

Review

Unveiling the Impact of Lactic Acid Bacteria on Blood Lipid Regulation for Cardiovascular Health

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Abstract: Lactic acid bacteria (LAB) are a group of microorganisms which are beneficial and well-characterized with respect to the flavor and texture of food products via fermentation. The accumulated literature has suggested that dietary intake of fermented foods rich in LAB is related to different health-promoting benefits; however, in recent years, emerging evidence suggests a contribution of LAB to blood lipid regulation and cardiovascular health via certain mechanisms. Different potential mechanisms for the lipid regulatory effects of LAB may include the interaction of hydroxymethylglutaryl-CoA (HMG-CoA) reductase and bile salt hydrolase activity and bile salt metabolism; gut microbiome modulation; and regulation of mRNA expression of genes related to fat metabolism in animal models and human studies. This review comprehensively aims to answer whether/how LAB influence blood lipids in both animal models and human studies while also uncovering the underlying mechanisms linking LAB to lipid metabolism.

Keywords: lactic acid bacteria; blood lipids; lipid metabolism; cardiovascular health; fermented food



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1. Introduction

Cardiovascular diseases (CVDs), one of the most important public health problems worldwide and the main cause of death due to diseases, include a group of cardiovascular diseases such as coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. According to the World Health Organization (WHO), 32% of mortalities worldwide in 2019 were attributed to CVDs, with an estimated 17.9 million deaths. Heart attacks and strokes were the cause of 85% of these mortalities [1,2]. In 2019, there were reported to be 523 million cases of total CVDs [3]. Arteriosclerotic plaque formation is an important common point in the pathogenesis of these diseases. With the erosion of this atherosclerotic plaque, thrombosis and then vascular occlusion may develop [4]. Ultimately, all these conditions may result in myocardial infarction, stroke, ischemia or even death [4]. Various factors such as age, gender, ethnicity, genetics, smoking, alcohol consumption, stress, hypertension, dyslipidemia, physical inactivity and nutrition play a role in the etiology of cardiovascular diseases [2]. Nutrition is among the most important modifiable risk factors for cardiovascular diseases. In order to reduce the risk of CVD, the

American Heart Association (AHA) recommends a diet in which fruits, vegetables and whole grains are predominant; fish, legumes and poultry are preferred as protein sources; and added sugar, sodium, saturated and trans-fat intake as well as red meat consumption is limited [5]. In addition to these general nutritional recommendations, recent studies have shown that different nutritional models—such as the ketogenic diet, specific foods such as berries, turmeric and green tea, and fermented foods that stand out with their antioxidant activities—may have a role in the prevention and/or treatment of cardiovascular diseases [6–10].

Fermented foods can show their protective effects against the risk of CVDs directly through probiotic activity or indirectly through the metabolites they form [10]. It is significant to note that not all fermented foods can be classified as probiotics, since containing live/active cultures is not enough for them to be accepted as probiotics. The International Scientific Association for Probiotics and Prebiotics' consensus proposes that the term 'probiotic' should only apply to live microorganisms which, when given in sufficient quantities, provide a health advantage to the host. This definition specifically rules out non-living products such as metabolic byproducts or deceased microorganisms from being categorized as probiotics [11]. Some lactic acid bacteria (LAB) are particularly well known for their high probiotic potential and the bioactive metabolites they produce during the fermentation process. Lactic acid bacteria are a group of bacteria that include genera such as *Lactobacillus*, *Lactococcus*, *Pediococcus*, *Enterococcus* and *Streptococcus* and are found in many fermented food groups such as fermented vegetables, meats and cereals, especially dairy fermented products [12]. Bioactive peptides, short-chain fatty acids, exopolysaccharides (EPSs) and vitamins such as folate, riboflavin, B12 and vitamin K2 (menaquinones) formed during LAB fermentation play a crucial role in the protection of cardiovascular health [10]. The type, strain and bacterial concentration used in fermentation and the matrix of the substrate food influence the formation of bioactive metabolites and shape the potential health effects of fermented food. Foods produced by fermentation using LAB are especially prominent in terms of bioactive metabolites. Examples of such bioactive metabolites are angiotensin-converting enzyme (ACE)-inhibitory peptides. The cholesterol-lowering properties of these LAB-derived EPSs are likely to arise by reducing cholesterol absorption in the intestine, stimulating the release of bile acids and binding cholesterol [12].

According to the results of a randomized controlled trial of diabetic patients, consumption of Ash-Kardeh, a traditional fermented food produced by LAB fermentation, for six weeks can improve high blood sugar, lipid profile and hypertension in type 2 diabetic patients, but does not affect low-density lipoprotein cholesterol (LDL-C) concentrations [13]. In another randomized controlled study of diabetic individuals, the change in the lipid profile of those who consumed milk fermented with probiotic bacteria (*Streptococcus thermophilus*, *L. casei*, *L. acidophilus* and *Bifidobacterium lactis*) and those who consumed traditional fermented milk (*Streptococcus thermophilus* and *L. bulgaricus*) for 8 weeks was similar [14]. Although not statistically significant, there was a slight decrease in triglyceride and LDL-C values in both groups, while there was no change in high-density lipoprotein cholesterol (HDL-C) values [14]. A brief overview of the clinical studies is provided in this section, and both clinical and preclinical studies will be discussed in detail in upcoming sections.

This review aims to answer whether/how LAB influence blood lipids in both animal models and human studies, while also uncovering the underlying mechanisms linking LAB to lipid metabolism.

2. Lactic Acid Bacteria's Metabolic Activities and Lipid Metabolism Modulation

There has been a lot of interest in understanding the mechanism between LAB and gut microbiota (GM). Restoring GM abundance and species diversity is the foremost positive effect of LAB. The antibacterial compounds produced by LAB have a direct impact on intestinal homeostasis and gut permeability reduction through the suppressing of microorganisms [15]. Reductions in serum cholesterol, inflammation and oxidative damage

can be achieved by the modulation of gut-derived metabolites by LAB. A large body of research has established causal links between processes that originate in the digestive tract and the onset of cardiovascular disease [15].

Different potential mechanisms for the lipid regulatory effects of LAB in humans have been proposed. One of them is about the interaction of the bile salt hydrolase (BSH) activity of LAB with the bile salt metabolism of the host. The resulting effect is a reduction in reabsorption of bile salts, a loss of feedback inhibition of the bile salt synthesis and increased conversion of cholesterol to bile salts. Another mechanism is the reduction in 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA reductase), which is a regulatory enzyme in cholesterol biosynthesis [16,17]. Furthermore, LAB-produced EPS acts as a cholesterol binder and an angiotensin-converting enzyme inhibitor [18–20]. It is necessary for LAB to be resistant to acid and bile in order for them to be effective in this function. Additionally, they must be able to suppress putrefactive bacteria that are present in the gastrointestinal tract (GIT) of the host [21]. It is crucial to note that the blood lipid regulatory effects of LAB are strain-dependent and cannot be attributed to all bacteria in the genus.

3. Human Studies

BSH is an enzyme synthesized by the intestinal microbiota that facilitates the breakdown of amide bonds in conjugated bile acids (BAs), leading to the liberation of free amino acids [22–24]. It is known that LAB and products containing LAB have a cholesterol-lowering effect due to the hydrolase–host interaction. LAB species, especially *Lactobacillus* species, have an advantage because they can colonize and survive in the small intestines. Probiotics with high BSH activity, such as *Lactobacilli*, survive better in the intestines, possibly due to their BSH genes, which may give them resistance to intestinal conditions [16].

The cholesterol-lowering effect of LAB has been most associated with BSH activity. Studies have shown that *Bifidobacterium* and *Lactobacillus* species contain BSH genes [23]. Foods containing these bacteria are known to break amide bonds and thus hydrolyze conjugated bile acids. Deconjugated bile salts are absorbed less efficiently than conjugated ones, thus causing a greater amount of free bile acid to pass into the feces [16,23]. Additionally, free bile salts are less efficient in the solubilization and absorption of lipids. Therefore, deconjugation of bile salts may lead to a decrease in serum cholesterol by increasing the demand for cholesterol for new synthesis of bile acids to replace those lost in the feces, or by reducing cholesterol solubility and, hence, absorption of cholesterol through the intestinal lumen [23]. Figure 1 shows the effect of LAB on cholesterol metabolism via BSH.

Many hypotheses have been proposed about the mechanisms by which probiotics lower cholesterol levels, most of which stem from in vitro experiments. The following have been identified as potential mechanisms: deconjugation of bile through BSH activity; binding of cholesterol to the probiotic cell surface and incorporation of cholesterol molecules into the probiotic cell membrane; production of SCFAs from oligosaccharides; co-precipitation of cholesterol with deconjugated bile; and conversion of cholesterol to coprostanol [17].

In addition, BSH-active bacteria can affect the farnesoid X receptor (FXR), a bile acid nuclear receptor, by altering the bile acid pool profile. Endogenous bile acids, such as chenodeoxycholic acid, lithocholic acid, deoxycholic acid and cholic acid, activate FXR to varying degrees, with conjugated forms showing reduced effectiveness compared to their unconjugated counterparts. A reduction in FXR activity has been shown to result in downregulation of its small heterodimer partner (SHP) and increased cholesterol catabolism and synthesis of bile acids by cholesterol 7 alpha-hydroxylase (CYP7A1). Downregulation of SHP results in upregulation of the liver X receptor (LXR). This leads to upregulation of adenosine triphosphate binding cassette transporters G5 and G8 (ABCG5/G8) [23]. Upregulation of ABCG5/G8 leads to a decrease in the intestinal absorption of cholesterol while also promoting its biliary excretion [23,24]. Another mechanism of the cholesterol-lowering effect of LAB is that they reduce the activity of HMG-CoA reductase, which is

the rate-limiting enzyme in endogenous cholesterol production [16,17]. The role of LAB in cholesterol metabolism is shown in Figure 2.

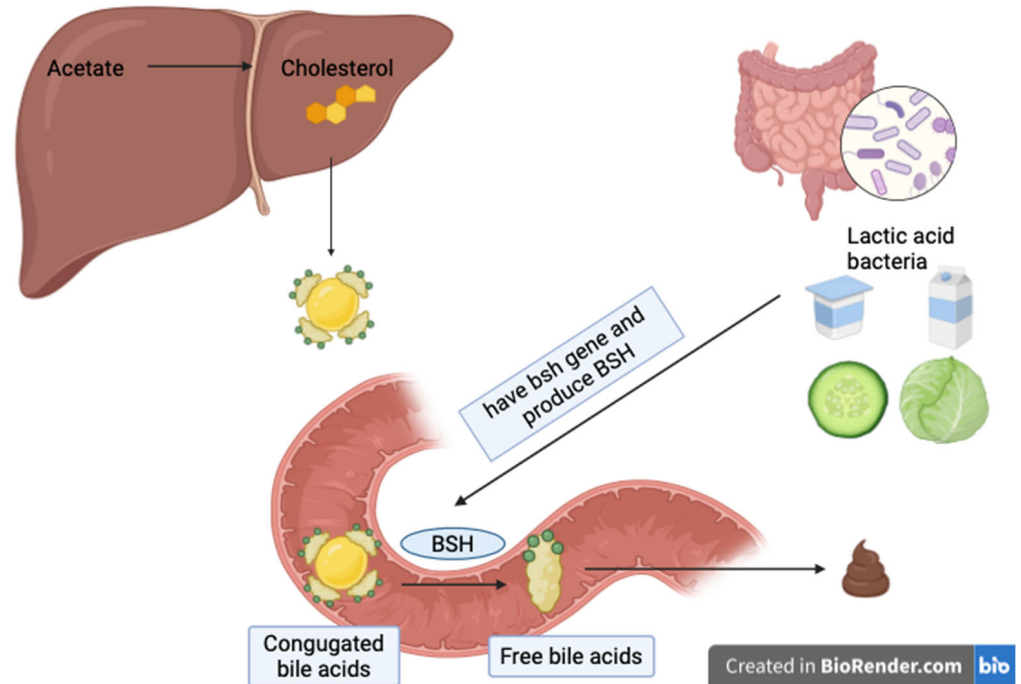


Figure 1. The possible mechanism of bile salt hydrolase and the associated effect of lactic acid bacteria on cholesterol metabolism.

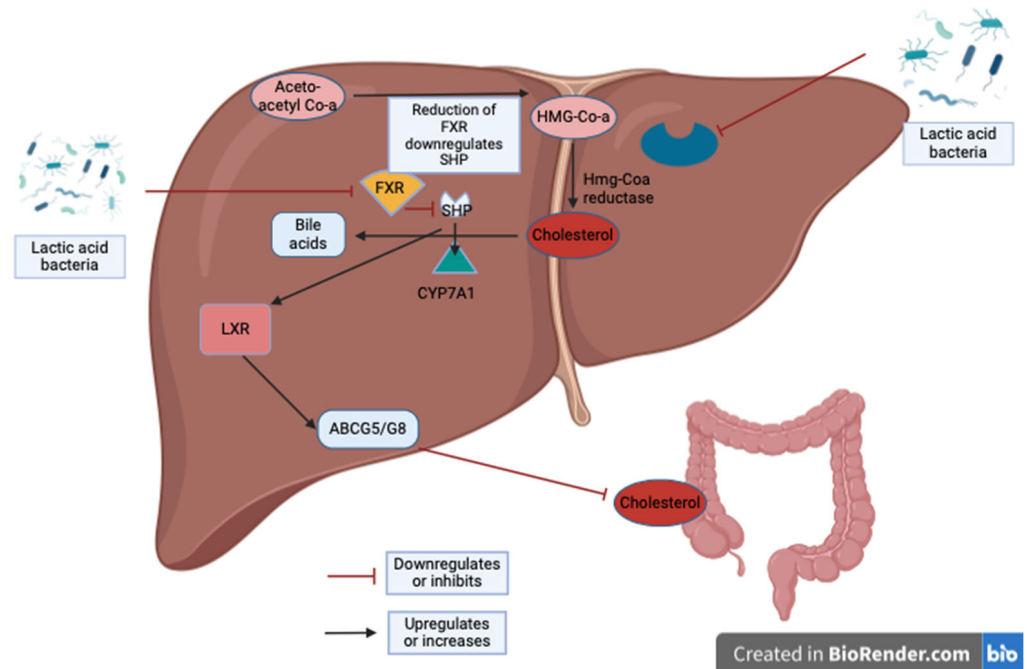


Figure 2. The role of LAB in cholesterol metabolism (FXR: farnesoid X receptor; CYP7A1: cholesterol 7 alpha-hydroxylase; SHP: small heterodimer partner; LXR: liver X receptor; ABCG5/G8: adenosine triphosphate binding cassette transporters G5 and G8).

LAB have the ability to produce EPSs, which could serve as prebiotics [19]. EPSs are polysaccharides that are released or bound to the bacterial cell wall [25]. In addition to making the cell more resistant to antibiotics, bacteriophages or phagocytosis, EPSs have the potential to physically shield cell walls against harmful chemicals, including nisin, lysozyme, and detergents [19]. Thanks to their prebiotic feature, EPSs may provide cardioprotective effects [20]. It has been shown that EPSs may act as inhibitors of ACE, which is a treatment for hypertension [18,20].

Several studies have investigated the effects of various probiotics and fermented foods containing LAB on lipid profiles in different populations. Furthermore, there are some meta-analyses of LAB effects on lipid profiles [26–29]. In a meta-analysis study including 33 randomized controlled trials, it was shown that probiotic interventions ameliorate changes in total cholesterol (TC) and LDL-C, including both fermented milk products and probiotics [28]. In a meta-analysis study including 11 randomized controlled studies that investigated the effect of probiotic use on the metabolic profile of individuals with gestational diabetes, it was proven that, compared to a placebo, probiotic use was significantly associated with improved TC [27].

There are many randomized studies in the literature investigating the effects of fermented foods containing LAB on lipid profiles. These studies have shown that fermented foods containing LAB may have a role in decreasing TC and LDL-C and increasing HDL-C [13,14,30–32] (Table 1). Salehi et al. [13] (2022) conducted a randomized controlled clinical trial in Iran where 23 individuals with type 2 diabetes received 250 g/day of Iranian fermented food Ash-Kardeh for 6 weeks. The intervention group exhibited a decrease in total cholesterol (TC) (-8.36 ± 3.35) and an increase in high-density lipoprotein cholesterol (HDL-C) ($+2.35 \pm 1.19$) [13]. The potential mechanism for the increase in HDL-C was explained by the sphingolipids present in the probiotic cell membrane influencing cholesterol translocation and blocking its absorption by binding to it. The probiotic properties of A-K may be one of the mechanisms leading to an improved lipid profile in type 2 diabetic patients. The sphingolipids present in the probiotic cell membrane affect the metabolism and cholesterol translocation in the body and block its absorption by binding to it, which results in an increase in HDL-C [13]. Ostadrahimi et al. (2015) investigated a probiotic fermented milk (kefir) in a randomized clinical trial with 60 diabetic patients for 8 weeks, resulting in a significant decrease in total cholesterol (from 197.86 ± 51.99 mg/dL to 186.07 ± 61.03 mg/dL) [14]. Jones et al. (2012) studied *L. reuteri* in capsules, observing a reduction in LDL-C by 11.64% and TC by 9.14% in 127 patients with hypercholesterolemia over 9 weeks [33]. Another clinical trial included 13 patients with hyperlipidemic symptoms and 10 healthy patients, demonstrating that kefir consumption resulted in decreased TC (5.71%) and LDL-C (5.31%) and increased HDL-C (8.58%) levels for dyslipidemic individuals over 8 weeks [30]. Fathi et al. (2017) conducted an 8-week randomized clinical trial with 75 overweight or obese premenopausal women, comparing the effects of kefir, milk and a control group, and found significantly lower levels of TC and LDL-C (-10.4 mg/dL, -9.7 mg/dL) in the kefir group compared to the control group [32]. In a 12-week randomized clinical trial, the effects of kefir were investigated in 48 patients with metabolic syndrome, observing reductions in TC (from 193 ± 27 to 189 ± 16 mg/dL), TG (from 196 ± 67 to 147 ± 44 mg/dL) and ox-LDL concentrations in females, along with an increase in HDL-C levels (from 44 ± 5 to 48 ± 3 mg/dL) [34]. On the other hand, Onge et al. (2002) reported that there were no significant changes in lipid levels in mildly hyperlipidemic patients over 4 weeks of consumption of kefir [31]. Analyzing the food given in the studies and revealing its bacterial composition and the amount of lactic acid bacteria it contains could help make comparisons with other studies. Due to the limited scope of the studies, which focused on certain ethnic or disease groups, the data collected cannot be extrapolated to other ethnic groups or the overall population.

Table 1. Randomized controlled clinical trials investigating lactic acid bacteria and lipid profiles.

Study Design	LAB Species	Intervention	Subjects	Duration	Main Results	Reference
Randomized controlled clinical trial	Not specified	Iranian fermented food Ash-Kardeh (250 g/day)	23 type 2 diabetes (intervention) 23 type 2 diabetes (control group)	6 weeks	While TC decreased, HDL-C increased significantly.	[13]
Randomized controlled clinical trial	<i>L. acidophilus</i> La5 and <i>Bifidobacterium animalis</i> subsp. lactis Bb12	Yoghurt or capsule form	156 overweight men or women	6 weeks	Neither capsule nor yogurt supplementation changed levels of blood lipids and blood pressure.	[35]
Randomized clinical trial	<i>L. amylovorus</i>	Beverages with powder CP1563 powder	100 overweight or obese females or males	12 weeks	Triglyceride, TC, LDL-C and diastolic blood pressure showed significant reductions.	[36]
Randomized, double-blind, placebo- and compliance-controlled parallel study.	<ol style="list-style-type: none"> 1. Fermented with two strains of <i>Streptococcus thermophilus</i> and two strains of <i>L. acidophilus</i> 2. Or two strains of <i>Streptococcus thermophilus</i> and one strain of <i>L. rhamnosus</i> 3. Or one strain of <i>Enterococcus faecium</i> and two strains of <i>Streptococcus thermophilus</i> (Commercial product) 	Fermented milk (yogurt) (450 mL/day)	80 healthy overweight or obese	8 weeks	When body weight variations were adjusted, LDL-cholesterol decreased by 8.4% in the commercial product group ($p < 0.05$).	[37]
Randomized clinical trial	<i>L. plantarum</i>	Probiotic form	60 patients, mean BMI 26.2 kg/m ²	16 weeks	When compared with a placebo, the lactic acid bacteria receiving group had more reductions in LDL-C and triglycerides and increases in HDL-C	[38]
Randomized clinical trial	<i>L. casei</i> , <i>L. acidophilus</i> and <i>Bifidobacteria</i>	Probiotic fermented milk (kefir) (600 mL/day) or conventional fermented milk (600 mL/day) (for the control group)	60 diabetic patients	8 weeks	Total cholesterol significantly decreased in the probiotic fermented group.	[14]
Randomized clinical trial	<i>L. reuteri</i>	Capsules with <i>L. reuteri</i> and capsules with placebo	127 patients with hypercholesterolemia	9 weeks	Comparatively, LDL-C was reduced by 11.64%, and total cholesterol was reduced by 9.14%.	[33]
Randomized crossover trial	Not specified	Kefir (500 mL/day) or milk (500 mL/day)	13 patients (mildly hyperlipidemic)	4 weeks	There were no changes in TC, LDL-C, HDL-C and triglyceride levels.	[31]
Randomized clinical trial	<i>L. reuteri</i>	Yogurts containing microencapsulated <i>L. reuteri</i> and placebo yogurt	114 patients with hypercholesterolemia	6 weeks	Significant reductions in LDL-C and TC in <i>L. reuteri</i> , including yogurt.	[39]

Table 1. Cont.

Study Design	LAB Species	Intervention	Subjects	Duration	Main Results	Reference
Prospective self-controlled clinical trial	Kefir was analyzed to confirm LAB content	Kefir (250 mL/day)	13 patients with hyperlipidemic symptoms, 10 healthy patients	8 weeks	For both groups, TC, LDL-C and triglyceride levels decreased while HDL-C levels increased.	[30]
Randomized clinical trial	Kefir	Kefir (1.6 mL/kg for females, 1.9 mL/kg for males) or placebo (curd)	48 patients with metabolic syndrome (24 kefir, 24 curd-receiving group)	12 weeks	In female group, TC-triglyceride and ox-LDL concentrations decreased while HDL-C levels increased.	[34]
Randomized clinical trial	Not specified	Kefir or milk or control group	75 overweight or obese premenopausal women	8 weeks	In kefir group, significantly lower levels of TC and LDL-C were observed when compared with control group.	[32]
Randomized controlled trial	<i>L. acidophilus</i> , <i>Bifidobacterium lactis</i>	300 g daily regular yogurt or 300 g probiotic yogurt	44 patients with metabolic syndrome	8 weeks	When compared with the baseline, triglycerides decreased and HDL-C increased significantly in probiotic yogurt group.	[40]
Randomized crossover trial	<i>L. acidophilus</i> 145, <i>B. longum</i> 913	300 g/day probiotic yogurt and normal yogurt	14 hypercholesterolemic 15 normocholesterolemic	6 months	In probiotic yogurt group, HDL-C significantly increased whereas there was no cholesterol-lowering effect.	[41]
Randomized controlled trial	<i>L. plantarum</i> SN35N, <i>L. plantarum</i> SN13T, (type C) or <i>Lactococcus lactis</i> A6 and <i>Streptococcus thermophilus</i> 510 (normal yogurt)	100 g/day yogurt made from plant-derived LAB or normal yogurt	68 healthy adults with symptoms of constipation or diarrhea	6 weeks	TC and LDL-C significantly decreased in <i>L. plantarum</i> SN13T-derived and normal yogurt groups.	[42]
Randomized two-way crossover trial	<i>L. acidophilus</i> (two strains) and traditional yogurt starters	3 × 125 mL of yogurt (with <i>Lactobacillus acidophilus</i>) or normal yogurt	30 healthy male adults	3 weeks	Consumption of the test product resulted in significantly lower values for TC and LDL-C.	[43]

Ivey et al. (2015) conducted a 6-week trial with 156 overweight men or women using *Lactobacillus acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12 in either yogurt or capsule form. However, neither supplementation showed significant changes in blood lipids or blood pressure. It has been suggested that the reason why the expected results were not obtained in this clinical study was related to the fact that the antihyperlipidemic effect of LAB may be more effective in individuals with borderline or high levels of cholesterol [35]. Nakamura et al. (2016) performed a 12-week randomized clinical trial with 100 overweight or obese females and males using *Lactobacillus amylovorus* in beverages with CP1563 powder, resulting in significant reductions in triglycerides, total cholesterol, LDL-cholesterol and diastolic blood pressure [36]. Lactic acid bacteria have been shown to increase expression of peroxisome proliferator activated receptor alpha (PPARα), which inhibits fatty acid synthesis and regulates triglyceride reducing steps and fatty acid beta oxidation [43,44]. Larsen et al. (2000) found that when adjusting for body weight variations, LDL-cholesterol decreased by 8.4% in the fermented yogurt group [37]. Similarly, Fuentes et al. conducted a 16-week randomized clinical trial with 60 patients using *L. plantarum*

in probiotic form, showing greater reductions in LDL-C (-20.5 mg/dL) and triglycerides (-33.3 mg/dL) along with an increase in HDL-C ($+2.8$ mg/dL) compared to the placebo group. The triglyceride-lowering impact may be explained by the probiotics' ability to improve fermentation and, hence, increase the colon's production of short-chain fatty acids [38]. Another study by Jones et al. involved yogurts containing microencapsulated *L. reuteri* in a 6-week randomized clinical trial with 114 hypercholesterolemic patients, showing significant reductions in LDL-C ($-7.54 \pm 2.38\%$) and TC ($-10.57 \pm 1.79\%$) [39]. In a randomized controlled trial involving 44 patients diagnosed with metabolic syndrome, the impact of daily consumption of either 300 g of regular yogurt or 300 g of probiotic yogurt containing *L. acidophilus* and *Bifidobacterium lactis* were investigated over an 8-week period [40]. The findings revealed that, when compared with baseline measurements, individuals in the probiotic yogurt group experienced a significant decrease in triglyceride levels (from 225 ± 65 to 189 ± 49 mg/dL) and a notable increase in HDL-C (from 43 ± 9 mg/dL to 46 ± 7 mg/dL). These results suggest a potential positive effect of probiotic yogurt consumption on lipid profile parameters in individuals with metabolic syndrome. In this study, it was said that a possible explanation for the decrease in blood triglyceride levels after probiotic administration was the modification of the energy pathways involved in fatty acid oxidation and the reduction in triglyceride synthesis. Probiotics achieve these changes by inhibiting the nuclear factor κ -light-chain-enhancer of the activated β cell NF- κ B pathway, which is responsible for activating β cells. Probiotics also affect the gut microbiota's short-chain fatty acid hormone axis and promote the breakdown of long-chain fatty acids in the liver and muscle tissues through beta oxidation [40,45]. There is growing interest in the potential benefits of LAB on lipid metabolism. However, the exact mechanism that is responsible for lipid reduction in humans is still not very clear. There are potential mechanisms proposed for cholesterol removal by LAB; however, some of these mechanisms are strain dependent. Therefore, the results of the studies cannot be generalized. It should also be emphasized that an equivalent environment provided to subjects in preclinical studies cannot be provided in human studies. It should not be forgotten that responses to LAB interventions can vary among individuals due to factors such as genetics, diet, lifestyle and the composition of the gut microbiota.

4. Lactic Acid Bacteria's Metabolic Activities and Lipid Modulation: Animal Studies

Lactic acid bacteria and *Lactobacillus* strains (specifically those which are accepted as probiotics) have been shown to have the potential of reducing the risk of CVDs [46–48]. These bacteria can regulate the body's metabolism at various levels, including molecular, cellular and population levels, leading to the lowering of blood glucose and blood lipids, the regulation of blood pressure and, ultimately, a reduction in the incidence of CVDs [15]. The potential impacts of LAB on blood lipids have been reported in both clinical and preclinical studies and several mechanisms have been described. The animal studies will be discussed in this section. It should be noted that LAB have the ability to reduce the cholesterol in dairy foods such as cheese [49]; however, these properties of LAB will not be discussed in this paper.

One of the most common proposed mechanisms between LAB and CVDs is that LAB, especially those which are isolated from fermented foods (kimchi, dahi, yogurt, kefir and other commonly consumed fermented foods), may affect the modulation of intestinal microbiota [15,50,51]. A growing body of experimental evidence supports a causal contribution of the gut microbiota to CVD. The evidence includes studies on gut microbiota transplantation, microbiota-dependent pathways and metabolites affecting host metabolism and CVD. Several metaorganismal pathways impacting CVD in animal models correlate with clinical associations in human studies. Specific gut microbial metabolites, such as trimethylamine N-oxide and phenylacetylglutamine, are linked to incidental CVD risks in large-scale clinical studies, with causal connections established through mechanistic animal model studies [52]. One of the most significant associations between CVDs and *Lactobacillus* is that these microorganisms (*L. acidophilus*, *L. brevis*, *L. paracasei*, *L. plantarum*,

L. casei, *L. helveticus*, *L. sakei*, *L. gasseri*, *L. alimentarius*, *L. coryniformis*, *L. johnsonii*, *L. panis*, *L. crispatus*, *L. amylovorus*, *L. curvatus* and *L. rhamnosus*) have the ability to inhibit the growth of pathogenic bacteria and reduce intestinal permeability, which improves intestinal dysbiosis. Intestinal dysbiosis, characterized by a decrease in beneficial microbiota, is associated with hypertension, a leading risk factor for CVDs [53]. Lactobacillus supplementation has been found to positively modulate the impaired microbiota and reduce blood pressure. Gut microbiota and its metabolites, such as trimethylamine-N-oxide (TMAO; modulation of inflammation, atherosclerosis), short-chain fatty acids (SCFA; modulation of inflammation) and bile acids (BAs; modulation of lipid metabolism), have also been implicated in the development, prevention, treatment and prognosis of CVDs. Numerous preclinical studies have reported similar mechanisms between LAB and the modulation of gut microbiota (Table 2).

Table 2. Relationship between lactic acid bacteria and blood lipids in animal models: a summary.

Animals	Intervention	LAB Species	Main Results	Proposed Mechanism/s	Reference
5-week-old Sprague Dawley male rats (n:32)	Four groups: 1. Normal diet 2. High-fat/high-cholesterol diet 3. High-fat/high-cholesterol diet + nonfermented control juice; and 4. High-fat/high-cholesterol diet + fermented EM juice Duration: 6-weeks	<i>L. plantarum</i> EM	<ul style="list-style-type: none"> - Rats in group 4 showed significantly reduced total cholesterol (serum and liver), triglyceride and LDL-cholesterol levels, as well as a reduced atherogenic index and lower cardiac factors in serum. - Decreased hepatic mRNA expression of HMG-CoA reductase and increased expressions of cholesterol 7α-hydroxylase and low-density lipoprotein receptor. 	<ul style="list-style-type: none"> - Inhibition of cholesterol synthesis and enhancement of cholesterol uptake and excretion 	[54]
7–8-week-old C57BL/6 J male mice (n:48)	Four groups: 1. Normal diet 2. High-fat diet 3. High-fat diet + positive control 4. High-fat diet + LP24 Duration: 8-weeks	<i>L. paracasei</i> 24	<ul style="list-style-type: none"> - Reduced body weight and fat deposition, liver oxidative stress injury; improvement in blood lipid levels and liver steatosis, and regulated fat metabolism-related factors in liver oxidative stress injury. - Regulation of abundance and diversity of gut microbiota by reducing the abundance of Firmicutes and the ratio of Firmicutes/Bacteroidetes and increasing the abundance of Akkermansia. 	<ul style="list-style-type: none"> - Regulating the gut microbiota and activating genes related to fat metabolism 	[51]
7–8-week-old male Wistar rats (n:45)	Nine groups: 1. Normal diet 2. The remaining eight groups: high-fat diet with one probiotic strain from each: FM9, Y57, FM6, Y55, FM16, Y59, FM12 and Y63 Duration: 30 days	<i>L. rhamnosus</i> FM9, <i>L. fermentum</i> Y57 <i>L. fermentum</i> FM12, <i>L. fermentum</i> FM16, <i>L. fermentum</i> Y55, <i>L. rhamnosus</i> Y59 and <i>L. fermentum</i> Y63	<ul style="list-style-type: none"> - The strains were compared to statins and showed similar effectiveness in improving total cholesterol, LDL, HDL, triglycerides and weight gain. - <i>L. rhamnosus</i> FM9 and <i>L. fermentum</i> Y57 were particularly effective, reducing serum cholesterol levels by 9% and 8%, respectively, compared to 5% for the statin-treated group. 	<ul style="list-style-type: none"> - Regulation of serum cholesterol and improvement in body weight 	[55]

Table 2. Cont.

Animals	Intervention	LAB Species	Main Results	Proposed Mechanism/s	Reference
4–6-week-old Wistar albino rats (either sex)	<p>Seven groups:</p> <ol style="list-style-type: none"> 1. Normal diet 2. Atherogenic diet 3. Atherogenic diet + standard antihyperlipidemic drug 4. Atherogenic diet + curd having 10⁷ probiotic strain PD2 5. Atherogenic diet + curd having 10⁹ probiotic strain PD2 6. Atherogenic diet + curd having 10⁷ probiotic strain PH5 7. Atherogenic diet + curd having 10⁹ probiotic strain PH5 <p>Duration: 4 weeks</p>	<i>L. fermentum</i> PD2 and PH5	<ul style="list-style-type: none"> - <i>L. fermentum</i> PH5 significantly reduced serum cholesterol (67.21%), triglycerides (66.21%) and LDL cholesterol levels (63.25%) compared to atherogenic diet. - <i>L. fermentum</i> PD2 and PH5 decreased cholesterol levels in the liver compared to an atherogenic diet. - <i>L. fermentum</i> PH5 reduced fecal coliforms and increased LAB in feces. 	<ul style="list-style-type: none"> - Lowering serum cholesterol, LDL-cholesterol and triglyceride concentrations 	[56]
8-week-old male Sprague Dawley rats	<p>Three groups:</p> <ol style="list-style-type: none"> 1. High-fat diet group 2. High-fat diet + simvastatin 3. High-fat diet + <i>L. plantarum</i> N-1 <p>Duration: 30 days</p>	<i>L. plantarum</i> N-1	<ul style="list-style-type: none"> - Total cholesterol and LDL-C levels in serum and total cholesterol in the liver decreased significantly in both N-1 and simvastatin. - HMG-CoA gene expression was considerably downregulated by 31.18% in the N-1 group. - Butyrate and valerate contents were significantly greater in N-1 than in other groups. 	<ul style="list-style-type: none"> - Production of the intestinal SCFAs and inhibition of the expression of HMG-CoA reductase 	[57]
6-week-old male Wistar rats	<p>Five groups:</p> <ol style="list-style-type: none"> 1. Standard diet 2. High-cholesterol diet 3. High-cholesterol diet + milk 4. High-cholesterol diet + <i>L. rhamnosus</i> MTCC:5957 fermented milk 5. High-cholesterol diet+ <i>L. rhamnosus</i> MTCC:5897 fermented milk <p>Duration: 3 months</p>	<i>L. rhamnosus</i> MTCC:5957 and <i>L. rhamnosus</i> MTCC:5897	<ul style="list-style-type: none"> - Probiotic-fermented milk reduced body weight, hyperlipidemia and hepatic lipids. - Probiotic-fermented milk increased cholesterol excretion in feces. - Probiotic-fermented milk increased antioxidant activities and decreased lipid peroxidation as well as mRNA expression of TNF-α and IL-6 in the liver. 	<ul style="list-style-type: none"> - Lowering hyperlipidemia and lipid peroxidation - Modulating oxidative and inflammatory responses 	[58]
Wistar strain albino male rats	<p>Three groups:</p> <ol style="list-style-type: none"> 1. Normal diet 2. High-fat fermented diet 3. High-fat unfermented diet <p>Duration: 4 weeks</p>	<i>L. acidophilus</i> (DSM 20242), <i>Bifidobacterium bifidum</i> (DSM 20082) and <i>L. helveticus</i> (CK60)	<ul style="list-style-type: none"> - Mixed culture of <i>L. acidophilus</i> (DSM 20242), <i>Bifidobacterium bifidum</i> (DSM 20082) and <i>L. helveticus</i> (CK60) reversed dyslipidemia by inhibiting fat absorption. - Also, this mixture inhibited the activity of HMG CoA reductase. 	<ul style="list-style-type: none"> - Lowering hyperlipidemia and inhibiting expression of HMG-CoA reductase 	[59]
Six-week-old male C57BL/6j mice	<p>Seven groups</p> <ol style="list-style-type: none"> 1. Normal diet 2. High-fat diet 3. High-fat diet+ <i>Companilactobacillus allii</i> WiKim39 4. High-fat diet + <i>L. lactis</i> WiKim0124 5. High-fat diet + non-fermented vegetable juice 6. High-fat diet + <i>C. allii</i> WiKim39-fermented vegetable juice 7. High-fat diet + <i>L. lactis</i> WiKim0124-fermented vegetable juice 	<i>Companilactobacillus allii</i> WiKim39 and <i>L. lactis</i> WiKim0124	<ul style="list-style-type: none"> - Both strains effectively ameliorated fat accumulation both in vitro and in vivo. - Fermentation metabolites of vegetable juice, which were indole-3-lactic acid, leucic acid and phenyllactic acid, had an inhibitory effect on lipid accumulation in vitro. - Both strains reduced weight gain and liver fat accumulation in vivo. 	<ul style="list-style-type: none"> - Inhibition of lipid accumulation and blood lipids via LAB and the metabolites of fermentation 	[60]

Table 2. Cont.

Animals	Intervention	LAB Species	Main Results	Proposed Mechanism/s	Reference
6-week-old C57BL/6J mice (half male and half female)	Six groups: 1. Low-fat diet 2. High-fat diet 3. High-fat diet + L-carnitine 4. High-fat diet+ <i>L. fermentum</i> CQPC04 (10 ⁸ CFU/mL) 5. High-fat diet+ <i>L. fermentum</i> CQPC04 (10 ⁹ CFU/mL) 6. High-fat diet+ <i>L. delbrueckii</i> subsp. <i>Bulgaricus</i> (10 ⁹ CFU/mL)	<i>L. fermentum</i> CQPC04	- <i>L. fermentum</i> CQPC04 reduced weight gain and visceral index in mice caused by a high-fat diet. - <i>L. fermentum</i> CQPC04 showed stronger effects in regulating lipid reduction in mice compared to L-carnitine and commercial <i>Lactobacillus delbrueckii</i> subsp. <i>Bulgaricus</i> .	- Regulation of lipid levels by restoring liver function and regulation of PPAR- α signaling pathways	[61]
6-week-old male C57BL/6N mice	Four groups: 1. Normal diet 2. High-fat diet 3. High-fat diet+ LAB-uninoculated kimchi 4. High-fat diet+ LAB-inoculated kimchi Duration: 8 weeks	<i>Leuconostoc mesenteroides</i> KCKM0828	- Body weight, body fat, organ weight, leptin and lipid levels dramatically dropped in the LAB group. - Obesity-related gene expression and lipid accumulation decreased in the LAB group in addition to modulation of the gut microbiome balance.	- Modulation of gut microbiota and regulation of gene expression levels	[62]

In addition to intestinal microbiota, regulation of mRNA expression of the genes related to fat metabolism has been shown to be another possible explanation for how LAB reduce blood lipids in animal models (Table 2) [54,57]. *L. plantarum*, *L. acidophilus* and *L. helveticus* decreased mRNA expression of HMG-CoA reductase and increased expressions of cholesterol 7 α -hydroxylase, which reduced total cholesterol, LDL-C and triglyceride levels, while in some cases an increase was seen in HDL-C levels [54,55,59].

HMG-CoA reductase plays a pivotal role in lipid metabolism. As a key enzyme in the mevalonate pathway, HMG-CoA reductase is responsible for generating mevalonate, which serves as a critical intermediate in the synthesis of cholesterol and various nonsterol isoprenoids, including geranylgeranyl pyrophosphate [63,64]. The reductase is subject to transcriptional, translational and posttranslational feedback mechanisms, ensuring cells maintain an adequate supply of essential nonsterol isoprenoids while preventing excessive accumulation of cholesterol and other sterols [65]. Dysregulation of HMG-CoA reductase is associated with several disorders such as hypercholesterolemia. Pharmacological inhibitors of this enzyme such as statins are widely used to lower cholesterol levels and reduce cardiovascular risk by modulating lipid metabolism [66]. As an alternative method, it has been revealed that LAB (*L. rhamnosus* FM9 and *L. fermentum* Y57) may be as efficient as statins in improving total cholesterol, LDL, HDL, triglycerides and weight gain [55]. Either alone or combined with rosuvastatin, *L. acidophilus* ATCC 4356 exerted a cholesterol-lowering effect in male rats fed with a high-fat diet for four weeks [67].

In addition to the discussed mechanisms, it is possible to find further lipid metabolism-related regulatory mechanisms attributed to LAB [68] (Table 1). *L. plantarum* CQPC01 (isolated from a fermented Chinese pickle) downregulated the expression of C/EBP- α and PPAR γ mRNA and upregulated the expression of CYP7A1, CPT1, LPL, CAT, SOD1 and SOD2 mRNA in C57BL/6 mice fed with a high-fat diet [68]. Furthermore, in the high-fat diet group, serum cytokine indicators, including IL-6, IL-1 β , TNF- α and IFN- γ , exhibited notably elevated levels, while IL-4 and IL-10 were significantly lower compared to LAB groups [68]. Taken together, LAB could serve as a promising candidate that is capable of alleviating the detrimental impacts of excessive lipids and obesity on the liver, thereby preventing dyslipidemia. Subsequent investigations and clinical trials will be undertaken to substantiate the efficacy of LAB strains in human subjects.

5. Conclusions

LAB are pro-technological, bioprotective and health-promoting cultures used in the food and pharmaceutical industry. In light of current trends in the market and greater consumer awareness of well-being, a detailed assessment of the health effects of LAB has been conducted. In accordance with that, the promising effects of LAB on lipid metabolism are currently attracting more and more attention. LAB are promising candidates for the alleviation of the detrimental impacts of dyslipidemia on cardiovascular health. Many mechanisms have been proposed with respect to the capacity of LAB to regulate blood lipids in different model organisms; however, the exact mechanism is still not very clear. Also, some of these mechanisms are strain dependent, and LAB with probiotic potential, in particular, stand out for lipid regulation. However, it should not be forgotten that lipidomic responses to LAB interventions can vary among individuals due to factors such as genetics, gut microbiome composition, diet and lifestyle habits, as well as the health status of individuals.

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