Food Science of Animal Products

Review Article

Probiotics and cholesterol metabolism: new frontiers in science from intestinal microecology to cardiovascular health

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Abstract: Cholesterol is essential for cell membrane structure and steroid hormone synthesis, but elevated serum low-density lipoprotein cholesterol can lead to atherosclerosis. Although traditional drugs such as statins are effective, they carry a risk of hepatotoxicity and muscle injury. Gut microbiota regulates cholesterol metabolism through the gut-liver axis, providing a new direction for the intervention of hypercholesterolemia. Probiotics reduce serum cholesterol through bile saline hydrolase activity, secondary bile acid conversion, and cwholesterol adsorption. This article reviews the mechanism and clinical transformation prospects of probiotics in reducing serum cholesterol.

Keywords: probiotics; cholesterol metabolism; intestinal microecology; next generation probiotics; clinical transformation

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1 Introduction

In recent years, the attention of the scientific community has gradually focused on an "organ" that has been ignored for a long time-intestinal microecology[1]. This complex ecosystem, composed of trillions of microorganisms, is not only involved in food digestion and nutrient absorption[2], but also serves as the "regulatory center" of human metabolism, conducting a continuous and profound dialogue with the host through its large genome[3] (microbiome) and diverse metabolites[4]. Numerous studies have revealed that dysbiosis is closely related to the pathophysiologic processes of various metabolic diseases such as obesity[5], type 2 diabetes[6], non-alcoholic fatty liver disease, and even cardiovascular disease[7]. Among them, the key role of gut microbiota in the host lipid metabolism, especially the regulation of cholesterol homeostasis[8], provides us with a new perspective to understand and intervene in hypercholesterolemia.

Probiotics, defined as "live microorganisms that, when ingested in sufficient quantities, can have a beneficial effect on the health of the host"[9], are one of the most direct and commonly used means of regulating the microecology of the intestinal tract. They are mainly derived from fermented foods or as dietary supplements and are widely accepted for their favorable safety profile[10]. Based on the role of gut microbiota in cholesterol metabolism, a fascinating scientific question arises: can we effectively interfere with cholesterol metabolism in humans by supplementation with specific probiotics as an adjunct to cardiovascular health? What is the strength of the scientific evidence behind this strategy? What is its specific biological mechanism of action?

This review aims to systematically review the frontier field of "probiotics and cholesterol metabolism". In this review, we will focus on the core molecular mechanisms of probiotics affecting cholesterol metabolism, and further analyze the direct and indirect regulatory pathways. Subsequently, evidence at all levels from animal models to human clinical trials was systematically reviewed to objectively evaluate the cholesterol-lowering efficacy of probiotics. Then we will discuss the efficacy variability of different strains of probiotics, and introduce the research progress of the "next-generation probiotics (NGP)" that have attracted much attention. Finally, we summarized the challenges of current application, and prospected future research directions and clinical transformation prospects, in order to provide a comprehensive and in-depth reference for researchers and clinicians in this field.

2 Core mechanisms of probiotic regulation of cholesterol metabolism: synergistic effects of multiple pathways and targets

The regulation of host cholesterol metabolism by probiotics is a complex and multi-dimensional process, which is not dominated by a single mechanism, but the result of synergistic action of multiple mechanisms in different parts of the body, such as intestine and liver. These mechanisms can be broadly categorized into three groups: direct physical effects on cholesterol in the intestinal lumen, indirect chemical modulation of host physiology through metabolites, and deeper effects on host gene expression and signaling pathways through the "gut-liver axis". Understanding these mechanisms is fundamental to assessing the potential of probiotics, screening for efficient strains and guiding clinical applications.

2.1 Directly acts on cholesterol in the intestine

Probiotics first meet dietary and biliary cholesterol directly in the "battlefield" of the intestines, physically reducing its absorption by the host.

2.1.1 Cholesterol assimilation and binding

Some probiotics, especially certain strains of *Lactobacillus* and *Bifidobacterium*, can actively absorb cholesterol molecules in the intestinal environment and incorporate them into their cell membranes or cell walls during their growth and reproduction[11]. The embedding of cholesterol can change the fluidity and permeability of the bacterial cell membrane, and enhance its resistance to bile salts, acidic environment and other stress factors. This process is equivalent to "locking" cholesterol in the body of the bacteria so that it cannot be absorbed by the epithelial cells of the small intestine and eventually excreted in the feces. Studies have shown that this assimilation ability is closely related to the growth state of the strain, with actively growing strains typically exhibiting greater cholesterol removal[12–13]. The efficiency of cholesterol assimilation showed significant strain specificity[14]. For example, *in vitro* studies have revealed significant differences in cholesterol removal rates among different *Lactiplantibacillus plantarum* strains[15]. In addition, such mechanisms were also found in probiotic animal products. The high number of lactic acid bacteria in Kefir and the increase of cholesterol binding capacity by 33.9% helped to reduce cholesterol in the gut. The researchers observed that fermentation of milk with Kefir culture at 24 °C for 24 h resulted in the assimilation of 28%–65% of cholesterol[16]. The weight of the contribution of this mechanism may be relatively limited in the overall lipid-lowering effect, but it constitutes the first line of defense for cholesterol-lowering by probiotics.

2.1.2 Co-precipitation with cholesterol

In the acidic environment of the upper small intestine, some probiotics have positively charged cell surfaces, whereas cholesterol and unbound bile acid molecules are negatively charged. By electrostatic attraction, probiotics can bind to these lipid molecules and form insoluble complexes or coprecipitates[17]. These large precipitates are difficult to absorb by the intestines, thus increasing fecal excretion of lipids. This process is considered to be a central part of "bile salt coprecipitation" and is one of the key physical mechanisms by which probiotics exert their effects. There may be a synergistic relationship between coprecipitation and cholesterol assimilation[18]. The conjugated bile acids are first hydrolyzed by probiotics through bile saline lyase (described in detail below), producing free bile acids and cholesterol are more likely to co-precipitate with the bacteria in an acidic environment, thereby amplifying the lipid-lowering effect.

2.2 Indirect regulation through metabolites

Probiotics are not only a physical barrier, but also an active biochemical factory. A variety of metabolites produced by probiotics can have far-reaching indirect effects on host cholesterol metabolism.

2.2.1 The role of bile saline hydrolase (BSH)

This is currently recognized as the most central and well-studied mechanism of cholesterol lowering by probiotics. Bile acids are synthesized by the liver using cholesterol and combined with glycine or taurine to form bound bile acids, which are stored in the gallbladder. After eating, conjugated bile acids are excreted in the bile into the small intestine to help emulsify and absorb dietary fat. Most conjugated bile acids are efficiently reabsorbed in the terminal ileum and returned to the liver through the portal vein, forming the so-called "enterohepatic circulation"[19]. BSH, a key enzyme, is produced and secreted by many probiotic strains[20]. The sole function of BSH is to sever the amide bond in conjugated bile acids, causing them to break down into free bile acids and amino acids[21]. Compared to conjugated bile acids, free bile acids have lower solubility, higher pK_a values, and are more easily protonated at physiological intestinal pH, resulting in much less efficient intestinal reabsorption[22].

Large amounts of free bile acids are excreted with the feces, disrupting the balance of the enterohepatic circulation. The liver senses the depletion of the bile acid pool and activates compensatory mechanisms. This process is mainly achieved by activating the farnesoid X receptor (FXR) signaling pathway in the liver nucleus[23]. The decrease in bile acid levels lifts the negative feedback inhibition of cholesterol-7α-hydroxylase (CYP7A1), the rate-limiting enzyme of the bile acid synthesis pathway, and the up-regulation of its activity accelerates the conversion of stored cholesterol into new bile acids by hepatocytes[23]. To replenish the cholesterol consumed, hepatocytes further up-regulate the expression of low-density lipoprotein receptor (LDLR) on their surface to capture more low-density lipoprotein cholesterol (LDL-C) from the blood (Figure 1). The net result of this chain reaction is a reduction in serum total cholesterol (TC) and LDL-C levels[24].

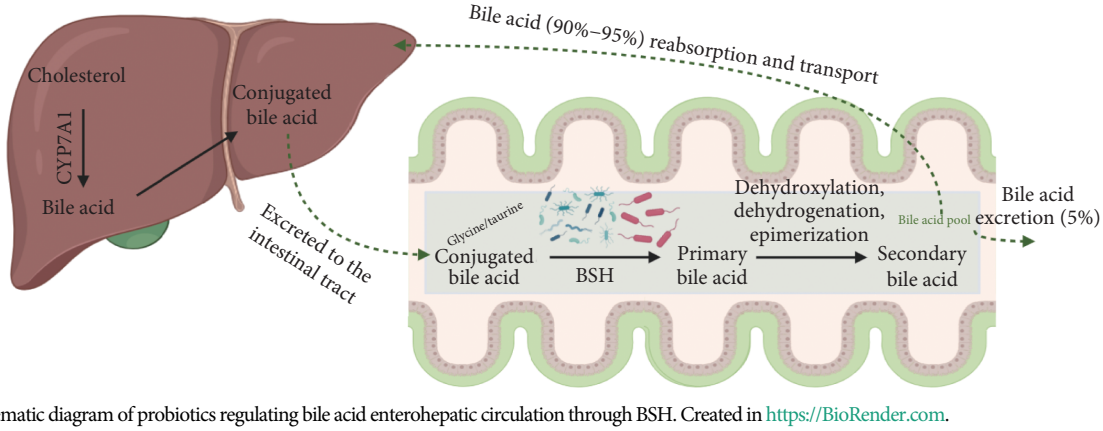

Figure 1 Schematic diagram of probiotics regulating bile acid enterohepatic circulation through BSH. Created in https://BioRender.com.

2.2.2 Production and effects of short-chain fatty acids (SCFAs)

Probiotics and other intestinal commensals are able to ferment dietary fibers that are indigestible to the host (e.g., inulin, oligofructose, etc.) to produce a range of SCFAs, including primarily acetic, propionic, and butyric acids[25]. In an animal study, supplementation of SCFAs (including acetate, propionate, butyrate, and valeric acid) reduced TC and non-high density lipoprotein cholesterol (HDL-C) levels in hamsters fed a high cholesterol diet, indicating the important role of SCFAs in the regulation of cholesterol metabolism[26].

SCFAs can reduce cholesterol levels in the host through five major pathways. One is to inhibit cholesterol synthesis by down-regulating the gene related to cholesterol synthesis by acetyl coenzyme A (CoA). After absorption into the portal circulation, propionic can act directly on hepatocytes and partially inhibit the activity of hydroxymethylglutaryl (HMG)-CoA reductase, thereby reducing endogenous cholesterol synthesis in the liver[27]. Although its inhibitory effect is much weaker than that of statins, as an endogenous regulatory substance, its long-term, mild effect cannot be ignored. The second is to enhance the conversion of cholesterol to bile acids by enhancing CYP7A1, the only rate-limiting enzyme in the liver that converts cholesterol to bile acids, thereby lowering cholesterol. It has been shown that oral administration of butyrate to mice on a high-fat diet can increase the expression of CYP7A1, which in turn alleviates atherosclerosis[28]. In addition, SCFAs can inhibit cholesterol absorption by regulating the expression of intestinal transporters or accelerate cholesterol elimination by regulating the ATP-binding cassette transporter A1, which in turn reduces cholesterol. A study have shown that butyrate intake can inhibit the expression of Niemann-pick C1-like 1 in the intestinal tissue of mice, increase the expression of transporter ABCG5/8, thereby inhibiting the absorption of cholesterol and increasing the excretion of cholesterol, and reducing the occurrence of atherosclerosis[29]. Butyrate serves primarily as the preferred energy substance for colonic epithelial cells and is essential for maintaining the integrity of the intestinal barrier. A healthy intestinal barrier prevents endotoxins such as lipopolysaccharide (LPS) from entering the bloodstream, which is a key factor in the development of chronic low-grade inflammation[30], which is closely related to insulin resistance and lipid metabolism disorders. Thus, butyric acid indirectly improves the metabolic environment of the whole body by "fixing the intestine"[31]. Finally, SCFAs act as signaling molecules to activate G protein-coupled receptors (e.g., GPR41, GPR43, GPR109A) on the surface of intestinal endocrine cells and immune cells, regulate the secretion of intestinal hormones such as glucagon-like peptide-1, which in turn systematically affects energy homeostasis, appetite, and lipid metabolism in the host[32].

2.2.3 Other metabolites

Exopolysaccharides (EPS): some lactic acid bacteria produce exopolysaccharides, which are high molecular weight carbohydrate polymers, during fermentation[33]. EPS has a high viscosity and can form a gel-like matrix in the intestine, physically encapsulating cholesterol, fat, and bile acids, preventing cholesterol, fat, and bile acids from coming into contact with the intestinal wall and preventing their absorption, and ultimately facilitating their elimination in the feces[34].

Conjugated linoleic acid (CLA): certain probiotic strains, such as some *L. plantarum* and *Lactococcus lactis*, are able to convert linoleic acid to CLA, which has a variety of biological activities[35–36]. Some animal studies have shown that CLA may be involved in the regulation of lipid metabolism by activating peroxisome proliferator-activated receptors and other nuclear receptors[37]. However, its cholesterol-lowering effect in humans and the specific mechanism still need to be confirmed by more studies.

2.3 Regulation of host gene expression and signaling pathways

Through the complex "gut-liver axis" dialogue, probiotics and their metabolites can penetrate into the molecular level to regulate gene expression and signaling pathways related to cholesterol metabolism in key host organs, mainly the liver and gut.

2.3.1 Genes related to liver cholesterol metabolism

Probiotic intervention can alter the intestinal environment and influence the profile of metabolites entering the portal vein, and these signaling molecules, upon arrival in the liver, can regulate the transcription of a range of key genes[38]. For example, a study in hypercholesterolemic rats found that not only the mRNA expression of *CYP7A1* (bile acid synthesis) and *LDLR* (LDL-C clearance) was up-regulated in rat liver after gavage of *Enterococcus faecium* 132 and *Lactobacillus paracasei* 201, but also sterol regulatory element binding protein-1c (*SREBP-1c*), which regulates LDL-C clearance. The mRNA expression of *CYP7A1* and *LDLR* was not only up-regulated, but also the expression of genes related to fatty acid and triglyceride (TG) synthesis, such as *SREBP-1c* and stearoyl coenzyme A desaturase-1, were down-regulated in the liver[39]. This suggests that the regulatory effect of probiotics is multi-targeted, both promoting both cholesterol catabolism and removal and inhibiting lipid synthesis.

2.3.2 Intestinal barrier and inflammatory pathways

As mentioned earlier, a healthy gut barrier is key to preventing systemic inflammation[40]. Probiotics can increase the expression of tight junction proteins (such as occludin, claudin-1, zonula occludens-1 (ZO-1)) between intestinal epithelial cells by producing SCFAs such as butyric acid, thereby strengthening the intestinal barrier and reducing its permeability[41–42]. This directly reduces the risk of LPS leakage from the gut lumen into the blood (i.e., metabolic endotoxemia). LPS is a major component of the cell wall of Gram-negative bacteria and is a potent ligand for the activation of Toll-like receptor 4 (TLR4). After LPS enters the blood, it activates macrophages in adipose tissue, liver and vessel wall, etc., and releases large amounts of pro-inflammatory cytokines (e.g., tumor necrosis factor α and interleukin-6) through classical inflammatory signaling pathways such as TLR4/nuclear factor κB (NF-κB)[43]. This chronic low-grade inflammatory state is an important contributor to insulin resistance and atherosclerosis[44]. By strengthening the intestinal barrier, probiotics reduce the inflow of LPS into the blood from the source, thereby inhibiting the downstream inflammatory cascade and creating a favorable internal environment for improving lipid metabolism[45] (Table 1).

Table 1 Summary of the main mechanisms by which probiotics regulate cholesterol metabolism.

Mechanism category	Specific mechanisms	Key molecules/ processes	Targets of action	Final result	References
Direct action	Cholesterol assimilation	Cell membrane/wall of probiotics	Intestinal lumen cholesterol	Reduced absorption of cholesterol, excreted with the bacteria	[12–16]
	Coprecipitation	Cell surface charge	Cholesterol and free bile acids in the intestinal lumen	Insoluble complexes are formed and excreted in the stool	[17–18]
Indirect regulation (through metabolites)	BSH	BSH	Conjugated bile acids	Interrupts the enterohepatic circulation and promotes the liver's consumption of cholesterol to synthesize new bile acids	[22–24]
	SCFAs	Propionic acid, butyric acid, etc.	Liver HMG-CoA and intestinal barrier	Inhibits cholesterol synthesis and improves systemic inflammation	[26–32]
	EPS	EPS gel matrix	Cholesterol and free bile acids in the intestinal lumen	Physical encapsulation to impede absorption	[34]
Gene and signaling pathway regulation	Regulation of liver genes	LDLR, CYP7A1, SREBP-1C, etc.	Liver cells	Increases cholesterol removal and reduces fat formation	[38–39]
	Strengthening the intestinal barrier	Occludin, claudin-1, ZO-1	Intestinal epithelial cells	Reduction of LPS entry and inhibition of the TLR4/NF-κB inflammatory pathway	[43–45]

3 Evidence system for cholesterol lowering by probiotics: from animal models to clinical studies

The scientific evaluation of the cholesterol-lowering effects of probiotics follows a rigorous chain of evidence from *in vitro* experiments, animal models to human clinical trials. Each level of evidence provides a unique perspective on understanding its potential and limitations. This section will systematically review and assess the strength and consistency of existing scientific evidence, presenting a comprehensive picture of research in this field.

3.1 Advances in animal modeling

Animal models provide an indispensable platform for exploring the *in vivo* effects and potential mechanisms of lipid-lowering effects of probiotics. By constructing hyperlipidemia models, researchers can systematically evaluate the intervention effects of specific strains under controlled conditions. The contribution and value of animal models is that they can explain the mechanism of cholesterol-lowering effect of probiotics through special animal models such as conventional animal models, sterile animal models, gene knockout animal models, so as to ensure the safety of probiotics in human experiments. High-fat diet-induced rodents, such as rats, mice, and golden hamsters, are the most commonly used models[46]. These animals rapidly develop elevated blood lipids, hepatic steatosis, and other pathological features similar to human hyperlipidemia after ingestion of a high-fat, high-cholesterol diet. Numerous animal experiments have consistently shown that supplementation with specific probiotic strains is effective in combating the negative effects of high-fat diets[47–49]. Commonly observed phenomena include significant reductions in serum levels of TC, "bad cholesterol" (LDL-C), and TG, with elevated or stable levels of "good cholesterol" (HDL-C) also observed in some studies. In terms of mechanism exploration, it was often found that the excretion of cholesterol and total bile acids in the feces of the animals in the probiotic intervention group was significantly increased, while the histological examination of the liver showed a significant improvement in fat accumulation (hepatic steatosis), which was highly consistent with the aforementioned mechanisms of BSH and inhibition of hepatic fat synthesis[50–51].

A study published in 2025 delved into the role of *Weissella confusa* MW051433 in a mouse model of high-fat diet-induced hypercholesterolemia. It was found that administration of this strain (from day 15 to 60) on the basis of high-fat diet (for 60 days) not only significantly improved the lipid profile of the mice (decreased TC, LDL-C, TG), but also greatly promoted the fecal cholesterol and bile acid excretion (increased by 70.48% and 123.21%, respectively). The reduction in the number of lipid droplets in hepatocytes was also confirmed by pathological examination of the liver. These results strongly suggest that this strain exerts its lipid-lowering effects primarily by promoting the biliary cholesterol excretion mechanism[52]. Another study showed that the Lab4 probiotic consortium plus *L. plantarum* CUL66 was shown to reduce serum cholesterol by modulating the expression of genes related to bile acid metabolism such as short heterodimer partner and *CYP7A1* in the liver of mice and increasing the levels of total and unconjugated bile acids in the feces[53].

Although animal models have provided valuable mechanistic insights, extrapolation to humans should be cautious. First, the gut microbiota and immune systems of experimental animals, especially those without specific pathogens, are markedly different from those of humans and the effects on cholesterol metabolism rate, microbiota composition, and receptor expression differed between mice and humans. Second, the dose of probiotics used in animal experiments, when converted to body weight, is usually much higher than the usual dose in human clinical trials. At the same time, human diseases are complex, and the pathological model of animal experiments also has a great limitation. On the other hand, individual differences and safety of long-term use are also important key factors in human experiments. Finally, animal models cannot fully simulate the complex dietary structure, lifestyle, and genetic background of humans. Therefore, positive results from animal experiments are an important prerequisite for initiating human trials, but cannot be directly equated with efficacy in humans[54].

3.2 Evidence from human clinical trials

Human clinical trials, especially randomized controlled trials (RCTs) and their meta-analysis, are the "gold standard" for assessing the cholesterol-lowering efficacy of probiotics. Over the past decade, the number and quality of clinical studies in this area have increased significantly.

3.2.1 Meta-analysis

Meta-analysis integrates the results of multiple independent RCTs through statistical methods, which can provide more reliable and generalizable conclusions. Multiple meta-analyses published in the last five years agree that, overall, probiotic supplementation has a statistically significant but moderate effect size (modest) effect on lowering TC and LDL-C levels. For example, a meta-analysis of 9 RCTs (involving 344 patients with metabolic syndrome) published in 2021 showed that prebiotics/synbiotics (a combination of probiotics and prebiotics) reduced TC levels by a mean of 6.66 mg/dL compared with placebo[55]. Another meta-analysis of patients with hypercholesterolemia (including 13 RCTs) also found that probiotics could significantly reduce TC and LDL-C, and noted that the lipid-lowering effect was more pronounced in subgroups using multi-strain combinations, intervention duration longer than 6 weeks, and use of higher doses ($\geq 10^{10}$ CFU/day)[56]. However, the analyses generally noted significant heterogeneity among the studies, with wide variations in results that were attributed to differences in strain species, dose, duration of the intervention, baseline cholesterol levels, and population characteristics.

3.2.2 RCT studies in specific populations

Patients with hypercholesterolemia are the most important target population for lipid-lowering studies of probiotics. Studies have shown that the lipid-lowering effects of probiotics are generally more pronounced in such populations than in healthy individuals. For example, one RCT found that patients with hypercholesterolemia experienced a meaningful decrease in LDL-C levels after taking a probiotic product containing *L. plantarum*[57].

Patients with metabolic syndrome, obesity and type 2 diabetes are often associated with dyslipidemia. Studies of them not only focus on lipid changes, but also often assess a range of metabolic markers such as body weight, waist circumference, blood glucose, insulin resistance and inflammatory markers. A report published in 2025 showed that Lab4 probiotic consortium (including *L. plantarum* CUL66, etc.) reduced body weight by 1.9% in overweight people in a 6-month RCT, and the weight loss reached 2.5% in people with high cholesterol[57]. This suggests that probiotics may confer indirect lipid-lowering benefits by improving overall metabolic health. Not only that, probiotic dairy products have also been evaluated in clinical trials. In an experiment involving prediabetic participants who consumed either nonfat or full-fat yogurt for three weeks, a significant increase in HDL-C was found after a full-fat yogurt diet, indicating that short-term consumption of yogurt dairy products has a beneficial effect on lipid profiles in prediabetic individuals[58]. In another study comparing the effects of fermented milk and non-fermented milk on fatty liver in men with abdominal obesity, significant changes in TC, LDL-C, HDL-C, and alanine transaminase (ALT) were found after 16 weeks of intervention, confirming the advantages of fermented yogurt products in reducing liver fat or improving metabolic risk[59].

Studies in healthy people have shown mixed results. Some studies did not observe significant lipid changes, which may be due to the fact that lipid levels in healthy individuals are inherently in a steady state with limited room for regulation. However, some studies suggest that long-term probiotic supplementation may help maintain cholesterol homeostasis and prevent lipid elevation. For example, a 2025 study published in *Gut Microbes* found that probiotic supplementation resulted in beneficial metabolic changes even in healthy individuals[60]. In addition, in a study of healthy men, products containing probiotic cheese were found to increase fecal fat excretion and improve health status[61] (Table 2).

Table 2 Summary of RCTs of probiotics and its products in lowering cholesterol in recent years.

Strains/products	Crowd characteristics	Dose (CFU/day)	Duration of intervention	Changes in main blood lipid indicators (compared with the placebo group)	References
Multi-probiotics	Patients with hypercholesterolemia	$> 10^{10}$	> 6 weeks	TC/LDL-C significantly reduced	[56]
Prebiotics/synbiotics	Patients with metabolic syndrome			TC decreased to 6.66 mg/dL	[55]
Lab4 probiotic consortium	Overweight/high cholesterol people		6 months	Weight loss (by 2.5% in those with high cholesterol) indirectly reflects improved lipid metabolism	[57]
Lacticaseibacillus rhamnosus GG (LGG)	Obese/type 2 diabetic patients	About 10^9	12 weeks	Improve lipid metabolism and reduce body weight	[62]
Full-fat yogurt	Participants with prediabetes		3 weeks of each experimental diet	Increased HDL-C concentrations and high-density lipoprotein size	[58]
Fermented yogurt products	Males with abdominal obesity		16 weeks	Decrease homeostatic model assessment for insulin resistance, TC, LDL-C, ALT and increase HDL-C	[59]
Probiotic yogurt	Patients with type 2 diabetes mellitus		12 weeks	Decrease TC, TG, LDL-C and increase HDL-C	[63]
High-calcium Cheddar cheese	Healthy males		2 weeks	Varying the calcium content within a cheese matrix significantly affected fasting LDL-C values	[61]
Goat cheese	Overweight and obese subjects		16 weeks	Increased plasma HDL-C, as well as in apolipoprotein B	[64]

4 Strain specificity and the rise of "NGP"

"Probiotics" is not a general concept, and its health effects are highly specific, strictly following the core principle of "strain determines efficacy". This means that the cholesterol-lowering effect of one type of *Lactobacillus* cannot be automatically extrapolated to another, and even different strains of the same strain may have different effects. Therefore, in-depth exploration of the differences of strains and active exploration of new strains with stronger efficacy are the key to the development of probiotics.

4.1 Strain variability of traditional probiotics

Traditional probiotics mainly refer to strains, represented by *Lactobacillus* and *Bifidobacterium*, which have been isolated from fermented foods (such as yogurt and pickles) and healthy humans for a long time and have a good history of safe consumption[65–67].

4.1.1 *Lactobacillus/Lactiplantibacillus*

Numerous studies have demonstrated that various *L. plantarum* strains (such as H6 and CUL66) exhibit significant cholesterol-lowering capabilities[48,53]. The underlying mechanism is multifaceted, involving not only efficient cholesterol assimilation and BSH activity but also the regulation of intestinal microbiota composition and the production of SCFAs. For instance, it has been suggested that *L. plantarum* may influence cholesterol metabolism through the modulation of intestinal *FXR* mRNA expression[68]. *L. rhamnosus* is known for its potent intestinal colonization and immunomodulatory effects. LGG is one of the most widely studied strains and has shown the potential to improve lipid metabolism and metabolic syndrome in several animal and human studies[69–70]. Some strains of *Lacticaseibacillus paracasei*, such as TISTR 2593, have been shown to help improve hypercholesterolemia in clinical trials, and the mechanism may be related to the regulation of liver cholesterol transport related genes[71].

4.1.2 *Bifidobacterium*

As the dominant genus in the gut of infants and young children, *Bifidobacterium* plays a significant role in maintaining intestinal health and regulating immunity[72–73]. Studies have shown that *Bifidobacterium longum* can indirectly improve diet-induced obesity and lipid metabolism disorders by improving intestinal barrier function, regulating bile acid signaling and reducing endotoxemia[74]. *Bifidobacterium animalis* subsp. *lactis* BB-12 is one of the most well-studied commercially available strains. It has been shown to regulate the structure of gut microbiota, combat obesity, and affect lipid metabolism by improving insulin sensitivity and reducing inflammation[75].

4.1.3 *Other strains*

Some strains of *Enterococcus* species, such as *E. faecium*, also show strong BSH activity and lipid-lowering effects[76]. However, due to the problems of opportunistic pathogens and antibiotic resistance in this genus, its safety as a probiotic needs to be more rigorously evaluated[77]. *Streptococcus thermophilus*, commonly used in yoghurt fermentation, was also found to have cholesterol-lowering activity[78].

4.2 Exploration of NGPs

With the development of high-throughput sequencing technologies such as metagenomics, scientists have been able to glimpse more of the uncultured "dark matter" in the intestinal microecology[79]. Studies have found that many key species closely related to health, especially metabolic health, are not probiotics in the traditional sense, are almost absent in conventional fermented foods, and are cultivated under harsh conditions. These intestinal commensal bacteria with great therapeutic potential are called NGPs or "live biotherapeutics"[80].

4.2.1 *Representative NGPs and their potential*

Akkermansia muciniphila: This is the brightest star of the NGPs. *A. muciniphila* are specialized anaerobes that feed on mucins in the mucus layer of the intestinal[81]. Numerous studies have shown that its abundance in the intestinal is negatively correlated with the risk of obesity, diabetes, and cardiovascular disease[82]. *A. muciniphila* dynamically maintain and strengthen the intestinal barrier by degrading mucin and stimulating intestinal goblet cells to produce new mucus. In addition, it produces SCFAs, such as propionic acid, and regulates systemic inflammation and glycolipid metabolism by interacting with the host immune system through its outer membrane proteins (such as Amuc_1100)[83]. Pasteurized (inactivated) *A. muciniphila* have even been found to have a stronger metabolic ameliorating effect than live bacteria, which facilitates their development as biologics[84].

Christensenella minuta: The abundance of this bacterium was found to be highly correlated with lower body mass index and visceral fat content, with a strong genetic predisposition[85]. Animal studies have shown that *C. minuta* supplementation can effectively inhibit high-fat diet-induced obesity and related metabolic disorders by mechanisms that may involve the modulation of intestinal flora, SCFAs production and lipid metabolism[86].

Parabacteroides spp.: a group of bacteria, including *Parabacteroides istasonis* and *Parabacteroides glyptosteinii*, that have been shown to reduce obesity, reverse insulin resistance, and improve fatty liver in animal models. The mechanism of action is thought to be related to their ability to produce succinic and secondary bile acids[87–89].

4.2.2 *Future perspectives*

NGPs represent a paradigm shift from "supplementation" to "restoration" of the intestinal microbiota, opening up an exciting path for the development of precision biological therapies for metabolic diseases such as hypercholesterolemia. However, the clinical translation of NGPs still faces many challenges: Firstly, as strict anaerobes, there are high technical barriers to their large-scale cultivation, production, and maintenance of activity; secondly, as a "new species" for the first time applied to the human body, their safety and long-term effects need to be verified through extremely strict preclinical and clinical studies; finally, the relevant regulatory approval pathways are still under exploration and establishment. Despite these challenges, NGPs are undoubtedly one of the most promising directions in the future research and application of intestinal microbiota.

5 Application challenges, future research directions, and conclusions

Although probiotics show bright prospects in regulating cholesterol metabolism, there is still a long way to go from laboratory studies to broad and precise clinical applications. It is very important to clearly understand the current challenges and limitations, and define the direction of future research to promote the healthy development of this field.

5.1 Challenges and limitations of current applications

5.1.1 Individualization differences

Individualized differences are the biggest challenge in probiotic application[90]. The effect of probiotics intervention was significantly different among individuals, showing "responders" and "non-responders". This difference is rooted in the complex intrinsic factors of the host, including the composition of the baseline gut microbiota (one side nurtures the other), the genetic background of the host (such as gene polymorphisms affecting cholesterol metabolism), dietary habits (especially dietary fiber intake), age, sex, and health status. For example, *Lactobacillus reuteri*, highly effective in animal models, reduced LDL by only 5%–9% in human trials with probiotic combinations, and some people did not respond[91]. An intestinal environment lacking a specific probiotic "food", a prebiotic, may not support effective colonization and functioning of supplemental strains. In addition, the functions of different strains are also significantly different, and it is necessary to accurately screen strains with clear functions in future studies[92–93].

5.1.2 Standardization issues

At present, there are a wide range of probiotic products in the market, but the industry standards are not yet uniform. The identification of strains, the calculation method of dose (colony forming unit (CFU)), the selection of dosage form (capsule, powder, and fermented milk), and the setting of the intervention program (duration and frequency) vary among different studies and products, which brings difficulties in the cross-section comparison of the results and clinical recommendations.

5.1.3 Viability and colonization

Probiotics are a "delicate" group of living microorganisms. From the factory, to shelf storage, to consumer intake, they need to go through the test of temperature and humidity. After entering the human body, it is necessary to pass through the two "dead-end gates" of stomach acid and bile acid. Ultimately, how many live bacteria can successfully reach the colon and colonize is a prerequisite for its effectiveness. How to improve the viability and colonization efficiency of strains is the core technical problem in product development.

5.1.4 Mechanistic complexity and causality

Cholesterol-lowering effects are the result of synergistic multiple mechanisms, and it is difficult for current studies to clarify which mechanism is dominant in a given individual. Probiotics regulate cholesterol through multiple pathways such as SCFAs, bile acid metabolism, and "gut-liver axis" signals (such as liver X receptor α/FXR), but the synergistic/antagonistic relationship between these pathways is not clear. In addition, further longitudinal studies are needed to confirm the causal relationship between the observed changes in gut microbiota and improvements in lipids. Are probiotics directly responsible for the lowering of blood lipids, or is it indirectly contributing to this effect by improving the overall gut environment? This question remains to be answered further.

5.1.5 Barriers to clinical translation

First of all, it is difficult to standardize the dose and course of treatment. The dose of probiotics in the intervention of cholesterol ranges from 4 weeks to 6 months, and it is difficult to determine the best plan. Secondly, the effects of long-term use of probiotics on cholesterol homeostasis and the risk of gene transfer have not been fully evaluated.

5.2 Future research prospects

In response to the above challenges, future research should be developed in a more precise, deeper and more collaborative direction.

5.2.1 Precision intervention

This is the ultimate goal to overcome individual differences. Future studies should make more use of multi-omics techniques (metagenomics, metatranscriptomics, metabolomics, and proteomics) to straticategorize the gut microbiota characteristics and metabolic phenotypes of subjects before intervention. By analyzing the common characteristics of "responders", it is expected to develop biomarkers that can predict efficacy, thereby enabling personalized probiotic/synbiotics regimen recommendation from "one size fits all" to "tailor-made".

5.2.2 Mechanisms for deeper excavation

A deep dive into the mechanics. Based on the existing mechanisms, more advanced molecular biology tools (such as gene editing, isotope labeling, and single-cell sequencing) are needed to further elucidate the specific signaling pathways of probiotic-host interaction. For example, what specific small molecule substances produced by probiotics are able to cross the intestinal barrier, enter the circulation, and bind to what receptors in liver cells to regulate LDLR expression? Answering these questions will provide us with more precise drug targets.

5.2.3 Synergistic strategies

Future research should not be limited to a single intervention of probiotics. Exploring the "probiotics plus" model has great application potential. For example, studying the synergistic effects of specific probiotics with specific prebiotics (synbiotics), such as fructooligosaccharides, galacto-oligosaccharides, could provide a "precision diet" of probiotics to maximize their efficacy[94]. Investigating combinations of probiotics with natural plant components, such as dietary polyphenols and red yeast rice, may produce additive or synergistic effects through different mechanisms[95–96]. More promising is to study the combination of probiotics with traditional lipid-lowering drugs, such as statins, to explore whether probiotics can enhance the efficacy of statins, or reduce their side effects, such as muscle damage, so as to achieve a "1 + 1 > 2" therapeutic effect[97]. For example, studies have shown that the combination of probiotics and lovastatin can improve the hepatic inflammatory response caused by the side effects of lovastatin without affecting the efficacy of the drug[98].

5.2.4 Clinical translation of NGPs

Large-scale, high-quality, multicenter randomized controlled clinical studies of next generation probiotics such as *A. muciniphila* must be strengthened to rigorously evaluate their efficacy and safety in different populations. At the same time, it is necessary to overcome the bottlenecks of industrialization such as anaerobic cultivation, preparation stability and cost control, and work closely with regulatory agencies to explore the establishment of approval pathways suitable for living biological drugs, and ultimately promote their growth from a "rising stars" in the laboratory to a "new drug" on the clinical shelf (Table 3).

Table 3 Future directions and key scientific issues of cholesterol lowering by probiotics.

Future directions	Key scientific questions	Research strategies and techniques
Precision intervention	How can individual responses to specific probiotics be predicted?	Multi-omics analysis (metagenomics, metatranscriptomics, metabolomics, and proteomics), machine learning model, and N-of-1 trial
Mechanisms for deeper excavation	What are the specific molecules of the probiotic-gut-liver axis dialog?	Gene editing, isotope labeling, and single-cell sequencing
Synergistic strategies	How do probiotics synergetic with diet and drugs?	Symbiotic design, co-administration RCT and network pharmacology analysis
Clinical translation of NGPs	How safe and effective are NGPs in humans?	Large-scale RCT, anaerobic culture and preparation technology development, and regulatory scientific research

5.3 Summary and conclusions

The prevention and treatment of hypercholesterolemia, a "silent killer" of cardiovascular health, are changing from one-drug interventions to more all-encompassing and individualized management regimens. In this regard, the intervention of intestinal microecology represented by probiotics opens up a promising new path for us. This article systematically reviews the scientific basis for the synergistic regulation of host cholesterol metabolism by probiotics through multiple mechanisms, including direct action, metabolite regulation, and gene signaling pathway regulation.

Synthesizing the available evidence, from animal models to human clinical trials, there is a general consensus in the scientific community that supplementation with specific probiotics can produce a modest but statistically significant reduction in serum TC and LDL-C levels. Although this effect cannot replace the status of first-line drugs such as statins, its potential in improving dyslipidemia and maintaining cardiovascular health as a safe and easily accepted auxiliary management tool should not be underestimated. However, it must be soberly recognized that the efficacy of probiotics is highly dependent on the specificity of the strain, the dose used, the duration of the intervention, and individualized factors in the host itself.

Looking forward to the future, with the in-depth application of multi-omics technology and continuous breakthroughs in the research of NGPs, we are moving toward a new era of "precision microecological nutrition". Through a deeper understanding of the complex interactions between probiotics and the host, we are expected to develop personalized probiotic interventions based on individual characteristics, or even entirely new living biologics. This will not only provide more effective weapons for the prevention and treatment of hypercholesterolemia, but also bring revolutionary new strategies for the whole field of metabolic diseases, and eventually transform the frontier exploration of science into the health and well-being of the people at hand.

Conflict of interest

There are no conflicting interests to disclose according to the authors.

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