

Review

The Administration of Probiotics against Hypercholesterolemia: A Systematic Review

Bhagavathi Sundaram Sivamaruthi ¹, Muruganantham Bharathi ¹, Periyannaina Kesika ¹, Natarajan Suganthi ² and Chaiyavat Chaiyasut ^{1,*}

¹ Innovation Center for Holistic Health, Nutraceuticals, and Cosmeceuticals, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand; sivamaruthi.b@cmu.ac.th (B.S.S.); bharathi.m03@gmail.com (M.B.); p.kesika@gmail.com (P.K.)

² Department of Nanoscience and Technology, Alagappa University, Karaikudi 630003, India; suganthyn@alagappauniversity.ac.in

* Correspondence: chaiyavat@gmail.com; Tel.: +66-53-944-340

Featured Application: The current review helps find a better probiotic strain or probiotic mixture to develop probiotic-based adjuvant therapy to control hypercholesterolemia.

Abstract: Hypercholesterolemia is a key factor in the progression of atherosclerosis and cardiovascular disease (CVD). CVD is a significant public health concern with a high death rate. Some of the main factors linked to CVD include genetics and lifestyle. Dyslipidemia has been one of the factors related to the onset of several CVD-related diseases. Several clinicopathological studies have shown a correlation between high cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-c), and CVD development. Probiotics have received a lot of attention for various beneficial effects, especially their ability to reduce blood cholesterol in humans. Probiotics were shown in several investigations to affect hypercholesterolemia by influencing cholesterol biosynthesis. The current review focuses on the human dietary interventions with probiotics and their effects on CVD risk factors and hypercholesterolemia. The outcomes are debatable and consider various parameters such as probiotic strain, dosing frequency, therapeutic response, dietary changes, and so forth. As a result, probiotics have the propensity to become dietary supplements in moderate/severe hypercholesterolemic patients, which significantly reduces the CVD risk.

Keywords: hypercholesterolemia; probiotics; cardiovascular disease; cholesterol

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1. Introduction

Hypercholesterolemia is a widespread hereditary metabolic disease caused by elevated serum levels of low-density lipoprotein cholesterol (LDL-c), leading to premature coronary artery disease [1]. Hypercholesterolemia is one of the leading causes of CVD, and when treated appropriately, it can reduce the risk of CVD-related morbidity and death. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommends LDL-c levels of 100 mg/dL are optimal and >160 is high [2]. It is predominantly caused by the mutation in low-density lipoprotein receptor (LDLR), apolipoprotein B-100 and proprotein convertase subtilisin/Kexin 9 (PCSK9), which leads to decreased LDL-c receptor absorption and evacuation from the circulation [3–5]. Due to the emphasis on lifestyle changes, most patients must use medications to achieve a sufficient decline in LDL-c levels. It also implies that any cholesterol-lowering medication should focus on LDL-c as the primary goal [6]. Statins are the most often prescribed treatment for hypercholesterolemia. Studies have shown that statins lower the risk of heart attack and mortality by 30–40% and lower LDL-c levels by 25–40% [7,8]. Statins are also combined with other small molecules such as ezetimibe, proprotein convertase subtilisin-kexin type 9 inhibitors, bempedoic acid, angiopoietin-like 3 protein inhibitors, and nutraceuticals to

treat hypercholesterolemic patients. At the same time, it develops intolerance [9–12]. However, statin usage is now widely known to be linked to various side effects and symptoms, including myositis, myalgia, rhabdomyolysis, cognitive impairment, liver dysfunction, neuropathy, pancreatitis, sexual development, and semen parameters [13–15].

Ayurveda is one of the oldest well-known medical practices in the world. Ayurvedic formulations are prepared based on the patient's diet, behavioral changes, patient assessment, detoxification, and rejuvenation condition [16–18]. The most widely used herbs to reduce cholesterol are garlic, guggulu, and arjuna [19–21]. However, there is no clear evidence for the direct correlation between herbs and hypercholesterolemia [21]. The extracts of red yeast rice (RYR) are currently the most effective cholesterol-lowering nutraceuticals, containing monacolin K, a reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. It improves the reduction of LDL-c associated with the improved function of the endothelium and arterial stiffness in CVD [22,23]. The prevalent use of RYR medications is still specific, and they should not be included in place of statins or other LDL-c lowering pharmacological approaches as the mainstay potential therapy for efficiently lowering CVD risk, especially in patients with high or very high CVD risk, as current guidelines highly suggested [24]. Due to medications' highest prices and side effects, the desire to use probiotics or mix probiotics treatment as an efficient solution.

In 2002, the World Health Organization described probiotics as “live microorganisms that, when consumed in sufficient quantities, offer the host a therapeutic benefit.” Several scientists from the International Scientific Association formally approved the definition for probiotics and prebiotics [25]. There may be some advantages of daily consumption of microorganisms, such as general health protection and disease prevention [26]. The first microorganism-rich diet is breast milk, containing up to 10^7 microbes per milliliter [27]. The emergence of chronic diseases has been attributed to decreasing everyday consumption of microbial-rich foods [28,29]. According to growing research, probiotics have been shown to decrease LDL-c and enhance the LDL/HDL ratio and lower blood pressure, inflammatory cytokines, insulin sensitivity, and mass index [30,31]. The administration of *Lactobacillus*, a well-known probiotic, may be considered as the essential treatment method for lipid-lowering effects and urinary tract infections [32,33]. As an adjuvant and complementary medicine, probiotics are often supplemented in the diet to manage metabolic and intestinal diseases [34]. The probiotic bacteria Bifidobacteria and lactobacilli may be used as prophylactic or therapeutic agents towards lowering cholesterol levels, enteric pathogens, and control of metabolic disorders in infants and adults. Several strains of the *Lactobacillus acidophilus*, *L. plantarum*, and *Lactococcus lactis* led to a reduced serum cholesterol level due to their ability to assimilate cholesterol available in vitro [35]. The evidence supporting probiotic microorganisms being given prophylactically to preterm newborns to avoid necrotizing enterocolitis, late-onset infection, and mortality is substantial. Still, it's restricted to the *L. reuteri* DSM 17938 species [36].

Probiotic preparations with or without pharmaceutical formulations have been shown to enhance the health of menopausal women [37]. Therefore, probiotic bacteria may benefit human health and maintain a healthy microbial gut [38]. However, additional research is needed to understand how probiotics may benefit the cardiovascular system by decreasing LDL-c substantially and figure out any potential detrimental health effects [39]. This study provides updated information about the reported beneficial effects of probiotic supplementations in hypercholesterolemic subjects.

2. Materials and Methods

The literature search was made in PubMed and web of science using a mixture of keywords 'probiotics and hypercholesterolemia' and 'hypercholesterolemia and cardiovascular disease.' The scientific reports were collected, which were published till 24 February 2021. The Method PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was used in this systematic review to set the selection criteria of the collected

clinical trials. Clinical studies have been included in the study concerning subjects with high and moderate CVD and hypercholesterolemia without the possibility of CVD.

3. Results

From 24 clinical trials, 17 full-text articles were considered after implementing the exclusion criteria and represented in Figure 1.

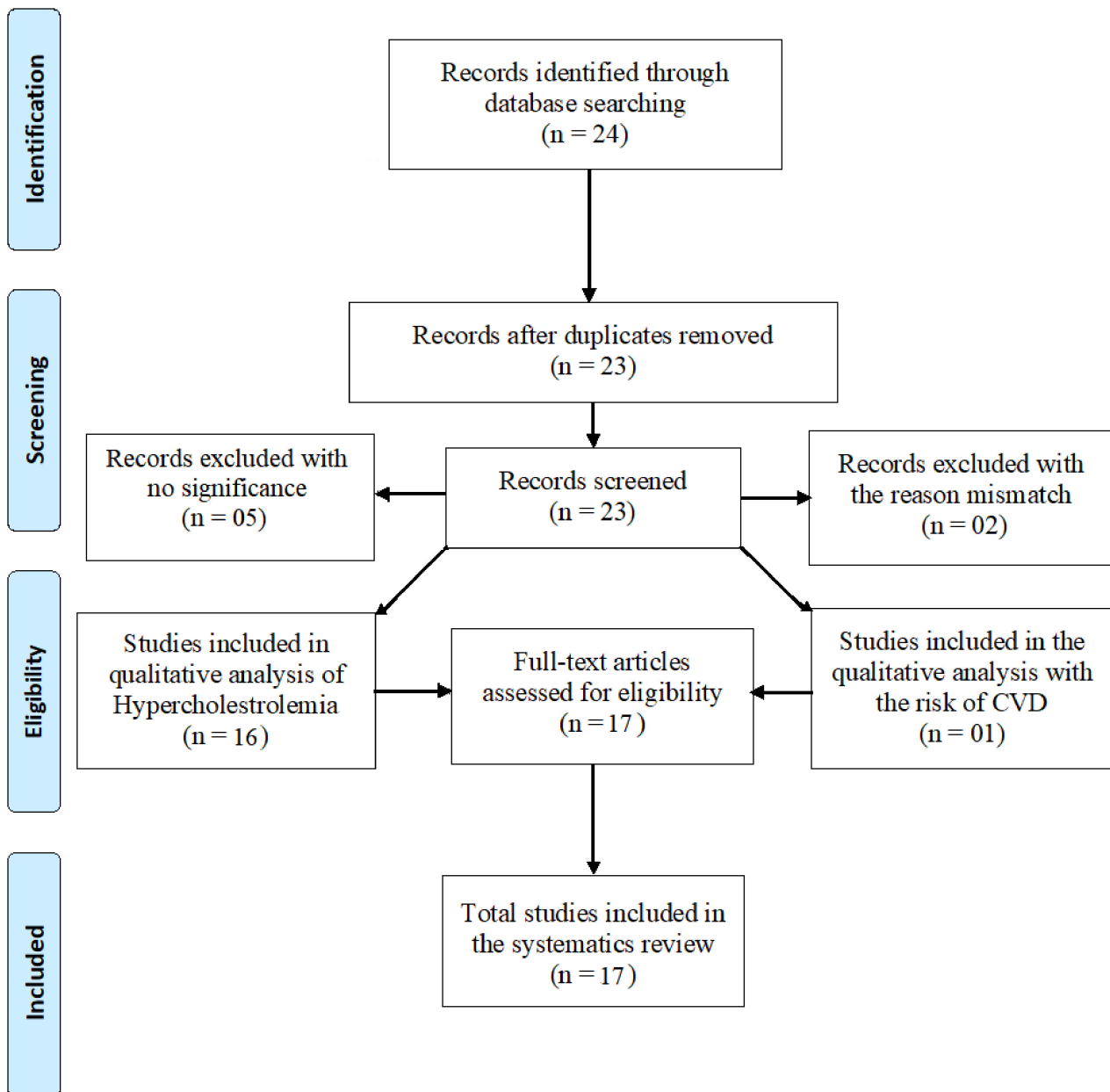


Figure 1. The PRISMA flow chart represents the selection criteria to review the effects of probiotics in hypercholesterolemic subjects.

The details of the reported studies on the influence of probiotics on hypercholesterolemia have been summarized in Table 1. The studies revealed the pilot/randomized controlled trial method to investigate the effects of probiotics in hypercholesterolemic patients. *Lactobacillus* (in nine studies), *Bifidobacterium* (in eight studies), and *Enterococcus* (in two studies) were the most widely studied genera in these reports. *Saccharomyces* and *Propionibacterium* were used in one study. The studies were planned to assess the effects of probiotics on the lipid profile, considered a crucial causative agent of CVD.

The 33 patients with low and without CVD risk were tested with *Bifidobacterium longum* BB536 and red yeast rice, which reduced the LDL-c level. The circulating levels of lathosterol in plasma, a marker of cholesterol synthesis, were also significantly reduced ($p = 0.0206$). It revealed that *B. longum* BB536 and red yeast rice affect the lathosterol biosynthesis [40]. *L. plantarum* ECGC 13110402 was administered with the proper regular diet to 23 people with normal to mildly hypercholesterolemia, which showed a significant difference in the LDL-c concentrations. *L. plantarum* ECGC 13110402 has high bile salt hydrolase activity, which reduced the LDL-c level and may lower the CVD risk [41]. The isoflavone-supplemented soy product fermented with *Enterococcus faecium* CRL 183 and *L. helveticus* 416 was administered to 17 patients. At the end of 42 days, the outcomes were observed that the probiotic intervention significantly reduced the LDL-c level (up to 14.8%) [42].

After eight weeks of daily supplementation to adults with hypercholesterolemia ($n = 11$) found that *Saccharomyces boulardii* var. *boulardii* CNCM I-1079 significantly reduced (about 15.5%) remnant lipoprotein particles. However, there are no significant changes in total cholesterol (TC), LDL-c, HDL-c, triglycerides (TG), TC/HDL-c, and non-HDL-c [43]. *L. reuteri* NCIMB 30242 with bile salt hydrolase functionality decreased the LDL-c and increased the circulating bile acid. *L. reuteri* NCIMB 30242 also increases the serum 25-hydroxyvitamin D (25.5%), which significantly reduces the risk of osteoporosis, CVD, diabetes, and some cancers [44,45]. It may reduce CVD risk and other chronic diseases [46]. However, further experiments are needed to warrant the statement.

The probiotic mixture comprised of *B. lactis* MB 2409, *B. bifidum* MB 109B, and *B. longum* BL04 showed a significant decrease in TC, LDL-c, and TG and an increase in HDL-c levels in dyslipidemic children [47]. Fuentes et al. reported that the supplementation of the probiotic mixture contains three strains of *L. plantarum* which significantly reduced the TC (13.6%), LDL-c, and oxidized LDL-c levels in hypercholesterolemic adults. It significantly reduces the CVD risk in hypercholesterolemic adults [48]. Moroti et al. described that the supplementation of a synbiotic mixture contains *L. acidophilus*, *B. bifidum*, and oligofructose effectively increased HDL-c and reduced the fasting glycemia in elderly people with type 2 diabetes mellitus [49]. The oral administration of *E. faecium* M-74 for one year reduces the LDL-c concentration significantly [50].

Iran Dairy Industries uses *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *Bulgaricus* for making their regular yogurt. Along with those two bacteria, *L. acidophilus* and *B. lactis* were used as a starter to prepare probiotic yogurt. The probiotic yogurt had a cholesterol-lowering effect in healthy hypercholesterolemic subjects. Likewise, the yogurt fermented with *L. acidophilus* and *B. longum* did not lower the TC and LDL-c but increased the level of HDL-c significantly, which helped to maintain the LDL-c and HDL-c ratio [51]. The detailed mechanism discussing crucial probiotics used in cholesterol-lowering effects was not elucidated fully. However, the study needs further clarifications using more volunteers and extended study duration [52].

Table 1. The outcomes of probiotic intervention in hypercholesterolemic subjects.

Authors	Type of the Study	Probiotics Used	Duration	Dose	Study Subjects	The Outcome of the Study
Ruscica et al., 2019 [40]	RCT	Lactoflorene Colesterolo®	12 weeks	1 sachet/day	Low CVD risk and LDL-c (130–200 mg/dL) subjects; 17 females, 16 males; Age = 18–70 years; Probiotic group, n = 16; Placebo group, n = 17	Improved the proatherogenic lipid profile
Costabile et al., 2017 [41]	RCT	<i>Lactobacillus plantarum</i> ECGC 13110402	12 weeks	4 × 10 ⁹ CFU/day	Normal to mild hypercholesterolemic subjects; 34 females, 15 males; Age = 30–65 years; Average BMI = 26.43 kg/m ² ; Probiotic group, n = 23; Placebo group, n = 23	Well-tolerated by the subjects, ECGC 13110402 could reduce CVD risk
Cavallini et al., 2016 [42]	RCT	Isoflavone-supplemented soy product fermented with <i>Enterococcus faecium</i> CRL 183 and <i>Lactobacillus helveticus</i> 416	42 days	11 × 10 ⁹ CFU/day (or) Probiotics with ~100 mg of total isoflavones	Mild hypercholesterolemic male subjects (TC: > 5.17 mmol/L); Age = 45–48; Probiotic soy product (SP) group, n = 17; Isoflavone supplemented probiotic soy product (ISP) group, n = 17; unfermented soy product (USP) placebo group, n = 15	Reduced the CVD risk in ISP group
Ryan et al., 2015 [43]	Pilot	<i>Saccharomyces boulardii</i> var. <i>boulardii</i> CNCM I-1079	8 weeks	5.6 × 10 ¹⁰ CFU twice/day	Hypercholesterolemic subjects; n = 11; 1 female, 10 males; Age = 38.27 ± 8.52 years; Average BMI = 28.02 kg/m ²	Lowered remnant lipoprotein level
Jones et al., 2013 [44]	RCT	<i>L. reuteri</i> NCIMB 30242	9 weeks	2 × 10 ⁹ CFU twice/day	Healthy hypercholesterolemic subjects (LDL-c > 3.4 mmol/L; TG < 4.0 mmol/L; Range of BMI = 22–32 kg/m ²); Probiotic group, n = 66 (38 females, 28 males; Average age = 50.48 ± 14.03 years); placebo group, n = 61 (34 females, 27 males; Average age = 47.59 ± 12.88 years)	Increased the circulating 25-hydroxyvitamin D in the probiotic group
Martoni et al., 2015 [46]	Pilot, RCT	<i>Lactobacillus reuteri</i> NCIMB 30242	4 weeks	Dose for hypercholesterolemic subjects: 3 × 10 ⁹ CFU/day for 1st week; 3 × 10 ⁹ CFU twice/day for 2nd week; 6 × 10 ⁹ CFU twice/day for 3rd week; 9 × 10 ⁹ CFU twice/day for 4th week. Dose for healthy normocholesterolemic subjects: 6 × 10 ⁹ CFU twice/day for 4-week intervention period	Hypercholesterolemic subjects (LDL-C > 3.4 mmol/L, TG < 4.0 mmol/L, Range of BMI = 23.0–32.5 kg/m ² and total BA < 10 mmol/L), n = 10 (males and females between 20–75 years old); Healthy normocholesterolemic male subjects (LDL-C < 3.4 mmol/L, average age = 37.75 ± 8.26 years), n = 4	Significantly influence bile acids metabolism

Table 1. Cont.

Authors	Type of the Study	Probiotics Used	Duration	Dose	Study Subjects	The Outcome of the Study
Guardamagna et al., 2014 [47]	RCT	<i>Bifidobacterium animalis</i> spp. <i>lactis</i> MB 2409, <i>B. bifidum</i> MB 109, and <i>B. longum</i> spp. <i>longum</i> BL04	12 weeks	1×10^9 CFU each strain/day	Dyslipidemic children; Probiotic group, n = 37 (22 females, 15 males; Average age = 11.1 ± 1.8 years; Average BMI = 18.9 ± 4.5 kg/m ²); placebo group, n = 36 (21 females, 15 males; Average age = 11.4 ± 2.4 years; Average BMI = 19.6 ± 3.4 kg/m ²)	Slightly improved the lipid profile in the probiotic group
Fuentes et al., 2013 [48]	RCT	<i>L. plantarum</i> CECT 7527, <i>L. plantarum</i> CECT 7528 and <i>L. plantarum</i> CECT 7529	12 weeks	1.2×10^9 CFU/day	Hypercholesterolemic subjects (Age = 18–65 years); Probiotic group, n = 30, Average BMI = 25.9 ± 0.45 kg/m ² ; Placebo group, n = 30, Average BMI = 26.0 ± 0.44 kg/m ²	Reduced the level of TC, LDL-c, and oxidized LDL-c in the probiotic group. Reduced the CVD risk
Moroti et al., 2012 [49]	RCT	<i>L. acidophilus</i> , <i>Bifidobacterium bifidum</i> , and Oligofructose	30 days	10^8 CFU/mL/200 mL/day; 2 g oligofructose/day	Elderly people with type 2 diabetes mellitus (total cholesterol > 200 mg/dL; TG > 150 mg/dL; glycemia > 110 mg/dL); Synbiotic group, n = 9, Average age = 55.47 ± 2.0 years, Average BMI = 27.70 ± 0.78 kg/m ² ; Placebo group, n = 9, Average age = 56.89 ± 1.7 years, Average BMI = 28.21 ± 0.85 kg/m ²	Significantly increased the HDL and decreased the glycemia in the synbiotic group.
Hlivak et al., 2005 [50]	RCT	<i>Enterococcus faecium</i> M-74 and selenium (Se)	60 weeks	Two $\times 10^9$ CFU/day; 50 μ g of Se	Hypercholesterolemic subjects Probiotic group, n = 20 (17 females, 3 males; Average age = 75.35 ± 1.49 years; Average BMI = 29.40 ± 0.86 kg/m ²); placebo group, n = 18 (14 females, 4 males; Average age = 78.05 ± 1.68 years; Average BMI = 29.08 ± 1.14 kg/m ²)	Reduced serum cholesterol level in the probiotic group
Kiessling et al., 2002 [51]	Cross-over study	Control yogurt containing <i>S. thermophilus</i> , <i>L. lactis</i>); Synbiotic (Probiotic Yogurt containing <i>S. thermophilus</i> , <i>L. lactis</i> , <i>L. acidophilus</i> 145, <i>B. longum</i> 913, and oligofructose)	21 weeks; Group 1 received control yogurt during the 1st period followed by synbiotic during 2nd period followed by control yogurt during 3rd period; Group 2 received control yogurt during the 1st and 2nd period followed by synbiotic during 3rd period; Each period duration is seven weeks.	300 g/day	Hypercholesterolemic (n = 14 females; Average LDL-C = 5.7 ± 1.6 mmol/L, Average TG = 1.3 ± 0.6 mmol/L, Average BMI = 24.2 ± 2.9 kg/m ² , Average TC = 7.6 ± 1.6 mmol/L), and Normocholesterolemic (n = 15 females; Average LDL-C = 4.1 ± 0.4 mmol/L, Average TG = 0.9 ± 0.4 mmol/L, Average BMI = 23.3 ± 3.4 kg/m ² , Average TC = 5.7 ± 0.6 mmol/L) subjects; Group 1, n = 18; Group 2, n = 11;	Long term consumption of yogurt (control and synbiotic) of both groups increased the serum HDL-c level

Table 1. Cont.

Authors	Type of the Study	Probiotics Used	Duration	Dose	Study Subjects	The Outcome of the Study
Ataie-Jafari et al., 2009 [52]	RCT	Probiotic yogurt containing <i>L. acidophilus</i> and <i>Bifidobacterium lactis</i> , <i>S. thermophilus</i> , <i>L. delbrueckii</i> ssp. <i>Bulgaricus</i> ; Regular yogurt containing <i>S. thermophilus</i> , <i>L. delbrueckii</i> ssp. <i>Bulgaricus</i>	Six weeks	3 × 100 g/day	Healthy hypercholesterolemic subjects (Average BMI = 26.1 ± 2.9 kg/m ² , TC = 5.68 ± 0.70 mmol/L, LDL-C = 3.60 ± 0.77 mmol/L, TG = 2.26 ± 0.84 mmol/L); Probiotic yogurt group, Ordinary yogurt group; n = 7 (5 females, 2 males) in each group	Significantly reduced the TC level in the probiotic yogurt group
Xiao et al., 2003 [53]	Pilot study	Control yogurt containing <i>S. thermophilus</i> , <i>L. delbrueckii</i> ssp. <i>Bulgaricus</i> ; Probiotic yogurt containing <i>S. thermophilus</i> , <i>L. delbrueckii</i> ssp. <i>Bulgaricus</i> and <i>B. longum</i> BL1	Four weeks	~10 ⁸ CFU/mL of <i>B. longum</i> BL1; 300 mL/day	Healthy moderate hypercholesterolemic male subjects; Control yogurt group, n = 16 (Age = 28–60 years; TC = 223–277 mg/dL); Probiotic yogurt group, n = 16 (Age = 31–59 years; TC = 221–272 mg/dL)	Lowered serum cholesterol level in the probiotic yogurt group
Larkin et al., 2009 [54]	Cross-over study (study of crossover groups of probiotic cohort or prebiotic cohort)	Soy (S) diet; Probiotic yogurt (PY) containing <i>L. acidophilus</i> , <i>B. bifidum</i> , and <i>Lactobacillus</i> GG; Control yogurt (CY); Prebiotic (resistant starch);	14 weeks; (2-week wash-in period before the study) two 5-week dietary periods (S + CY, S + PY in probiotic Group 1 and vice versa in probiotic Group 2) (S, S + RS in prebiotic Group 1 and vice versa in prebiotic Group 2) separated by a 4-week washout period	1 × 10 ⁸ CFU/day	Mild hypercholesterolemic subjects (men and post-menopausal women) (TC > 5.5 mmol L/1, LDL-c > 3.0 mmol L/1); Age ≥ 45 years; Probiotic group 1 (4 females, 6 males); Probiotic group 2 (2 females, 4 males); Prebiotic group 1 (3 females, 6 males); Prebiotic group 2 (3 females, 3 males)	Significant reduction of TC in probiotic groups. Reduction in TC and LDL-c in prebiotic groups. The lipid-lowering effect observed in probiotic and prebiotic groups are not associated with the involvement of isoflavone
Greany et al., 2004 [55]	RCT	SPI (or) SPI + <i>L. acidophilus</i> DDS-1, and <i>B. longum</i> (or) MPI (or) MPI + <i>L. acidophilus</i> DDS-1, and <i>B. longum</i>	Six weeks	10 ⁹ CFU/day and 26 ± 5 g milk proteins	Healthy mildly hypercholesterolemic (HC) postmenopausal women (n = 25) (TC > 5.17–6.59 mmol/L, 200–255 mg/dL; Average age = 57.8 ± 1.2; Average BMI = 25.7 ± 1.0 kg/m ²); Normocholesterolemic (NC) postmenopausal women (n = 12) (TC < 5.17 mmol/L, <200 mg/dL; Average age = 57.0 ± 1.5; Average BMI = 24.7 ± 0.9 kg/m ²) subjects; n (based on diet) for both soy protein diet and probiotic diet (HC, n = 48; NC, n = 23), and for both milk protein diet and probiotic free diet (HC, n = 48; NC, n = 24).	Soy protein improved the plasma lipid profile, while probiotic intervention does not show any positive response

RCT: Randomized controlled trial; CVD: Cardiovascular disease; Lactoflorene Colesterolo[®]: 1 × 10¹⁰ UFC *Bifidobacterium longum* BB536, Red yeast rice extract (10 mg monacolin K), 16 mg niacin, 20 mg coenzyme Q10; TC: Total cholesterol; LDL-c: Low-density lipoprotein-cholesterol; HDL-c: High-density lipoprotein-cholesterol; TG = Triglyceride; BMI = Body mass index; Probiotic yogurt: *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *Bulgaricus*, and *L. acidophilus* and *B. lactis* were used to prepare probiotic yogurt; SPI: Soy protein isolate; MPI: Milk protein isolate.

4. Discussion

The results were correlated with the study of milk products fermented with *B. longum*, which reduces the serum lipids in healthy moderate hypercholesterolemic male adults [53]. The isoflavone-supplemented soy product fermented with *E. faecium* CRL 183 and *L. helveticus* 416 significantly improves the lipid profile in moderately hypercholesterolemic men subjects. The fermented soy product has an anti-inflammatory effect and activates estrogen-receptor complex mechanisms, thereby reducing the LDL-c level. It reduces the serum LDL-c level, and no significant changes were noted in HDL-c and TG levels [43]. The reported results were established previously by Larkin et al. [54] and Greany et al. [55]. However, this study does not include women subjects to estimate the estrogen effects in women. In addition, pickled mustard greens fermented with lactic acid bacteria were beneficial for lowering cholesterol [56]. The possible benefit of a natural health mixture containing *B. longum* BB536 and RYR (Red Yeast Rice) extract involves two different pathways to facilitate LDL-c and TC reduction. RYR extracts inhibit the liver's cholesterol production, and *B. longum* BB536, by its high bile salt hydrolase function, reduces intestinal cholesterol absorption [40]. In addition, the expression of LXRA and LXRB/NPC1L1 genes plays a critical role in the absorption of intestinal cholesterol in vitro [57–59]. *L. plantarum* ECGC supports the bile acid function, which reduces the cholesterol in mildly hypercholesterolemic adults without any impact on gastrointestinal and gut microbiota that can be possibly the best natural cholesterol-lowering supplement [42]. However, available data indicate that the study does not target severe hypercholesterolemic patients to claim the results are accurate.

S. boulardii var. *boulardii* CNCM I-1079 supplementation lowered remnant lipoprotein. TG-rich lipoproteins are linked to the incidence and development of coronary artery disease, regardless of LDL-c levels [43]. However, the precise lipoprotein lowering mechanisms of *S. boulardii* is undisclosed, and the safety and tolerance of the strain were also not evaluated in this study. The safety risk management criteria are required to measure the safety of probiotics. However, due to the wide variety of microorganisms, it is also important to determine the unique hazards connected with each probiotic, including the risk factors associated with the host and the complex interaction between the probiotic, host, and nutrition constituents [60,61].

L. reuteri NCIMB 30242 was found to raise bloodstream bile acid levels involved in several metabolic activities, including energy balance, lipid metabolism, and inflammatory control [62,63]. The administration of *Bifidobacterium* species claimed to be involved in the control of dyslipidemia in hypercholesterolemic children by improving lipid profile [48]. However, to elucidate the precise molecular mechanisms of action of *Bifidobacterium* in dyslipidemic children, further studies and clinical examination are needed.

L. reuteri NCIMB lowers cholesterol and reduced sterol absorption. Authors have also analyzed the increased circulation of 25-hydroxyvitamin D in serum during *L. reuteri* NCIMB administration and found that the level of vitamin D was increased at the end of the study. The increased vitamin D level improves the proper intestinal colonization of probiotics, prevents pathogenic bacterial invasion, reduces chronic inflammation, and maintains enterocyte cell integrity [45,64,65]. Women who consumed yogurt containing *L. acidophilus* 145 and *B. longum* 913 regularly for six months had higher HDL-c levels and improved LDL-c/HDL-c ratio [52]. Fukushima and Nakano reported that a probiotic mixture diet containing *Bacillus*, *Lactobacillus*, *Streptococcus*, *Clostridium*, *Saccharomyces*, and *Candida* decreased cholesterol synthesis in rats' liver. The *L. acidophilus* strains removed cholesterol by binding to the intestine surface area, making it less obtainable for absorption in the intestine [66]. Likewise, *L. plantarum* KCTC3928 and *L. acidophilus* ATCC 43121 enhanced the conversion of HMG-CoA and cholesterol to mevalonate and bile acid, respectively, reducing the LDL-c level in hypercholesterolemic patients [67–69].

The probiotic mixture of *L. plantarum* CECT 7527, 7528, and 7529 improves the cholesterol profile and reduces the CVD risk in hypercholesterolemic patients [48]. However, the over-growth probiotics mixture may lead to gut dysbiosis, affecting physiology, gut-brain axis function, and other secondary disease outcomes in the host [70,71]. Further studies

are needed to warrant the tolerance and safety of long-term consumption of a mixture of *L. plantarum* strains. The consumption of *L. acidophilus*, *B. bifidum*, and oligofructose increases the HDL-c level, reduces CVD risk, and significantly reduces the blood sugar level [49]. Ataie-Jafari et al. stated that probiotic yogurt consumption significantly decreases the total lipid content and reduces the CVD risk [51].

The administration of *E. faecium* M-74 enriched with selenium reduces the LDL-c level. However, no significant changes were noted in HDL-c and TG levels. Further studies are required to meet the safety and tolerance criteria [50].

The yogurt fermented with *B. longum* BL1 has the highest efficacy in lowering serum cholesterol in moderately hypercholesterolemic subjects [53]. However, there are no significant changes in HDL-c, TC, and TG levels. Furthermore, studies are needed to warrant the efficacy of *B. longum* BL1. Therefore, probiotics are the natural replacements that could be beneficial to improve the lipid profile and reduce the CVD risk without causing adverse effects, unlike statin drugs.

5. Conclusions

Our review concluded that probiotics against hypercholesterolemia could act as an alternative medicine to reduce the CVD risk and other diseases. The obtained clinical trailed data confirm the positive effect of probiotic consumption against hypercholesterolemia. As a result, additional research is needed to understand how probiotics can benefit the cardiovascular system and perhaps other ailments and test out any potential adverse health effects. The present literature review strongly recommends further clinical studies with various mixtures and dosages of probiotics in a greater number of volunteers. Finally, it appears that the potential of probiotics to decrease cholesterol depends on species and strain. *L. acidophilus* was found to reduce cholesterol levels. Similarly, a fermented milk product containing *B. longum* 913 and BL1 reduced the LDL-c cholesterol levels in the blood. The *L. plantarum* and *L. reuteri* lowers LDL-c levels while increasing vitamin D synthesis. Therefore, the strains of *L. acidophilus*, *B. longum*, and *L. plantarum* used in this study may have hypocholesterolemic properties.

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