Review Article

Role of Probiotics for the Treatment of Cardiovascular Disease - A Systematic Review

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ABSTRACT

Cardiovascular Disease (CVD) is a long-term progressive disease that frequently results in irreversible harm to vascular structures, manifesting as atherosclerosis and adverse clinical results like arterial thrombosis, myocardial infarction (MI) and stroke. Hypercholesterolemia, especially low-density lipoprotein cholesterol (LDL-C), are a recognized risk factor for CVD. The development and advancement of CVD are linked to various risk factors, with gut microbiota (GM) attracting significant attention over the last two decades. Gut microbiota significantly impacts on human health. Specifically, gut dysbiosis is closely connected to various acute or chronic dysfunctions of the cardiovascular system in the host. Previous research has shown that the development of CVD is closely associated with an imbalance in intestinal microbiota and inflammatory response. In recent decades, numerous studies have shown that the GM is crucial in human metabolism and various disease conditions, including CVD. The intestinal microbiome and its metabolites play a significant role in the development of CVD. Growing evidence suggests that diets enriched with functional foods containing probiotics which can affect intestinal flora and safeguard beneficial bacteria in the digestive system, play a role in preventing and lowering the risk factors associated with CVD. Probiotic microorganisms have been utilized to restore imbalanced intestinal microbiota and assist in lowering the likelihood of developing obesity, diabetes, hypercholesterolemia, oxidative stress (OS), CVD and metabolic dysfunction. Therefore, this review summarizes the potential dietary intervention that interact with GM such as probiotics as preventive and therapeutic strategies for managing CVD.

Keywords: Probiotics; Gut microbiota; cardiovascular disease; Inflammation; Oxidative stress.

INTRODUCTION

Cardiovascular disease is the primary cause of death globally[1]. It mainly affects heart or blood vessels, the most common conditions include coronary artery diseases (CAD) (angina pectoris and MI), heart disease, stroke, arrhythmia, thromboembolic disease and venous thrombosis[2]. A poor diet has long been acknowledged as a significant contributor to cardiovascular illness prevalence. A link between nutrition and cardiovascular occurrences was established via the factors influencing metabolic stress and obesity namely, body fat and the existence of visceral fat[3]. A significant risk factor for CVD is irregular blood lipid levels. Specifically, an elevated amount of LDL-C levels in the bloodstream elevate the likelihood of developing CVD[4]. The risk of microvascular issues and cardiovascular death is more in patients with type 2 diabetes mellitus (T2DM), insulin resistance (IR) and dyslipidemia[5].

Studies reported association of GM with the onset of various cardio-metabolic conditions, such as obesity, T2DM and CVD.[3] Alteration of GM (dysbiosis) as a key primary causal factors that contribute to the inflammation and CVD[1,6]. Researchers have identified different mechanism via dysbiosis contributes to the onset of CAD (Fig. 1) such as increase in gut permeability and metabolic endotoxemia[1]. Dysbiosis can raise ROS (reactive oxygen species) and lipopolysaccharides (LPSs) and lower short chain fatty acids (SCFAs) in the intestine. These changes all lead to elevated OS and inflammation, which in turn causes endothelial dysfunction, arterial hypertension and volume homeostasis all of which are crucial in patients with heart failure (HF) [7].

The microbiome, especially in the colon helps to ferment food (proteins, carbohydrates and dietary fibers), converting them into metabolites or microbial byproducts, e.g., SCFAs and secondary bile acids. Therefore changes in the composition of GM could contribute to preserving human metabolic equilibrium and cardiovascular health[3]. Dietary supplements, commonly known as functional foods, may provide positive impacts on different factors that contribute to the likelihood of CVDs[2].

Moreover, substantial evidence is being gathered (Table 1) concerning the administration of probiotics and their positive impact on lowering cardiovascular risk factors[6]. Probiotics are defined by the World Health Organization (WHO) as "live microorganisms that confer health benefits on the host when administered in adequate amounts[7]. As documented in the previous reports that co-supplementation of 8×10^9 colony-forming unit/gm (CFU) of probiotics, which included *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri* and *Lactobacillus fermentum* (each at 2×10^9), along with 50,000 IU of vitamin D administered biweekly for 12 weeks to individuals with T2DM and coronary heart disease (CHD), resulted in beneficial effects on mental health parameters, inflammatory markers, total antioxidant capacity (TAC), glycemic control and high density lipoprotein cholesterol (HDL-C) [5]. Functional foods may provide positive impacts on multiple risk factors associated with CVDs[3].

However, there is limited knowledge regarding the functions of probiotic supplements as essential dietary

elements in the prevention and management of CVD. Hence, the objective of this review is to explore the function of probiotic, in the prevention and management of CVDs as supported by existing studies and clinical findings.

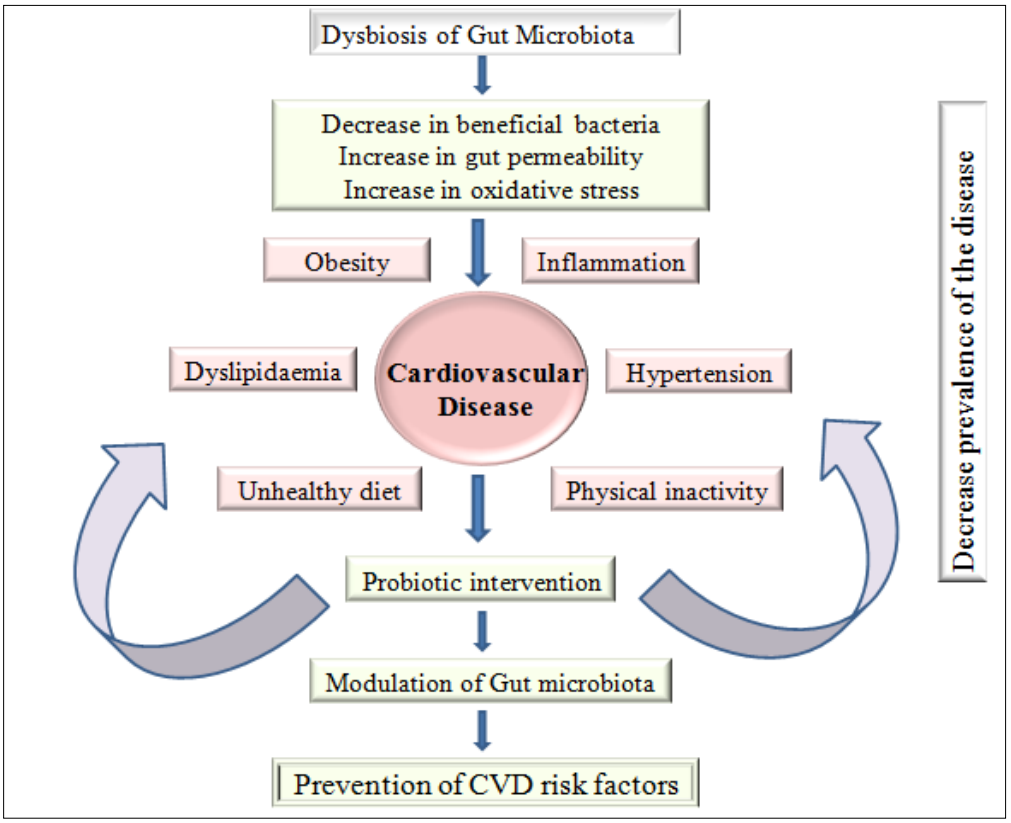

Figure 1: Schematic representation of role of gut dysbiosis in pathophysiology of CVD and prevention of CVD risk factors by Probiotic intervention

PROBIOTICS

Probiotics are made up of variety of healthy microbes. The majority of these are members of lactic acid bacteria (LAB) family, which includes *Enterococcus, Bifidobacterium, Lactobacillus* and *Streptococcus*. Probiotic strains are mostly found in fermented foods, such as kimchi, kefir, yogurt, sauerkraut etc. which are consumed by humans. In clinical research probiotics may be employed in a food, based on a number of criterias. These criterias include: (1) accurate identification, characterizing and maintaining probiotic strains (2) maintaining probiotics under study in living conditions and (3) making sure the probiotics are alive at the study site[8]. *Lactobacillus rhamnosus, Lactobacillus reuteri, bifidobacteria,* and specific strains of *Lactobacillus casei, Lactobacillus acidophilus-group, Bacillus coagulans, Escherichia coli* strain Nissle 1917, specific *enterococci*, particularly *Enterococcus* faeciumSF68 and the yeast *Saccharomyces boulardii* are a few of the commonly used probiotic microorganisms. The effects of probiotics are highly strain-specific and not broadly applicable. Fewer studies have demonstrated that multi-strain probiotics are more effective[9]. Probiotics were first introduced by Elie Metchnikoff in 1900s, who noted that native, long-living Bulgarian populations used for fermented milk, which contained LAB and that milk had a positive effect on health[10]. According to WHO regulations, a probiotic food's live cell count at the time of human consumption cannot be less than 10^6 cells per milliliter or gram of product; however, clinical studies have found that a therapeutic dose of 10^8–10^9 cells per milliliter is recommended. Stomach juice and bile salts should not harm the probiotic since the microorganism needs to survive and not perish during transit through the digestive system. Probiotics should stick to the intestinal surface after overcoming this chemical barrier so that their health-promoting properties can be realized. Additionally, it might be required to repeatedly consume probiotic products if the intestine is not colonized by probiotic microorganisms[2,9]. Probiotics have been shown to have positive effects on human health and the ability to prevent disease through a variety of mechanisms, including competing with pathogenic microorganisms, antagonistic pathogens, gut microbiome modification and host immune response modulation[8].

Moludi J et al., reported in a recent randomized double-blind, placebo-controlled study that the patients supplemented with probiotic capsule daily for 12 weeks containing a *Lactobacillus rhamnosus* 1.6×10^9 CFU showed significant reduction in biomarker level of inflammation, metabolic endotoxemia and rise in interleukin-10 (IL-10) but not in toll-like receptor 4 (TLR4). The result demonstrates anti-inflammatory and anti-endotoxemic property of probiotics among CAD patients. Probiotics may have anti-

inflammatory properties through reducing the expression of inflammatory cytokines and encouraging the GM to produce SCFAs. It has been reported that dysbiosis caused by endotoxemia and chronic inflammation increases a participant's risk of developing CADs. In patients with CAD, activation by LPS led to an increase in plasma levels of cytokines such as interleukin-1 beta (IL-1β). Probiotics may counteract these effects by supporting the improvement or restoration of the composition of a healthy GM[1].

Moludi J et al., reported to conduct a single-center, double-blind, placebo-controlled stratified randomized clinical study with MI patients who underwent percutaneous coronary intervention (PCI). Patients received probiotic capsules containing *Lactobacillus rhamnosus GG* 1.6 × 10^9 CFU of bacteria for three months result in significant decrease in the markers of cardiac remodeling (CR) such as trimethylamine N-oxide (TMAO), transforming growth factor-β (TGF-β) and inflammatory biomarkers such as high-sensitivity C-Reactive Protein (hs-CRP) in MI patients. One strong and reliable predictor of HF is hs-CRP, which is a measure of persistent low-grade inflammation. Furthermore, because TMAO is a pro-atherogenic substance, it may raise the chance of developing CR. Absorption of LPS, TMAO levels and resulting CR development can all be decreased with probiotic treatment. A direct link between dysbiosis and an increased risk of HF has been suggested by earlier research. The development of toxic metabolites like TMAO is significantly influenced by the GM. It has been observed that TMAO levels are associated with GM at phylum as well as family level[6]. Diabetic patients with CHD randomly assigned to probiotic supplements containing *Bifidobacterium bifidum* 2×10^9, *Lactobacillus casei* 2×10^9, *Lactobacillus acidophilus* 2×10^9 CFU/day led to an increase in the plasma TAC and glutathione (GSH) levels and significant reduction in serum hs-CRP compared to placebo. This study demonstrated that taking probiotics for 12 weeks had beneficial effects on improving total-/HDL-C ratio, HDL-C level, inflammatory markers and OS by Raygan F et al[5].

Kullisaar T et al., reported that goats' milk fermented with the human antioxidative *lactobacilli strain, Lactobacillus fermentum* ME-3 (150gm/day) showed anti-atherogenic effect because all the effects on plasma lipoproteins that have been observed such as reduced levels of oxidized low density lipoprotein (oxLDL), decreased conjugated diene level of lipoprotein fraction (LPF) and increased oxidation resistance of LPF have an anti-atherogenic nature[11]. M. Song et al., reported that *Lactobacillus acidophilus* NS1 administration lowers plasma LDL-C in an HFD (high fat diet) fed mouse model by upregulating hepatic low density lipoprotein receptor (LDLR) expression. Rats fed with *L. acidophilus* NS1 HFD showed reduction in hepatic cholesterol and triglycerides (TG) levels with decrease in plasma LDL-C by upregulating hepatic LDLR expression. Oral administration of *L. acidophilus* increases the expression of sterol regulatory element binding protein 2 and LDLR in the liver, which was subsequently inhibited by high fat intake, resulting in a reduction in plasma cholesterol levels. *Lactobacillus acidophilus* NS1 could be a helpful probiotic for lowering cholesterol in dairy products, improving hyperlipidemia and improving hepatic lipid metabolism[12]. Naruszewicz, M et al., reported to conduct a controlled double-blind placebo study. Participants supplemented with 400 mL/d of the test product containing *Lactobacillus plantarum* 299v (*L. plantarum*) for 6 weeks showed decrease in LDL-C, leptin, IL-6 and fibrinogen concentrations and increase in HDL-C concentration in experimental group. Administration of *L. plantarum* in smokers lowers the adherence of monocytes and tumor necrosis factor (TNF) activated human umbilical vein endothelial cells (HUVECs)[13]. Rodas De B Z et al., reported that supplementation of *L. acidophilus* (2.5 x 10^{l1} total cells per feeding) or 1.4% dietary calcium in diet did not change HDL-C level but reduced serum concentration of LDL-C, total cholesterol (TC) and bile acid to show hypocholesterolemic action in swine[14]. Zhang F et al., reported that rats fed with a HFD supplemented with *Enterococcus faecium* WEFA23 significantly decreased body weight, serum lipid levels (triacylglycerols (TAG), TC and LDL-C), IR and blood glucose level[15].

YOGURT

Yogurt contains probiotics, made from the fermentation of lactic acid (LA) in milk by *Lactobacillus bulgaricus* and other LAB species. Probiotics have a wide range of positive health effects, such as lowering stomach pH, enhancing immune system performance and producing antimicrobial compounds. The anti-inflammatory and anti-oxidative properties of yogurt contributed to the presence of LA, folate and conjugated linoleic acid. As a treatment approach to lower cholesterol, TNF-α, OS, improve IR, and treat obesity-related problems such as non alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS), yogurt plays a part in altering the intestinal bacterial flora and intestinal barrier integrity. In NAFLD patients, symbiotic yogurt consumption improved hepatic features[15,16].

In a randomized, triple-blind clinical trial, 90 congestive heart failure (CHF) patients randomly assigned to take ordinary yogurt or probiotic for 10 weeks. After intervention probiotic yogurt groups showed significant increase in the levels of tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) which may help patients to achieve a better inflammatory state by Pourrajab B et al[17]. sTWEAK is a type II transmembrane glycoprotein and a member of the TNF superfamily that acts by binding to Fn14 which is a small transmembrane type I protein[18]. The level of sTWEAK could be used as a marker of mortality and prognosis in patients with non-ischemic heart failure, chronic stable heart failure and chronic kidney failure as it mainly affect on inflammatory cytokine release and apoptosis stimulation by Comertpay E et al[19]. Agerholm-Larsen L et al., reported to decrease LDL-C and increased fibrinogen level in participants supplemented with 450 ml fermented milk products (yoghurt) daily for 8 weeks in a randomized, double-blind, placebo- and compliance-controlled, parallel study[4]. One of the study has reported that yogurt containing *Lactobacillus acidophilus*, *L bulgaricus*, and *Streptococcus*

thermophilus and exercise alone did not show any significant impact on biomarkers of CVD. Beside to this, reduction in TG and hs-CRP level was observed in combination group result in the prevention of CVD. In healthy individuals, yoghurt and exercise decreased TG and hs-CRP levels more than either of them did alone by Kim HK et al[20].

Administration of probiotic yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 showed beneficial effects on oxLDL serum level in CHF patients, whereas no significant effects on apolipoprotein B-100 (ApoB100) and N-terminal pro-B-type natriuretic peptide (NTproBNP) levels. Although reduction in the pentraxin-3 (PTX3) level observed in both probiotic and ordinary yogurts compared to the baseline. Probiotics may have an effect on serum oxLDL levels by increasing TAC in a number of ways, such as: 1 - capturing ferrous and cupric ions and preventing metal ions from catalyzing the oxidation; 2 - using catalase and superoxide dismutase as their own antioxidant enzymatic systems or promoting the host's antioxidant system; 3 - producing several metabolites with antioxidant activity. 4-preventing OS by altering the pathways for protein kinase C, mitogen-activated protein kinase, nuclear factor kappa B (NF-kB) and Nuclear Factor (erythroid-derived 2)-like 2 (Nrf2) - Kelch-like ECH-associated protein 1 (Keap1) - Antioxidant Response Element (ARE). The fifth strategy involves controlling the enzymes that produce ROS, such as cyclo-oxygenase expression, nicotinamide adenine dinucleotide phosphate oxidase (nitrogen oxidase) activity and cytochrome P450 enzyme activities. The sixth strategy involves controlling the GM's composition and preventing the overgrowth of pathogenic bacteria, both of which can lead to decreased OS as reported by Pourrajab B et al[7].

A randomised, double blind study was conducted on patients with MetS. Participants were randomly assigned to receive 300 gm daily regular yoghurt or 300 gm probiotic yoghurt for 8 weeks. Probiotic yoghurt enriched by adding cultures of *Bifidobacterium lactis* Bb12 and *Lactobacillus acidophilus* La5. After 8 weeks of the intervention, there was a significant increase in HDL-C and decrease in serum TG level observed in the probiotic yoghurt group. No significant difference was observed in inflammatory parameters. Probiotics are thought to be a novel therapeutic approach for treating and preventing dyslipidemia and atherosclerosis by altering the GM by Rezazadeh L et al[21]. A single-blind, randomized crossover study was conducted on 14 healthy participants with serum TC level 5.17–7.76 mmol/l. Administration of probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* caused a significant reduction in serum TC when compared with the ordinary yogurt. These bacteria may reduce cholesterol through inhibition of dietary cholesterol absorption from the small intestine by binding to cholesterol and bile acids in their cells or by promoting excretion following bile acid-bacterial cell binding and cholesterol assimilation by LAB by Ataie-Jafari A et al[22].

Rezazadeh L et al., reported that patients with MetS participated in randomized, double-blind, placebo-controlled clinical trial. Supplementation of 300 gm/d probiotic yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 for 8 week resulted in a significant decrease in serum plasminogen activator inhibitor type 1 (PAI-1) and vascular cell adhesion molecule-1 (VCAM-1). However no significant changes were observed in intercellular adhesion molecule 1 (ICAM-1) levels. Metabolic syndrome is associated with elevated levels of adhesion molecules, such as VCAM-1, ICAM-1 and PAI-1, which are vascular inflammatory markers for endothelial dysfunction. High concentrations of adhesion molecules have been shown to positively correlate with CVDs. It was expected that VCAM-1 reductions would enhance endothelial function and lower cardiovascular risk caused by MetS[23]. In double-blind cross-over study participants were administered with milk fermented by yogurt starters and *Lactobacillus acidophilus* and contained 2.5% fructo-oligosaccharides, 0.5% vegetable oil and 0.5% milk fat. This significantly decreases LDL-C, TC and the LDL=HDL-ratio but no significant effect observed on serum HDL-C and TG by Schaafsma G et al[24].

In a single-blind, random-allocation, parallel study, subjects with hypercholesterolemic assigned with 200gm of fermented milk (FM) containing human *Lactobacillus acidophilus* L1 (L1 FM) and *L. acidophilus* strain ATCC 43121 (ATCC FM) of swine origin. Consumption of L1 FM significantly decreases serum cholesterol, LDL-C and HDL-C concentrations. Consumption of ATCC FM significantly reduced HDL-C whereas no significant reduction in serum cholesterol, LDL-C and TG was observed. Thus, regular intake of FM containing an active cholesterol-reducing *L. acidophilus* could decrease estimated risk for CHD by 6 to 10% by Anderson JW et al[25]. A single-blind, parallel group study conducted with *bifidobacterium* yogurt and placebo yogurt in healthy men. The study also carried out on rats fed with cholesterol-enriched experimental diet. Intake of milk fermented with *Bifidobacterium longum* strain BL1, significantly reduced serum concentrations of LDL-C, TC and TG, beside to this no change in serum concentration of HDL-C was observed. The current findings suggest that the probiotic *B. longum* strain BL1 may help lower serum lipid levels by Xiao JZ et al[26].

Lokapirnasari w et al., reported that supplementing combination of 0.5% *Bifidobacterium sp* with 0.5% *Lactobacillus acidophilus* probiotic decreases cholesterol level through modifying lipid metabolism, assimilating and incorporating cholesterol in the cell membrane of probiotics, converting cholesterol in the gut into coprostanol, and suppressing the expression of the intestinal cholesterol transporter in enterocytes, Niemann-Pick C1 like 1 (NPC1L1)[27]. Some of the studies also reported supplementation of yogurt of low-fat milk at a dose of 16 oz/day for 4 weeks has no effect on Plasma level of cholesterol, LDL-C and HDL-cholesterol in normolipidemic males[28]. Ivey KL et al., reported that participants (overweight men and women) supplemented with

Lactobacillus acidophilus La5 and *Bifidobacterium animalis* subsp *lactis* Bb12 at a dose of 3.0 x10^9 CFU/d in a week in randomized, controlled, parallel, double blind, factorial study. Results showed no significant change in blood pressure, heart rate and serum lipid parameters such as TC, LDL-C, HDL-C and TG[29].

Mohamed DA et al., reported that when diabetic rats treated with control stirred yoghurt and fortified probiotic stirred yoghurt either with 1% or 2% of beetroot powder. Results indicate decrease in the TG, TC, non-HDL-C, LDL-C and VLDL-C. The beetroot contain numerous bioactive compounds such as antioxidants, dietary nitrate, polyphenols, betanin, vitamins, minerals (sodium, potassium, iron, magnesium, copper, calcium, zinc and phosphorus) which play an important role as cardioprotective agents as well as in the prevention of dyslipidemia. Dietary fibers present in the beetroot helps to improve bile acid and SCFAs which suppress the blood cholesterol concentration. In addition it helps to promote proliferation of beneficial bacteria which showed positive effect by decreasing blood lipid concentration. Treatment with stirred yoghurt and fortified probiotic stirred yoghurt with beetroot has preventive effect on dyslipidemia and hypercholesterolemia via HMG-CoA reductase enzyme inhibition[30].

KEFIR

Kefir is a probiotic beverage, has been recognized as a popular health promoting fermented milk and a source of organisms, that uses kefir grains as a starter[31]. Kefiran is an exopolysaccharide that is isolated from kefir grains and produced by *Lactobacillus kefiranofaciens*[32]. According to previous studies kefir showed immune-modulatory properties, serum cholesterol-lowering potential and angiotensin converting enzyme inhibitory activity. Specific microorganisms isolated from kefir have been linked to these characteristics as well as others like bile salt hydrolase activity. It has also been demonstrated that kefir and peptides derived from it are beneficial in reducing obesity and NAFLD. All of these traits suggest that kefir may have a beneficial effect on MetS through diet-related changes, direct interactions with the host, or modifications to the microbiota and related metabolic profile[31]. Kefir contains a number of bioactive peptides that have been shown to have antihypertensive, antimicrobial, immune-modulatory and anti-oxidative properties. Recent clinical studies have shown that consuming probiotic-rich foods can reduce the intensity of symptoms and have an impact on MS patients' anthropometric and biochemical outcomes[33].

Hyeon Kim D et al., reported that based on the previous in *vitro* studies three kefir isolates such as *Leuconostoc mesenteroides* (*Leuc. mesenteroides*) DH4 (low survivability, high cholesterol reduction), *Lactobacillus kefiri* (*L. kefiri*) DH5 (high survivability, high cholesterol reduction), and DH7 (high survivability, low cholesterol reduction) selected to investigate their anti-obesity effects by using an HFD-induced obesity in mouse. Kefir isolate *L. kefiri* DH5 showed reduction in cholesterol, LDL-C, TG and fewer *Proteobacteria* and *Enterobacteriaceae* than the mice in HFD-saline group[34]. Yilmaz I et al., reported to conduct a prospective, self-controlled, 8-week clinical trial on dyslipidemic men and women and consumption of kefir on a regular basis helped to reduce the levels of TC and LDL-C. In dyslipidemic individuals, dysbiosis may impair the metabolism of bile absorption and cholesterol. The probiotic kefir regulates the dysbiosis which led to decrease in cholesterol[35]. Chang GR et al., suggested that kefir peptides (KPs) prevented hyperlipidemia and potential harm to the liver and muscle in ApoE −/− mice as it help to reduce serum levels of TC, oxLDL, malondialdehyde (MDA), alanine transaminase, aspartate aminotransferase (AST), and creatine kinase (CK). It was suggested that KPs inhibited inflammatory responses in ApoE −/− mice by reducing serum TNF-α and the local expression of TNF-α, IL-1β, and macrophage-specific CD68 markers in aortic tissues. In the aortic roots KPs decreases the deposition of lipid, collagen and calcium minerals, indicating that KPs prevented the calcific advancement of atherosclerotic plaques[36].

Mert H et al., reported that administration of kefir in MI induced by Isoproterenol (ISO) can protect the heart tissue with its antioxidant characteristic and minimize the toxic damage caused by ISO. Kefir group showed significantly lower TG and very low density lipoprotein (VLDL) level whereas no significant change was observed in HDL-C levels. Cardiac marker enzymes such as AST, CK, MDA, advanced oxidation protein products and lactate dehydrogenase were decreased significantly and level of GSH increased by kefir administration[37]. Uchida M et al., suggested that rabbits receiving high cholesterol diet to develop atherosclerotic lesions with or without kefiran. Kefiran reported to decrease blood cholesterol and blood pressure (BP). The liver's TC, free cholesterol, cholesteryl ester levels and number of atherosclerotic lesions in the kefiran group were significantly lower, indicating kefiran group may be more likely to promote cholesterol catabolism. The reduction in the area of atherosclerotic lesions can be attributed to three possible reasons: (i) reduction in inflammation (ii) decrease in cholesterol accumulation in macrophages and (iii) decrease in serum lipid levels[32]. Jascolka T et al., reported that Apo E KO mice received Kefir solution for 4 weeks, significantly increased HDL-C and decreased TG level but did not change TC, LDL-C and blood glucose levels. According to these findings, kefir supplements may have improved the lipid profile[38]. Silva-Cutini MA et al., reported that prolonged kefir treatment in spontaneously hypertensive rats improved cardiac function by lowering BP, sympathetic activity, improving cardiac contractility and improving calcium-handling proteins. According to these results, kefir may be used as a coadjutant to lower BP because of its positive effects on the condition[39].

Friques et al., reported that vascular endothelial function was significantly improved after taking probiotic kefir daily for 60 days in spontaneously hypertensive rats. The mechanism underlying the positive effects of kefir was the restoration of vascular endothelium architecture, decrease in OS, increase in nitric oxide bioavailability and

simultaneous contribution of endothelial progenitor cell recruitment[40]. Liu JR et al., reported that consuming soyamilk, milk kefir or soyamilk-kefir appeared to lower TAG and serum TC in hamsters. The soyamilk-kefir and milk-kefir diet groups had significantly higher serum HDL-C concentrations than milk diet group. Furthermore, compared to the soyamilk diet groups, the hamsters from the soyamilk kefir diet groups had lower concentrations of non-HDL-C[41]. Administration of the soluble, non-bacterial fraction of kefir for 4 weeks caused a significant reduction in vascular lipid deposition and TNF-α/IL-10 but did not change cholesterol serum levels in $LDLr^{-/-}$-deficient mice. The benefits of using kefir has potential application as an adjuvant in the prevention of atherosclerosis by Santanna AF et al[42]. Bourrie B et al., reported that supplementation of traditional kefir (IR10, Ger2, UK4, IR9, and ICK [Indeterminate Country Kefir]) to HFD induce obesity in mice significantly lowered cholesterol levels. Liver TG were significantly reduced in the ICK kefir group when compared to HFD control group. The ICK, IR10 and commercial kefir groups showed a significant decrease in expression of fatty acid synthase (FASN), however reduction in peroxisome proliferator-activated receptor gamma (PPARγ) expression only showed in the ICK fed group[31]. A single-center, multi-arm, parallel-group, outpatient, randomized controlled trial conducted on healthy overweight or obese premenopausal women. The participants randomly allocated to kefir, milk and control group. Participants receiving kefir significantly showed beneficial effect on serum lipid profile by Fathi Y et al[43].

In obesity KPs may mediate the lipid metabolism pathway. Administration of KPs to obese rats used to prevent lipogenesis in the livers by significantly lowering the FASN protein. By raising the protein expressions of phosphorylated AMP-activated protein kinase (p-AMPK), PPAR-α, and hepatic carnitine palmitoyltransferase-1 (CPT1) in the livers, KPs also increased fatty acid oxidation. Furthermore, administration of KPs was found to significantly reduce mRNA levels of TNF-α, IL-1β, and TGF-β, which showed inflammatory responses that modulate oxidative damage by Tung YT et al[44]. In this randomized, double-blind, placebo-controlled clinical trial conducted on 48 patients with MetS. Ghizi A et al., suggested that Kefir treatment decreases serum level of non-HDL-C, TG, LDL-C, VLDL-C, oxLDL cholesterol and increases HDL-C serum levels which help to reduce the risk for CVD, evaluated by the Framingham score. Risk of CVD increases with high level of hs-CRP which leads to form endothelial lesion by mediating the formation, destabilization and rupture of atherosclerotic plaques. Kefir treatment significantly improved LDL-C levels, systolic blood pressure (SBP) and diastolic blood pressure (DBP), which accounts for the observed reduction in the risk of CVD[33]. Tung C M et al., indicated that atherosclerotic lesion development in HFD-induced atherosclerotic *ApoE*$^{-/-}$ mice was improved by oral administration of KPs. Kefir administration showed reduction in aortic lipid deposition, OS, macrophage accumulation in plaques, systemic IL-1β, TNF-α levels, aortic root fibrosis and enhanced endothelial function. Furthermore, *in vitro* cell studies also demonstrated that KPs suppresses endothelial cell activation and THP-1 monocytes adhesion and migration under oxLDL conditioned cell cultures. These results suggested that KPs play a role in anti-atherosclerosis potentially by modulating the immune cell responses, reducing ROS and oxLDL production and regulating cytokine related pathways[45].

CHEESE

Cheese is a good alternative for the delivery of probiotics into the intestine and as a result has been the subject of various marketing and research studies in recent years. Numerous strains of probiotic bacteria have been successfully added into different types of cheeses including *lactobacilli* (*Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, and Lactobacillus gasseri*) and *Bifidobacterium spp.* (*Bifidobacterium animalis ssp. lactis, Bifidobacterium longum, Bifidobacterium bifidum, and Bifidobacterium infantis*) and to a lesser extent, *Propionibacterium freudenreichii ssp. Shermanii*[46].

Da Silva Costa N et al., reported that rats with chronic kidney disease received 20 g/day of minas cheese with *Lactobacillus acidophilus* La-05 (10^8-10^9 log CFU/g) for 6 weeks. Supplementation of probiotic-enriched minas cheese exhibited lower plasmatic SOD activity and a decrease in cardiomyocyte diameter when compared to rats fed with conventional minas cheese group suggesting a promising cardioprotective effect[47]. Sharafedtinov KK et al., reported to conduct a randomized, double-blind, placebo-controlled, parallel pilot study on 25 subjects with obese hypertensive patients, ingested with probiotic cheese containing *Lactobacillus plantarum* TENSIA 1.5x1011 CFU/g. Following three weeks of consumption of 50 gm/d of 26% fat cheese, there was a reduction in LDL-C, TG and TC in both the probiotic groups. Supplementation of probiotic cheese help to reduce arterial BP, body mass index and the risk of MetS in obese hypertensive patients. Relaxation of the blood vessel by in vitro production of nitric oxide by the TENSIA strain which is also associated with decrease in excess formation of ROS could be the mechanism of action to lower the arterial BP[48].

Lollo PCB et al., reported that rats with hypertension ingested with 20 g/d probiotic minas frescal cheese (PMFC) for 15 days showed beneficial effect on arterial hypertension. According to the previous studies, heart mass can rise in cases of hypertension for this reason, it appears that continuing to consume probiotic-rich minas cheese may be beneficial. Furthermore, the animals fed with probiotic cheese during the 15-days of experiment, experienced a lesser increase in heart mass than the animals fed conventional cheese or a control diet. Results indicate significant improvements in blood lipids, i.e. TC, TG, LDL-C and HDL-C, which decrease the risk of hypertension. Hypertension has been linked to increased levels of TG and LDL-C and decreased levels of HDL-C. Therefore, PMFC may act by improving dyslipidemia, which in turn lowers the risk

for the development of hypertension[49]. Zhang L et al., reported that mice received high-cholesterol diet and given probiotic cheese once a day at a dose of 0.2 g/kg body weight (low dose of *Lb. plantarum* K25, HFLK group), and (high dose of *Lb. plantarum* K25, HFHK group) control cheese at a dose of 1.8 g/kg body weight. Within four weeks, the HFHK and HFLK group experienced a maximum reduction in TC and LDL-C. In vivo, *Lb. plantarum* K25 produced hypocholesterolemic results. The results of this study showed that the HFLK and HFHK groups significantly improved LDL-C/HDL-C and TC/HDL-C ratios, with the high dose feeding being more effective[50].

Incorporation of cholesterol into the cellular membrane during bacterial growth in the small intestine and cholesterol binding to bacterial cell surface are two potential mechanisms for the reduction of cholesterol following probiotic consumption. Additionally, active bile salt hydrolase deconjugates bile acids enzymatically, increasing their rate of excretion, which reduces the amount of cholesterol that is available for intestinal absorption. This may result in lower blood cholesterol level. Disorders of lipid metabolism are often associated with hypertension, which is more common in people with hypercholesterolemia than in people with normal cholesterol levels[49]. Atherosclerotic rabbits were administered with traditional fermented cheese whey (TFCW) containing probiotics for 4 weeks. Both low and high dose of TFCW significantly lowers the serum concentration of TC, TG, LDL-C and significantly increases HDL-C level. Significant decrease was observed in CRP, ICAM-1 and VCAM-1 with TFCW supplementation which results improvement in inflammatory condition in atherogenic rabbits. Histopathological study of aorta from atherosclerotic rabbits showed decrease in accumulation of atherosclerotic lesion which shows favourable effect. Seven LAB species which are probiotics were isolated from TFCW. These LAB species may be responsible to improve symptoms of atherosclerosis[51]. Rats with hyperlipidemia administered with cheese supplementation with probiotics. Supplementation with probiotics showed increase in HDL-C level and significant decrease in LDL-C, TC, liver enzyme such as ALT, AST and ALP[52].

SUMMARY

From the evidence, we can conclude that CVD associated with dyslipidemia are consider as leading causes of death or disability in many countries. Consequently, standard values of serum lipid levels are crucial, particularly for minimizing the risk factors of these diseases. A beneficial impact of functional products with probiotic bacteria on health is their ability to lower serum lipid levels[35]. Jie and colleagues examined the GM in individuals with atherosclerotic CVD and found notable differences, including elevated levels of *Enterobacteriaceae* and *Streptococcus* spp. Gut bacteria can generate metabolic products from food that can impact the cardiovascular health of the host[3]. Oxidative changes in LDL levels are typically linked to an inflammatory process that is associated with atherosclerosis[53]. Consuming probiotics may lower inflammation and OS by increasing the generation of SCFAs in the colon[5]. Raygan F et al reported that improved glucose homeostasis parameters, HDL-C levels and the overall HDL-C ratio resulting from probiotics intake in diabetic patients with CHD might be linked to their role in lowering inflammatory cytokines and blocking the NF-κB pathway[5]. In the present study clinical data suggested some of the cardioprotective mechanism of probiotics such as decrease in TG, LDL-C, VLDL-C, cholesterol level, reduction in inflammatory and cardiac biomarkers, metabolic endotoxin, increase in HDL-C, TAC and protection of oxLDL. The processes through which probiotics exert hypolipidemic effect include cholesterol assimilation, bile salt deconjugation, fermentation of dietary non-digestible carbohydrates leading to SCFAs production and modulation of the microbiota[53]. Mann and Spoerry were the first to propose the potential impacts of consuming probiotics on lipid metabolism through fermented milk intake. Studies reported some of the probiotic strains such as *L. bulgaricus, L. reuteri,* and *B. coagulans* that have demonstrated hypocholesterolemic benefits. Research involving humans consuming *L. acidophilus* L1 milk showed a notable decrease in serum cholesterol levels[9]. Based on this clinical studies we can summarize that the probiotic supplementation could provide beneficial therapeutic effects for individuals with CVD by changing the composition of GM.

Overall in this review, probiotics have been discussed with respect to their positive effect on prevention and management of CVD. The consumption of probiotics is crucial for restoring the normal gut flora, promoting the growth of helpful bacteria and lowering the likelihood of CVD development. Several studies reported the role of probiotics in hypercholesterolemic, dyslipidemic, hypertension, CAD though limited data is available with other CVD's. Further research is required with other CVD's and over extended duration to establish the positive impacts of probiotic supplementation.

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Table 1: Effect of Probiotics on various risk factors of CVD

Probiotics	Patient	Dose	Effect	References
Lactobacillus rhamnosus	CAD participants	1.6 × 10^9 CFU	Reduction in inflammatory biomarker, metabolic endotoxemia and increase in IL-10. No change in TLR4	1
Fermented milk products (yogurt)	Obese male and female	450 ml/daily	Reduction in LDL-C and increased fibrinogen	4
Bifidobacterium bifidu, *Lactobacillus casei*, *Lactobacillus acidophilus*	Diabetic patients with CHD	2×10^9CFU/day	Reduction in fasting plasma glucose, total-/HDL-C ratio, hs-CRP and increase in TAC and GSH level	5
Lactobacillus rhamnosus GG	MI patients who underwent PCI	1.6 × 10^9 CFU (3 months)	Significant reduction in CR markers such as TMAO, TGF-β and hs-CRP	6
Yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12	CHF patients	300 mL	Reduction in oxLDL and PTX3 serum level, no significant effects on ApoB100 and NTproBNP levels	7
Milk fermented with the *lactobacilli strain, Lactobacillus fermentum ME-3*	Healthy subjects	150 gm/day	Reduction in oxLDL, conjugated diene level of LPF and increased oxidation resistance of LPF	11
Lactobacillus plantarum 299v	Subjects with heavy smokers	400 mL/d	Reduction in LDL-C, leptin, IL-6, fibrinogen, decrease adherence of monocytes (40%) and TNF–activated (36%) HUVECs and increase in HDL-C concentration	13
Probiotic yogurt	CHF patients	----	Significant increase in sTWEAK level	17
Yogurt (*Lactobacillus acidophilus*, *L bulgaricus*, and *Streptococcus thermophilus*) and exercise	Healthy participants	83gm	Reduction in TG and hs-CRP level	20
Yoghurt *containing B. lactis* Bb12 and *L. acidophilus* La5	Patients with MetS	300gm	Significant increase in HDL-C and decrease in serum TG level but no significant change in inflammatory parameters	21
Probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis*	Mildly to moderately hypercholesterolemic subjects	3×100 gm/day	Significant reduction in serum TC	22
Probiotic yogurt containing *Lactobacillus acidophilus La5* and *Bifidobacterium lactis Bb12*	Patients with MetS	300 gm/d	Reduction in serum PAI-1 and VCAM-1 but no significant change in ICAM-1	23
Milk fermented by yogurt starters and *Lactobacillus acidophilus,* and contained 2.5% fructo-oligosaccharides	Healthy participants	125 ml yogurt and 2.5% fructo-oligosaccharides	Significant decrease in LDL-C, TC and the LDL=HDL-ratio but no change in serum HDL-C and TG	24
Fermented milk containing human *L. acidophilus* L1 (L1 FM) and swine *L. acidophilus* strain ATCC 43121 (ATCC FM).	Hypercholesterolemic subjects	200gm	Significant reduction in serum cholesterol, LDL-C and HDL-C concentrations (L1 FM). Significant reduction in HDL-C and no change in serum cholesterol, LDL-C, TG (ATCC FM)	25
Bifidobacterium longum strain BL1	Healthy men	3×100 ml	Significant reduction in LDL-C, TC and TG. No change in HDL-C	26
Yogurt	Normolipidemic males	16 oz/day for 4 weeks	No significant change in cholesterol, LDL-C and HDL-C	28
Lactobacillus acidophilus La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12	Overweight men and women	3.0 x10^9 CFU/d for 6 weeks	No significant change in TC, LDL-C, HDL-C, TG, blood pressure and heart rate	29
Kefir	Dyslipidemic men and women	250 ml	Reduction in TC and LDL-C	35
Kefir drink	Healthy overweight or obese premenopausal women	2 servings/d	Significant decrease in LDL-C, TC, TC/HDL-C, non-HDL-C and LDL-C/HDL-C	43

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