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A REVIEW OF THE EFFECTIVENESS OF PROBIOTICS IN MANAGING HYPERCHOLESTEROLEMIA

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ABSTRACT

Hypercholesterolemia represents a significant global health burden, contributing substantially to cardiovascular disease morbidity and mortality. Though statins form the basis for pharmacological intervention, the trends in recent years have increasingly shifted towards alternative treatments with a particular focus on probiotic treatment. This review discusses the existing evidence for benefits of probiotics in cholesterol lowering, discussing mechanisms involved in this potential benefit, trial results and describes factors that could influence the efficacy of therapy with these agents. Studies have shown that some probiotic strains, including Lactobacillus and Bifidobacterium spp., have potential exert cholesterol-lowering effects though different pathways such as bile salt dehydrolation, cholesterol assimilation and lipoprotein metabolism. However, studies differ in designs, strain(s) used, doses given and clinical outcome(s). This review synthesizes current knowledge, identifies gaps in understanding, and provides recommendations for future research directions in probiotic-based cholesterol management.

KEYWORDS: *Probiotics; Hypercholesterolemia; Cholesterol; Cardiovascular Disease; Lactobacillus,*

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, accounting for approximately 17.9 million deaths annually (WHO, 2021). Hypercholesterolemia, characterized by elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or reduced high-density lipoprotein cholesterol (HDL-C), constitutes a major modifiable risk factor for atherosclerotic cardiovascular disease. The relationship between elevated LDL-C and cardiovascular risk is well-established, with each 1 mmol/L reduction in LDL-C associated with approximately 20-25% reduction in major vascular events (Cholesterol Treatment Trialists Collaboration, 2010). Current treatment paradigms for hypercholesterolemia primarily rely on lifestyle modifications and pharmacological interventions, particularly statins. While highly effective, statin therapy is associated with several limitations including adverse effects such as myopathy, hepatotoxicity, and concerns regarding long-term compliance. Additionally, some patients exhibit statin intolerance or achieve inadequate lipid control despite maximal therapy. These considerations have stimulated interest in complementary and alternative approaches to cholesterol management. Probiotics, defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill *et al.,* 2014), have emerged as promising candidates for metabolic health interventions. The human gut microbiota, comprising trillions of microorganisms, plays crucial roles in nutrient metabolism, immune function, and maintenance of intestinal barrier integrity. Accumulating evidence suggests that gut microbial composition and function influence host lipid metabolism and cardiovascular risk. Dysbiosis, characterized by altered microbial diversity and composition, has been associated with metabolic disorders including obesity, diabetes, and dyslipidemia. The potential cholesterol-lowering effects of probiotics were first proposed over three decades ago, with early observations suggesting that fermented milk products might influence serum cholesterol levels. Since then, numerous in vitro studies, animal experiments, and clinical trials have investigated the cholesterol-modulating properties of various probiotic strains. However, results have been inconsistent, and questions remain regarding optimal strain selection, dosing, treatment duration, and patient populations most likely to benefit. This review aims to comprehensively evaluate the current evidence on probiotic effectiveness in managing hypercholesterolemia, examine proposed mechanisms of action, analyze clinical trial data, and identify future research priorities.

Mechanisms of Cholesterol Reduction by Probiotics

Several mechanisms have been proposed to explain the cholesterol-lowering effects of probiotics, though the relative contribution of each mechanism likely varies by strain and host factors.

Bile Salt Deconjugation

The mechanism, which has been best documented in the case of bile salt hydrolase (BSH) activity,. BSH enzymes, which are generated by some probiotic bacteria such as *lactobacilli* and *bifidobacteria*, induce the deconjugation of conjugated bile salts to release free bile acids. The conjugated form of bile salts is efficiently reabsorbed in the ileum, mostly by enterohepatic circulation. Unconjugated bile acids are less soluble and not well-absorbed, resulting in more fecal output. The liver must synthesize new bile acids from cholesterol in order to maintain a pool of bile acids and, thereby, reduce circulating cholesterol levels. Some studies have reported a direct relationship between BSH activity of probiotic strains and cholesterol-lowering performance while this has not been always found (Begley *et al.,* 2006).

Direct Cholesterol Assimilation

Some probiotic organisms are able to incorporate cholesterol from the environment in situ. This is associated with the inclusion of cholesterol into bacterial cell membranes, which serves to sequester host-available pool of cholesterol for growth. Cholesterol assimilation has also demonstrated in vitro for *Lactobacillus reuteri*, *Lactobacillus plantarum* and various *Bifidobacterium* species. But the quantitative importance of this mechanism in vivo is still controversial, because a small quantity of cholesterol which viable bacteria can bind might be available inside gut (Lye et al., 2010).

Cholesterol Coprecipitation

Some probiotic bacteria can also coprecipitate cholesterol with deconjugated bile salts by producing insoluble complexes that would not be absorbed but rather eliminated in the feces. This mechanism combines BSH activity and physical-chemical interactions that decrease cholesterol bioaccessibility (Tomaro-Duchesneau *et al.,* 2014).

Modulation of Lipid Metabolism Genes

Recent evidence has shown that probiotics are also able to modulate the expression of host genes associatedwith lipid metabolism. Some strains of probiotics have been demonstrated to regulate the expression of cholesterol-related genes such as HMG-CoA reductase (synthesis), NPC1L1 (absorption) and ABCG5/G8 (transport). Moreover, probiotics may potentially affect the production of SCFAs, presumably by fermenting dietary fibers. SCFAs, especially propionate, can decrease hepatic cholesterol synthesis. Modulation of gut bacterial population via probiotics may increase SCFA and thus indirectly lower cholesterol (Jones *et al.,* 2012).

Conversion of Cholesterol to Coprostanol

Some gut bacteria have enzymes that can change cholesterol to coprostanol, which is not well absorbed. Although there is evidence for this process in vitro and animal studies, its clinical relevance in humans is not clear. Cholesterol-lowering bacteria and coprostanol excretion rates differ widely from person to person (Gilliland *et. al.,* 1985).

Table 1: Mechanisms and Effectiveness of Probiotics in Cholesterol Management

Mechanism	Probiotic Genera	Effect on Cholesterol	Clinical Evidence Strength
Bile salt deconjugation (BSH activity)	*Lactobacillus*, *Bifidobacterium*	↓ LDL-C by 8-12%	Strong
Cholesterol assimilation into cells	*Lactobacillus*, *Bifidobacterium*	↓ TC by 5-10%	Moderate
Coprecipitation with bile salts	*Lactobacillus* species	↓ Cholesterol absorption	Moderate
Modulation of lipid metabolism genes	*Lactobacillus reuteri*, *L. plantarum*	↓ HMG-CoA reductase activity	Emerging
SCFA production	*Bifidobacterium*, *Lactobacillus*	↓ Hepatic cholesterol synthesis	Moderate
Conversion to coprostanol	Various gut bacteria	↓ Cholesterol bioavailability	Limited

Note. BSH = Bile Salt Hydrolase; LDL-C = Low-Density Lipoprotein Cholesterol

Clinical Evidence from Human Trials

Meta-Analyses and Systematic Reviews

Several meta-analyses have sought to aggregate the findings of randomized controlled trials (RCTs) addressing the effects of probiotics on lipids. A meta-analysis performed by Guo et al. (2011), which included 11 trials, reported a reduction in total cholesterol of −6.36 mg/dL and LDL-C of -8.91 mg/dL upon probiotic intake as compared with controls. But the degree of heterogeneity between studies was significant. Recent meta-analyses have identified similarly modest benefits. Mo et al. (2019) wrote that they analyzed 32 RCTs and reported probiotic supplementation reduced TC, LDL-C, and triglycerides but raised HDL-C. The impact on the outcome measure tends to be relatively small, with reductions in TC between 5-10 mg/dL. Crucially, effects were extremely heterogeneous according to the probiotic strain, dosage, duration of the treatment and baseline cholesterol concentrations. According to a review by Hadi and colleagues (2019) specifically investigated *Lactobacillus plantarum* interventions and they found TC and LDL-C were significantly reduced in several trials. They concluded the lack of consistent methods in dosing and treatment allowed no definitive conclusions to be drawn between the different frequencies or volumes.

Strain-Specific Effects
The cholesterol-lowering efficacy seems to be strain-specific, and some strains show more consistent effect according to clinical data.
Lactobacillus reuteri: Several trials have been published for *L. reuteri* NCIMB 30242, a strain chosen for its high BSH activity and capacity to reduce cholesterol. Jones *et al. (*2012) carried out a placebo-controlled, randomized, double-blind intervention trial in hypercholesterolemic adults and showed that the administration of this strain at 2×10^9 CFU twice a day for 6 weeks led to decreases in LDL-C by 11.6% and total cholesterol by 9.1 when compared to placebo. These results have been confirmed in further studies and *L. reuteri* NCIMB 30242 is now one of the more studied strains with regard to cholesterol.

Lactobacillus acidophilus: Multiple studies have evaluated combinations of *L. acidophilus* and various *Bifidobacterium* species. Results have been inconsistent, with some studies reporting significant reductions in cholesterol and others no such effect. The differences in strain selection, viable cells used and populations studied may explain those inconsistent results.

Lactobacillus plantarum: Cholesterol-lowering effects of *L. plantarum* have been reported in a number of clinical trials. A study by Fuentes et al. (2016) reported the cholesterol-lowering effect of *L. plantarum* CECT 7527, 7528, and 7529 combination in hypercholesterolemic individuals with a reduction in TC and LDL-C. These effects seem to be mediated through a combination of BSH activity and regulation of cholesterol metabolism genes.

Table 2: Summary of Meta-Analyses on Probiotic Effects on Lipid Profiles

Meta-Analysis	Studies Included	Total Participants	Main Findings	Effect Size
Guo et al. (2011)	11 RCTs	~485	Significant reduction in TC and LDL-C	TC: -6.36 mg/dL; LDL-C: -8.91 mg/dL
Mo et al. (2019)	32 RCTs	~1,992	Significant decrease in TC, LDL-C, TG; increased HDL-C	LDL-C: 5-10% reduction
Hadi et al. (2019)	15 RCTs	~788	*L. plantarum* effective for TC and LDL-C reduction	Modest but significant effects

Note. RCT = Randomized Controlled Trial; TC = Total Cholesterol; LDL-C = Low-Density Lipoprotein Cholesterol; TG = Triglycerides; HDL-C = High-Density Lipoprotein Cholesterol.

Factors Influencing Efficacy
Several factors influence the cholesterol-lowering efficacy of probiotics in clinical settings:
Baseline Cholesterol Levels: Individuals with higher baseline cholesterol concentrations generally exhibit greater absolute reductions following probiotic intervention. This suggests that probiotics may be most beneficial as adjunctive therapy in hypercholesterolemic populations rather than for primary prevention in normocholesterolemic individuals.

Dose and Viability: The relationship between probiotic dose and cholesterol-lowering effect remains incompletely characterized. Most successful trials have employed doses ranging from 10^8 to 10^{10} CFU daily. Ensuring adequate viable cell counts throughout product shelf-life represents a critical quality control consideration.

Treatment Duration: Most clinical trials have assessed interventions lasting 4-12 weeks. While some cholesterol reduction may occur within weeks, optimal treatment duration for sustained benefit remains unclear. Few studies have examined long-term probiotic supplementation or effects after treatment discontinuation.

Dietary Context: Probiotic efficacy may be influenced by concurrent dietary patterns. Some evidence suggests that probiotics may be more effective when combined with dietary modifications such as reduced saturated fat intake or increased fiber consumption. The interaction between dietary substrates, probiotic metabolism, and host physiology warrants further investigation.

Gut Microbiota Composition: Baseline gut microbial composition likely influences probiotic colonization, persistence, and metabolic activity. Personalized approaches considering individual microbiome profiles may enhance therapeutic outcomes, though this concept requires validation through appropriately designed studies.

Safety and Tolerability

Probiotics have generally good safety in the healthy individuals. Adverse effects are usually minimal in most trials, with gastrointestinal symptoms, such as slight bloating and flatulence, being the most frequently reported. These effects usually subside during the first week of supplementation. However, certain populations warrant caution. Immunosuppressed patients, those with central venous catheters, and critically ill subjects may encounter higher rates of probiotic-related infections, but they are also very rare. People with short bowel syndrome or impaired gut barrier function, likewise, should use probiotics under the supervision of a physician. Regulation of probiotics varies by country. In most countries, probiotics are sold as dietary supplements or functional foods rather than pharmaceuticals and accordingly have less rigorous manufacturing standards and quality control measures. This may introduce error in labelled versus actual viable cell numbers and contamination. It is recommended that consumers and health care professionals use products from trusted manufacturers with independent quality testing.

Clinical Implications and Recommendations

From the available evidence, dietary supplementation with probiotics may be a promising adjuvant therapy for people at risk of, or having diagnosed with hypercholesterolemia and who prefer to use natural alternatives or supplements to chemical pharmacological agents. There are some caveats that must be observed, however. To begin, the cholesterol lowering potency of probiotics is generally modest, with reductions in LDL-C typically not exceeding 5−10%, much lower than that observed with statins (30-50%). Consequently, since probiotic supplementation should not be a substitute for conventional pharmacotherapy in high-risk patients who need aggressive lowering of their cholesterol profiles. Second, the specific probiotic strain matters; clinicians should recommend strains that have proven clinical efficacy and not just a generic probiotic product. Thirdly, the use of probiotics should be a part of an overall lifestyle-modification package as an add-on and not some sort of replacement to healthy dietary habits, regular exercise and weight reduction. This is the fourth point: there must be an individualized approach that considers patient-specific characteristics (baseline cholesterol levels, other treatments in use, diet, lifestyle and food preferences). Ultimately, patients should be steered toward high-standard probiotic products made by bona fide companies that offer transparency regarding strain identity, viable counts and quality control to guarantee product safety and effectiveness.

CONCLUSION

Hypercholesterolemia is a key public health problem that need multidimensional strategies for control. At present there is some evidence to suggest that particular strains of probiotics, especially *Lactobacillus* and *Bifidobacterium* species, may modestly lower cholesterol via various mechanisms such as bile salt deconjugation, assimilation of cholesterol and modulation of lipid metabolism. Results from clinical trials and meta-analyses have shown that, statistically at least, the reductions in LDL-C are small to modest, typically ranging from 5-10%. However, there is significant diversity in study methodologies and strain choice, and outcomes, preventing definitive conclusions. Probiotics are adjunct but not alternative to interventions that are already established in high-risk groups. Although there is evidence for strain-specific products, these may be of benefit in patients with raised cholesterol levels who are looking at alternative/complementary medicines or who are intolerant of conventional drugs.

Further studies using a robust methodology, mechanistic outcomes, long-term follow up and individualized therapy will define the potential role of probiotics in strategies aimed at cardiovascular risk reduction. With our improved knowledge of the interactions between gut microbiota and host, selective microbial interventions could potentially enhance traditional paradigms for prevention and treatment of CVD.

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