure and a lower number of Faecalis bacterium prausnitzii when compared to controls. Additionally, butyrate levels increased while trimethylamine N-oxide levels decreased in chronic heart failure [34]. One of the well-researched chemical compounds, TMAO, generated by the gut microbiota has a beneficial association with early atherosclerosis [35]. This substance generates arterial thrombus, promotes prothrombotic platelet function, and enlarges atherosclerotic plaque. Another experiment showed that in female mice, a choline diet raised the levels of TMAO, which were generated by the gut microbiota, and

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encouraged the growth of atherosclerosis [36]. Furthermore, lipopolysaccharide (LPS), a module of Gram-negative bacteria's microbial cell walls, may impair cardiovascular function and raise the risk of CVD. Animal models exposed to low-dose lipoprotein stimulation (LPS) developed atherosclerosis and vascular inflammation [37].

Furthermore, individuals with the highest burden of CVD were particularly noticeable for having circulating endotoxemia (LPS). The ensuing endotoxemia is linked to decreased survival, heart damage, signs of malnourishment, and systemic inflammation [38]. The most common digestive acids are produced by the liver and subsequently undergo additional breakdown by the gut bacteria to become intermediate digestive acids. Certain people's enterohepatic circulations include large concentrations of secondary bile acids that are exclusively formed by intestinal bacteria, which may contribute to the development of multiple disorders, including cardiovascular disease [39]. As a result, one new CVD risk factor is the makeup of commensal bacteria and their metabolites.

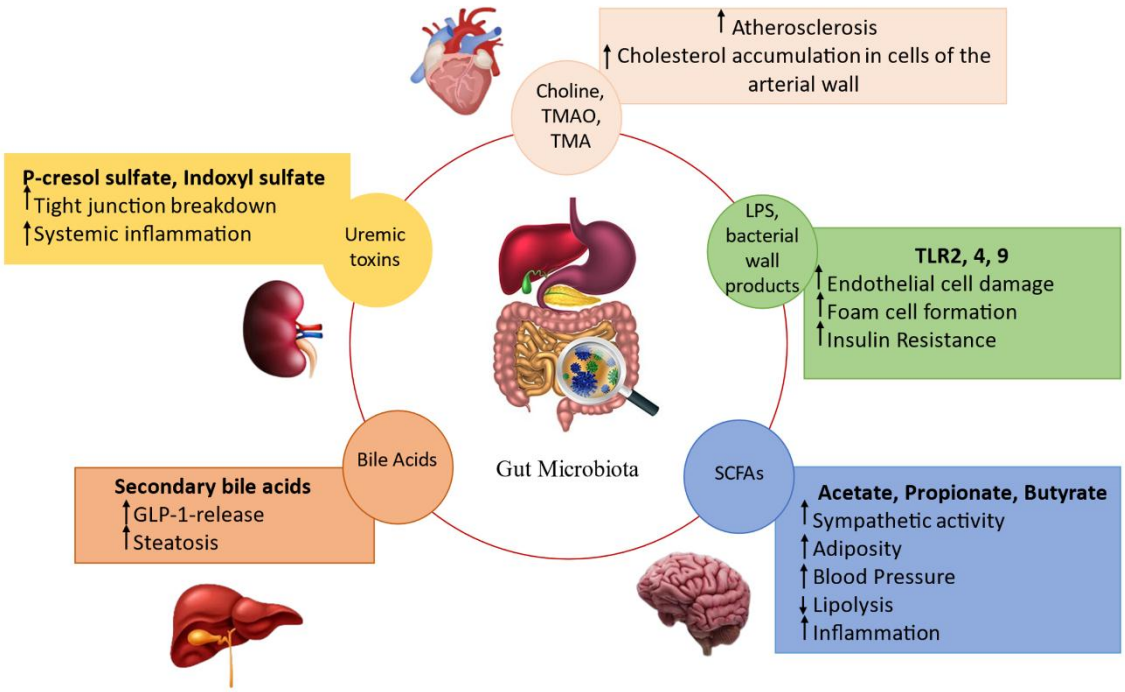

Figure 1 Gut Microbiota and possible molecular pathways linked to cardiovascular diseases

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Probiotic and Prebiotic Interventions for Various Diseases (Table 1)

Disease	Product	Probiotic strain	Reference
Diabetes mellitus	Prebiotic	*Eubacterium* and *Bifidobacterium*	[40]
Diabetes with coronary heart disease (CHD)	Probiotics with vitamin D	*L. zisttakhmir*	[41]
Type 2 diabetes with CHD	Probiotic	*L. casei, L. acidophilus, B. bifidum*	[42]
Coronary artery disease (CAD) in men	Probiotic	*L. plantarum 299v*	[43]
CAD	Probiotic	*L. rhamnosus* GG (LGG)	[44]
Hypertension	Probiotic	*Lactobacilli*	[45]
Obesity, metabolic syndrome, and lifestyle	Probiotic	*Bacteroides*, *Prevotella*, and *Porphyromonas*	[46,47]
Overweight, CHD, and diabetes	Symbiotic	*L. casei* T2 strain, *L. acidophilus* T16 strain, *B. bifidum* T1 strain	[48]
Ischemic stroke	Probiotic	*C. butyricum*	[49]
Heat stroke	Probiotic	*B. licheniformis* (BL, CMCC 63516)	[50]

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Role of Probiotics in Cardiovascular Diseases

The concept that some germs are good for the human body has been around since antiquity. It is well known that Plinius the Elder recommended consuming fermented milk-based drinks to ease digestive issues.

The Greek word probiotics, which signifies life, is where the term "probiotic" originates. The definition of "probiotic," as defined by Lilly and Stillwell in 1965, was "a microorganism that influences the pH level of the gastrointestinal microbiome." Probiotics were first recognized to be effective by Fuller in 1989 when he described them as "living, microbial dietary components" [51]. Probiotics were described as "living microbes that, when absorbed in appropriate quantities, provide beneficial effects to the individual" by FAO and the World Health Assembly of the WHO in 2002 [52].

Most of the nineteenth century's probiotic investigations concentrated on lactic acid bacteria that are present in milk and yogurt, specifically Lactobacillus acidophilus and Lactobacillus casei. The host's medical condition depends on the diversity of lactic acid bacteria in the gut, according to 1970 statements made by Ilyich Metchnikoff, who is generally seen as the probiotics' inventor [53]. A type of probiotic bacteria that is safely used for an extended period is lactic acid bacteria. Milk-based items containing this microbe are approved by the FDA [54].

Humans always have beneficial microbes in their salivary glands and gastrointestinal tracts; they are consumed as an alternative to daily meals all around the globe. For hundreds or perhaps thousands of years, they have also been frequently employed to maintain the freshness of goods including cheese, sauerkraut, salami, and soy sauce [51].

Probiotics are hypothesized to bind to intestinal epithelial cells and release bacteriocins and organic acids, which are antibiotics that stop the transmission of harmful bacteria. Microorganisms that are present in the digestive tract vary; in the human colon, the range of Bifidobacteria is 8×10^4 to 2.5×10^{13} cells, whereas the range of Lactobacillus bacteria is 4×10^4 to 3.2×10^{12} (mean 4×10^9 cells). Lactic acid bacteria belong to the initially discovered species of bacteria that colonize the uncontaminated gastrointestinal tracts of children. During nursing, it is believed to make up 95%

of the entire microbial population, making it the biggest component of the intestinal microflora [51].

According to WHO recommendations, the recommended dosage of probiotic meals is 108–109 cells per 1 ml or 1 g of product. Moreover, the active cell population of the meal at the stage of an individual's ingestion cannot be more than 106 cells per milliliter or gram of substance. Saliva and stomach acid aren't supposed to kill probiotic bacteria because they have to live and not die while passing through the gastrointestinal tract. Probiotics are supposed to stick to the intestinal wall once they have crossed the lipid layer so that their beneficial effects can be recognized. Also, a daily intake of probiotic supplements could be required if beneficial microorganisms are not inhabiting the intestinal tract [51].

Probiotics can boost the general innate inflammatory reaction by raising the secretion of several inflammatory substances, killer cells from the gut, and monocytes. By boosting the quantity of immunoglobulin and A+ cells, they can also strengthen the immunity of the gastrointestinal tract [55]. Probiotics are also helpful in metabolism and can help in the interruption of lactose. They are also capable of improving the production of certain vitamins along with the utilization of ions like calcium, zinc, iron, and manganese. Several diseases, including nausea and vomiting, intestinal inflammation, and liver failure, can be prevented by probiotics. According to the study, probiotics also appeared to exhibit anti-oxidative, pro-apoptotic, and anti-proliferative qualities [56].

Fundamental Mechanisms of Probiotics in Cardiovascular Diseases

Sanchez et al. state that probiotics have been demonstrated to enhance human health through four different mechanisms: improving the cellular barrier's performance, battling infections for energy and binding receptors, the effect of immunity on other organs and the synthesis of neurons, and immune stimulation [57]. The primary impacts of probiotics on cardiovascular disorders are actively being researched, and it looks like they may be quite complex. While the exact mechanisms behind probiotics' positive effects on cardiovascular disorders likely involve decreasing high cholesterol levels, reducing hypertension, and minimizing oxygen consumption,

we focus here on the probiotics' beneficial impacts on cardiovascular diseases through regeneration of gut microbiota imbalance and antibacterial reactions [58].

As observed via the gut microbiota

The major threat to strokes and heart attacks, plaque accumulation, may be caused by modifications to the gastrointestinal tract. It's a result of the fact that a variety of enzymes associated with the gut microbiota can regulate oxygen consumption, the production of urea, the breakdown of lipids, and inflammation [59]. A potential connection between changes in the intestine and ischemic cardiovascular disorders has been proposed by Karlsson et al.'s entire-genome sequencing project [60]. When the people suffering from heart disease were compared to normal volunteers, the prevalence of Collinsella was higher, while the number of Rothia and Eubacterium species was lower. In addition, the F/B level is substantially lowered in patients who suffer from cardiovascular disease. Subsequently, as Emoto et al. revealed in 2016 and 2017, individuals with CHD showed a significant drop in Bacteroidetes, such as Bifidobacterium and Prevotella, whereas Lactobacilli increased in quantity [61]. A. muciniphila and increased clostridial abundances were among the structural alterations in the gut microbiota brought on by stroke in several animal studies [62]. Further, abnormalities in the gut microbiome were seen in a mouse with occlusion of the middle cerebellum model, a different cerebral infarction scenario. These changes included a decrease in species diversity and an increase in Bacteroidetes [63]. The gut microbiome of patients who suffered strokes also showed increased bacterial species and reduced biodiversity [64].

Current treatments for dyslipidemia linked to atherosclerosis come with a long list of negative effects. More research has been done on the prevention of atherosclerosis using nutraceuticals made from food after fermentation by probiotic microorganisms than with pharmaceutical drugs [65].

There is a significant association between the risk of heart disease and several gut-derived substances, most commonly trimethylamine oxide, as well as subtle changes in the gastrointestinal microbiome [66]. The protein found in the gut microbiota and the oxygenase/reductase complex found in the gastrointestinal tract collaborate to manufacture trimethylamine from the omega-3

fatty acids, carbohydrates, and phosphodiesterase found in food [67]. Following its formation, this molecule penetrates the bloodstream through the entrance vein. It undergoes additional hepatic metabolism by an enzyme named flavin-containing monooxygenase, leading to the production of trimethylamine oxide. Probiotics may help prevent atherosclerosis by improving trimethylamine oxide [68]. The microbiota may undergo metabolic changes as a result of probiotic supplementation. The number of different pathogenic bacteria was decreased, and the colon's capacity to create SCFAs was altered when fermented milk containing B. animalis subsp. lactis was given [69]. Diseases like diabetes and dyslipidemia that affect the bile acid metabolism may be the result of damage to this system. Because they restore basic bile acids, activate bile salt hydrolase in microorganisms, and aid in the bacterial production of secondary bile acids and other intermediary molecules, lactobacilli are crucial for the biosynthesis of bile acids. The employment of different antibacterial techniques to manipulate the microbiota therapeutically may be beneficial for the treatment of illnesses related to the cardiovascular system [70]. As good producers of antimicrobials, lactobacilli, and other lactic acid bacteria may help in preventing cardiovascular disease by promoting the growth of healthy microbes and inhibiting Gram-negative bacteria in the GI tract from generating lipopolysaccharides.

As observed via inflammation

Low-grade inflammation is brought on by several chronic conditions, including cardiovascular disease. The three primary inflammation-promoting mediators—TNF-α, IL-1, and IL-6—have higher concentrations in the blood in cardiovascular diseases when compared to normal conditions. IL-6, C receptor protein (CRP), complementary structure, group of differences 40 (CD40), and myeloperoxidase (MPO) are a few of the markers of inflammation in chronic cardiovascular disease [71]. Probiotics are administered in their original isolates or in combined form along with various medications to lower hs-CPR and other signs of inflammation in individuals suffering from acute cardiovascular disease [72]. Probiotics have also been shown to have beneficial effects on coronary artery disease by reducing the creation of protein knots and inflammatory mediators like TNF-α [73]. Even though these trials showed probiotics to have beneficial impacts on atherosclerosis and cerebral infarction, their exact route of action is still unknown.

The gastrointestinal microbiota's makeup may vary as a result of probiotic treatment, and this could impact the SNS and its associated cardiometabolic processes by changing the kinds and quantities of neurotransmitters [74].

The intestinal barrier is fortified, and an innate and adaptive immune response is set off when probiotic bacteria come into contact with IECs or immune cells through TLRs. This involves the synthesis of several chemokines, anti-inflammatory metabolites, and cytokines. Furthermore, probiotic bacteria upregulate the expression of Goblet and Paneth cells, tight junction proteins, and mucin [75].

Role of Prebiotics in Cardiovascular Diseases:

Prebiotics only include chemicals that promote the growth of microorganisms, not actual bacteria. Since they are not broken-down during digestion, they arrive in the intestinal lumen undigested and ready to work. Food ingredients must fulfill specific requirements to be classified as prebiotics. These include having a recognized organic arrangement, being tolerant to the adverse reactions caused by mineral salts, gastrointestinal acids, and hydrolysis of proteins in the digestive tract, presenting an environment for varieties of helpful microbes, encouraging the development and functioning of essential microbes in the intestines, and having a track record of positive health effects.

Soybeans, raw oats, and breast milk are a few foods that contain prebiotics [76]. Onions, chicory, asparagus, and artichokes are examples of plants that contain oligosaccharides, which are the most widely used prebiotics [51]. Through fermentation and the growth of advantageous bacterial species, oligosaccharides may have a positive effect on the gastrointestinal system. For instance, fructo-oligosaccharide encourages bifidobacteria to proliferate in vivo. The number of colonic bifidobacteria is similarly increased by oligofructose and inulin [77]. According to Hsu et al., rats' gut microbiota and the malignant growth of intestinal tumors are impacted by xylo- and fructo-oligosaccharides. Probiotic products are increasingly commonly added to animal-based and beverage products, including nutritional beverages [78]. According to a current study by Cherry et al., seaweed contains components of polysaccharides that may function as prebiotics [79].

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Fundamental Mechanisms of Prebiotics in Cardiovascular Diseases

There are theories regarding how prebiotics affect the health of their hosts. First, gut bacteria may ferment prebiotics added to meals or found in naturally occurring objects. This will change the makeup, structure, and metabolic activity of gut bacteria [80]. Second, prebiotics have the power to alter the gut's ecology, lowering alkalinity and preventing the spread of gut infections [81]. Despite its beneficial effects on immune function, the third pathway receives scant evidence from the available data. Prebiotics have been shown to have a favorable impact through a variety of pathways, two of which will be examined and distilled down to be: regulation of the gut flora [82].

As observed via the gut microbiota

By preserving healthy gut flora and restoring homeostasis, prebiotics enhance the well-being of individuals [83]. Saccharolytic bacteria are primarily responsible for their fermentation; they also alter the gut microbiota's makeup and encourage the development of lactic acid bacteria and Bifidobacterium, two beneficial bacterial species [84]. These microorganisms additionally possess the ability to stop dangerous microbes from growing. It has been demonstrated that a prebiotic compound containing bioactive chitin fatty acids and processed cereal germ is good for heart failure and congestive heart failure. This complex also helps to promote the growth of diverse probiotic species and rebalance gut microbiota dysbiosis [85].

Prebiotics can ferment the gut microbiota's metabolites. Among other SCFAs, the gut bacteria digest prebiotics to produce acetate, propionate, and butyrate. These metabolites have been linked to decreased body mass index, improved gut permeability, and lower blood glucose levels [86]. Complimentary lipid proteins, deorphanized G protein-coupled receptors, and sensory transmitter 78, which has a stronger tolerance for acetate and propionate, are examples of SCFA binding sites. One more thing that SCFAs do is stop histone deacetylase. By controlling the chromosome arrangement, histone deacetylase inhibitors may promote genes and, in turn, regulate gene activity [87].

It has been demonstrated that various CVD risk variables are inversely correlated with SCFAs. Through Olfr78 and FFAR3, acetate and propionate have been shown to control blood pressure in

knockout animal models. In rats with angiotensin II-induced hypertension, butyrate lowered blood pressure mostly by down-regulating the expression of renin and kidney protein receptors [88]. Increased gut permeability is brought on by hyperglycemia in obesity and insulin resistance, and this leads to a chain reaction of inflammation [89]. In particular, SCFAs have a critical role in controlling epithelial veracity through tight junction proteins, which is essential for preserving gut health. For instance, butyrate acts on nucleotide-binding oligomerization domain-like receptors (NLRs) to regulate tight junction complex proteins, which in turn modulate inflammation [90]. Furthermore, SCFAs help control energy intake and appetite to prevent obesity [91]. Moreover, SCFA can influence glucose homeostasis by enhancing insulin sensitivity, strengthening the intestinal barrier, and boosting antioxidant and anti-inflammatory properties [92].

The use of prebiotics, especially fibers or the SCFAs they generate in the gut, has been demonstrated to be protective against CVD overall through a variety of mechanisms, such as altered gut flora, histone deacetylation, enhanced gut epithelial permeability, which reduces total and LDL cholesterol, as well as hs-CRP, and a decline in the prevalence of CVD risk factors such as obesity, diabetes, and hypertension.

As observed via inflammation

Prebiotics play a critical role in regulating the host's defenses and immunological system. Prebiotics of various kinds have been shown to have distinct immune-mediated roles in the innate and adaptive immune systems. Prebiotics are most frequently observed to affect dendritic cells in particular. As the main metabolites of the prebiotics, three main types of SCFAs exert distinct immunomodulatory effects on the colon. Propionate causes dendritic cells to produce Foxp3, but acetate does not; this is probably because the HDAC enzyme is absent [93].

Moreover, as these compounds produced by microbes are involved in neuroactivational-mediated cerebral communication, the gut microbiota may also affect host physiological conditions and brain activity through SCFAs. Tyrosine hydroxylase, a key enzyme in the synthesis of dopamine and noradrenaline, is expressed more when butyrate and propionate are present, which can control neurotransmission [94].

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Additionally, data indicates that propionate may decrease dopamine and the neurotransmitters indoleamine, serotonin, and GABA [95]. Thus, through the gut-brain axis, SCFAs may modulate the immune system.

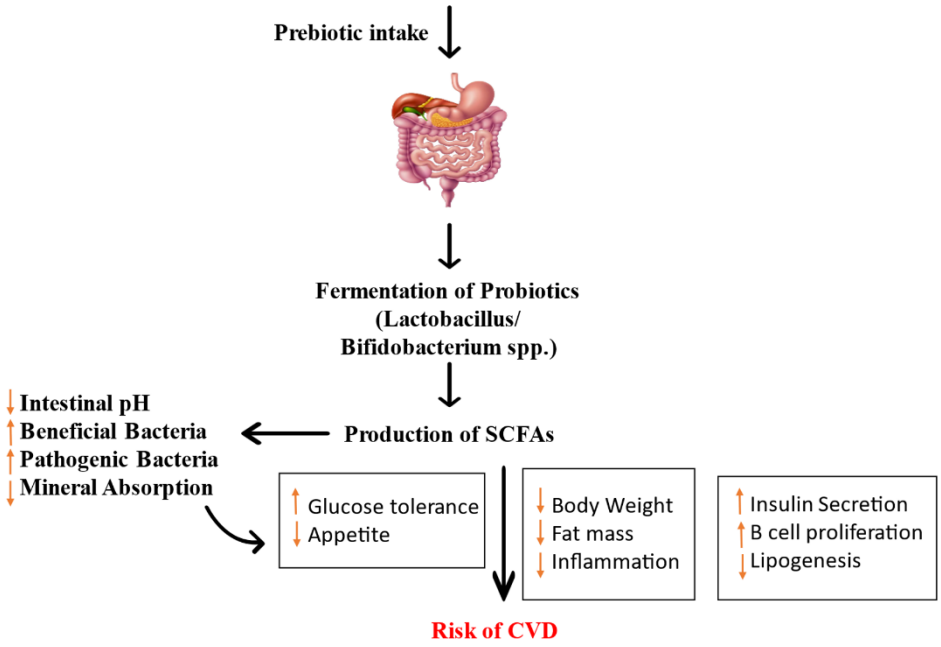

Figure 2 Mechanisms of beneficial role of Probiotics and Prebiotics in Reduction of Cardiovascular diseases

Conclusion

Probiotics and prebiotics play a crucial role in re-establishing the proper balance of gut flora, which promotes the development of healthy microbes and lowers the chance of long-term diseases like heart disease. Consequently, it is widely accepted that these chemicals are interesting as building blocks for new meals with useful qualities. The investigation into these subjects is still in its early stages.

Researchers must fully elucidate the role of native microbiota in human health and wellness in addition to producing reliable predictive estimations of the relationship between microbial cultures and native intestinal microbes. Then and only then will it be feasible to establish the optimal

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dosages for individuals to take to either decrease or maintain cardiovascular disease, as well as to successfully customize probiotic and prebiotic therapy and determine how long to take supplements. The approaches used in the intricate and relatively new subject of gut microbiome research are by no means uniform or harmonized. Small sample numbers and a dearth of alternatives are common in clinical research. Given the variety of techniques used for sample collection, manufacturing, and storage, this is an important problem. It was demonstrated that there is a chance of artifact introduction due to these technical variations. Numerous advanced bioinformatics techniques have been used to manage the massive amount of information produced when microbiota, metabolomes, genomes, and transcriptomes are assessed in cohort or intervention studies. Additional observational and randomized intervention trial research is required in this area. Therefore, carefully designed experiments that consider the gut microbiota, molecules, family history, and lifestyle variables are needed to be developed to further the existing state of knowledge.

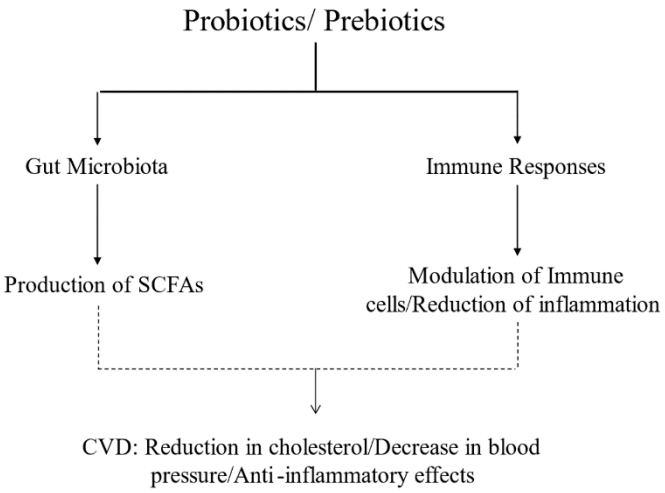

Figure 3 Summary of the mechanisms of the beneficial role of probiotics and prebiotics in CVD via gut microbiota and immune responses

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