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Review Article

Global Research Landscape on *Lactobacillus*-Based Interventions for Hypercholesterolemia: A Bibliometric and Systematic Review of Scientific Evidence and Therapeutic Efficacy

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Abstract: The rising prevalence of hypercholesterolemia has increased interest in Lactobacillus-based probiotic interventions as complementary approaches for lipid management. This study synthesizes clinical evidence and research trends to evaluate the efficacy of Lactobacillus supplementation in improving cholesterol profiles. A systematic review was performed following PRISMA 2020 guidelines and registered in OSF with methodological quality assessed using the Critical Appraisal Skills Programme (CASP) Checklist for RCTs, including randomized controlled trials published between 2015 and 2025. Concurrently, a bibliometric analysis of Scopus and PubMed metadata, conducted using Biblioshiny and VOSviewer, characterized global publication trends, leading authors, and thematic structures. The bibliometric analysis demonstrated rapid scientific growth, notable regional clustering in East and Southeast Asia, and evolving research themes related to gut microbiota and metabolic regulation. Seven randomized controlled trials involving 357 adults with dyslipidemia consistently reported reductions in low-density lipoprotein cholesterol (LDL-C) and total cholesterol for several *Lactobacillus* strains, particularly *L. paracasei* and *L. plantarum*. No significant effects were identified for high-density lipoprotein cholesterol (HDL-C) or triglycerides. Mechanistic evidence indicates the involvement of bile salt hydrolase activity, modulation of apolipoproteins, and anti-inflammatory pathways. In summary, this integrated analysis demonstrates that Lactobacillus supplementation is associated with LDL-C reduction ranging from approximately 2.16 to 28.2 mg/dL, with a favorable safety profile, and represents a promising adjunctive strategy for hypercholesterolemia. The results also highlight significant opportunities to strengthen global research collaboration.

Keywords: bibliometric analysis; hypercholesterolemia; *Lactobacillus*; lipid profile; systematic review

1. INTRODUCTION

The global wellness industry has undergone substantial expansion over the past decade, with recent market on the global wellness economy exceeded USD 6.76 trillion in 2024 and continues to grow at an annual rate of 7.9%, propelled mainly by heightened demand for microbiome-modulating products, nutraceuticals, and probiotic-based interventions for cardiometabolic health [1]. This trend is clinically significant, as hypercholesterolemia remains one of the most prevalent modifiable risk factors for cardiovascular disease worldwide [2], and growing patient interest in complementary approaches has coincided with concerns regarding statin tolerability and long-term pharmacological adherence. Probiotics, especially strains of the Lactobacillus genus, are among the fastest-growing categories in the functional food and dietary supplement sectors [2,3,4]. This growth reflects an expanding evidence base suggesting that specific Lactobacillus strains may beneficially influence

lipid metabolism, inflammatory processes, and gut microbial balance—factors integral to cardiometabolic risk modulation [4,5,6,7].

Clinical research suggests that supplementation with Lactobacillus species can significantly reduce serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), although results vary by strain and study design. A meta-analysis of randomized controlled trials found that consumption of probiotic Lactobacillus, particularly *L. plantarum* and *L. reuteri*, was associated with significant reductions in TC and LDL-C levels in human subjects [5,7,8]. However, effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were less consistent [11]. For example, subgroup analyses in this meta-analysis indicate that L. plantarum supplementation significantly reduced TC and LDL-C, with sustained interventions and single-strain formulations showing greater efficacy [12]. Moreover, recent randomized clinical trials demonstrate that supplementation with *Lactobacillus paracasei* TISTR 2593 resulted in significant decreases in serum LDL-C and improvements in markers of oxidative stress and inflammation in subjects with hypercholesterolemia [10,11].

Despite this expanding clinical evidence, several critical knowledge gaps remain. Prior systematic reviews [10,11], have evaluated probiotics as a broad category without isolating Lactobacillus-specific effects or distinguishing strain-level responses across individual lipid parameters, limiting the translational applicability of their conclusions to clinical practice. Furthermore, while meta-analyses have reported overall reductions in TC and LDL-C, inconsistencies across strain types, dosing regimens, and study populations have precluded consensus on optimal strain selection, dose–response relationships, and therapeutic windows across heterogeneous clinical groups [7]. Beyond the clinical dimension, no existing review has integrated bibliometric mapping with clinical synthesis to simultaneously characterize the global research trajectory and the therapeutic evidence base for Lactobacillus-specific interventions in hypercholesterolemia. Such integration is necessary to contextualize where the field stands scientifically, identify dominant research actors and themes, and guide future collaborative priorities. The present study addresses these gaps through a dual-methodology approach combining a PRISMA 2020-compliant systematic review with a comprehensive bibliometric analysis of Scopus and PubMed records from 2015 to 2025.

Bibliometric approaches have become increasingly valuable for elucidating the developmental trajectory of scientific domains, particularly in pharmacological and biomedical research. Prior analyses demonstrate that bibliometrics can effectively capture publication dynamics, conceptual evolution, and the distribution of research actors across countries and institutions [12, 13, 14]. These works collectively illustrate how structured bibliometric mapping provides insights beyond conventional narrative reviews, enabling a more comprehensive characterization of how emerging therapeutic fields mature over time. In this context, applying bibliometric analysis to Lactobacillus-based interventions in hypercholesterolemia research offers a systematic means of situating the expanding evidence base within the broader scientific landscape.

Moreover, although research output on Lactobacillus probiotics has increased significantly over the past decade, comprehensive bibliometric assessments of the structural dynamics of research remain sparse. Existing bibliometric analyses utilizing Scopus data have identified key trends in probiotic research, including rapid growth in publication volume and thematic foci such as viability, functional foods, and Lactobacillus plantarum, suggesting expanding scientific interest but highlighting the need for field-specific synthesis [15,16]. To address these gaps, the present study employs an integrated approach that combines a systematic review of clinical evidence with a bibliometric analysis of global research trends from 2015 to 2025. This dual methodology will enable comprehensive evaluation of Lactobacillus supplementation's effects on lipid outcomes, including LDL-C, TC, HDL-C, and TG, while simultaneously characterizing patterns of scientific productivity, thematic evolution, and global collaborations within the field. By synthesizing both clinical and bibliometric evidence, this review provides a robust, multidimensional understanding of the therapeutic potential of Lactobacillus supplementation and the evolving scientific landscape supporting it.

2. MATERIALS AND METHODS

2.1. Protocol and Registration

The methodology of this systematic review was formulated and implemented in full compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency and reproducibility. The study protocol was prospectively developed and registered on the Open Science Framework (OSF) (Registration DOI: 10.17605/OSF.IO/7W8NP), aiming to mitigate bias, avert administrative redundancy, and ensure transparency of the predefined analytical methodologies. This review combines a conventional systematic synthesis of clinical efficacy with an extensive bibliometric analysis to delineate the scientific environment and evolutionary patterns of Lactobacillus research from 2015 to 2025.

2.2. Eligibility Criteria

Studies were chosen according to the PICO (Population, Intervention, Comparator, and Outcome) framework. The target population comprised adults (aged ≥18 years) with a confirmed diagnosis of hypercholesterolemia or dyslipidemia. The intervention involved supplementation with any Lactobacillus species, whether delivered as a single strain or as part of a probiotic blend, in diverse forms such as capsules, powders, or fermented functional foods. Comparators comprised placebo groups or standard care devoid of probiotic intervention. The primary outcomes of interest were alterations in Low-Density Lipoprotein Cholesterol (LDL-C) and Total Cholesterol (TC). In contrast, the secondary objectives were High-Density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG). Only peer-reviewed Randomized Controlled Trials (RCTs) published from January 2015 to December 2025 were included. Pediatric populations, pregnant women, and individuals on unstable lipid-lowering medications were excluded to ensure cohort homogeneity.

2.3. Information Sources and Search Strategy

A systematic search was conducted across three principal electronic databases, namely Scopus, PubMed, and ScienceDirect, to ensure a thorough identification of relevant studies. The search timeframe was explicitly delineated from January 2015 to December 2025 to encompass recent developments in probiotic research and cholesterol management. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using Boolean operators (AND/OR). To ensure reproducibility, the full search strings and the complete list of search terms used for each database are detailed in Appendix Table 1. To further mitigate the possibility of overlooking eligible trials, a manual "snowballing" search was conducted by examining the reference lists of all included studies and pertinent past reviews.

2.4. Study Selection Process

After preliminary record identification, all citations were imported into reference management software to eliminate duplicates systematically. The selection process was executed in two autonomous phases by two evaluators to reduce selection bias. Initially, titles and abstracts were evaluated against the established PICO criteria. During the second step, the whole texts of potentially pertinent articles were obtained and meticulously examined to verify compliance with inclusion criteria. Discrepancies among the reviewers about study eligibility were reconciled through consensus or by consulting a third senior investigator. The ultimate count of studies incorporated in the qualitative synthesis, along with the explicit rationale for the exclusion of full-text publications, is thoroughly recorded in the PRISMA 2020 Flow Diagram.

2.5. Data Extraction and Management

Data from the included studies were extracted using a consistent, pre-tested data collection instrument to ensure uniformity. The collected datasets included study characteristics (first author, year, country, and design), participant demographics (population, sample size, and age), and specific intervention parameters (strain type, CFU dosage, administration frequency, and vehicle/formulation). Quantitative outcome data, encompassing Mean and Standard Deviation (SD)

for all lipid markers at baseline and post-intervention, together with 95% Confidence Intervals (CI) and p-values, were systematically documented to enable subsequent synthesis.

2.6. Risk of Bias Assessment

Due to anticipated heterogeneity in intervention characteristics, study populations, and outcome measures, a narrative synthesis approach was selected for this systematic review rather than a statistical meta-analysis. The methodological quality of the included randomized controlled trials was assessed using the Critical Appraisal Skills Programme (CASP) Checklist for RCTs. This validated tool evaluates 11 key aspects of study quality, such as clarity of the research question, adequacy of randomization, participant accountability, blinding procedures, baseline comparability, equal treatment, comprehensiveness of reporting, precision of estimates, and applicability of findings. The vote-counting method used to summarize the direction of effect across studies included a step in which findings from higher-quality studies were given greater weight in the overall synthesis and interpretation. This approach ensured that both the direction and quality of the evidence were incorporated into the narrative synthesis's conclusions.

2.7. Bibliometric Analysis

The bibliometric analysis was conducted using 191 documents retrieved from Scopus and PubMed. All records were exported in compatible formats and subsequently merged using the "merge collection" utility within Biblioshiny (version 5.0), the web-based interface of the Bibliometrix R package [14,15]. The merged dataset was standardized and consolidated into a single .xlsx file to ensure uniformity of metadata fields. Biblioshiny was employed as the primary analytical environment to compute descriptive bibliometric indicators by "analysis" and "synthesis" utilities to generate graphical visualizations.

To enhance the robustness of network-based insights, VOSviewer (version 1.6.20) was used to construct complementary visual analyses, including co-authorship networks and co-occurrence term maps [16,17]. These analyses used only Scopus metadata due to its format compatibility and superior completeness of its citation fields. Before visualization, metadata was cleaned for duplicated author names, inconsistent keyword spellings, and fragmented affiliations. All visual outputs were exported as .png files at high resolution, while numerical results and processed metadata were saved as .xlsx files for further interpretation and reproducibility.

2.8. Data Synthesis

The data synthesis for this study was performed using a dual-analytical framework, combining a qualitative systematic synthesis with an extensive bibliometric assessment. The comprehensive synthesis aimed to assess the clinical efficacy and safety of different Lactobacillus strains in the management of hypercholesterolemia. The essential parameters generated included fundamental lipid indicators, including Low-Density Lipoprotein Cholesterol (LDL-C) and Total Cholesterol (TC). Moreover, specialized biomarkers and secondary outcomes, including High-Density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG), identified during data extraction, were integrated to provide a comprehensive perspective on the probiotic's metabolic effects. The results were classified according to the specific bacterial strains utilized (e.g., L. plantarum versus L. paracasei), the dosage delivered in Colony Forming Units (CFU), and the intervention length, which generally spanned from 6 to 12 weeks. Furthermore, the synthesis accounted for various delivery formats, including capsules, fermented milk, and yoghurt.

A bibliometric analysis was conducted to delineate the intellectual framework and global research trends in the topic from 2015 to 2025. The metadata from the acquired literature were analyzed using VOSviewer and the Biblioshiny R package from Bibliometrix to depict academic networks. This analysis incorporated term co-occurrence mapping to delineate fundamental research themes and their temporal progression. The bibliometric component assessed research production by analyzing metadata, publications, citation growth, co-authorship, and main topic synthesis. This study integrates two methodologies to deliver a comprehensive clinical evaluation of Lactobacillus

supplementation and a broad analysis of the progression of the scientific literature on probiotic treatments for cholesterol management over the last 15 years.

3. RESULTS AND DISCUSSION

3.1. Study Selection and Bibliometric Analysis Results

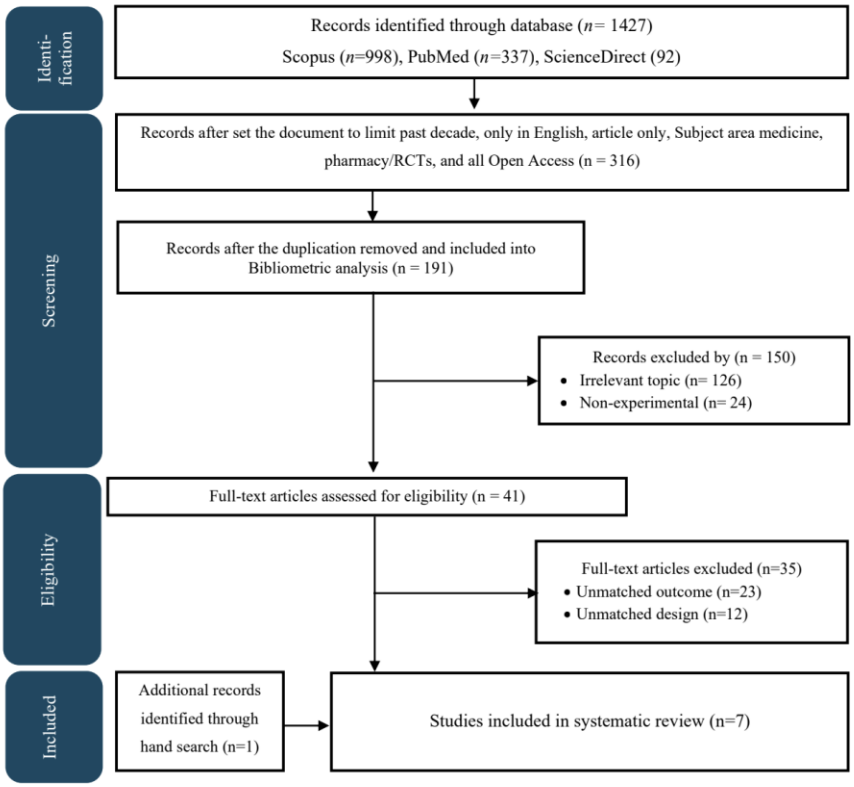


Figure 1. PRISMA Flowchart

The study selection procedure was conducted in strict compliance with the PRISMA 2020 principles to guarantee transparency and reproducibility. A thorough search of electronic databases produced a substantial quantity of initial records, which were then processed through a multi-stage screening procedure that included duplicate elimination and subsequent title and abstract assessment. In accordance with the established PICO criteria, appropriate full-text papers were examined, leading to the final inclusion of research that met all methodological standards. The methodical process of article identification, screening, and the particular grounds for exclusion are clearly encapsulated in the PRISMA Flow Diagram (Figure 1).

3.1.1. Publication Trends and Research Growth

The bibliometric assessment of 191 publications issued between 2015 and 2025 indicates that Lactobacillus-based interventions for hypercholesterolemia constitute a rapidly emerging research domain, with *Frontiers in Microbiology*, *Nutrients*, and *Gut Microbes* emerging as the most influential scholar disseminations in the field. The field is characterized by an annual growth rate of 15.15%, with a marked escalation in scientific production beginning in 2020 and sustained through 2025. The average document age of 4.25 years and mean citation count of 24 per publication collectively reflect both the novelty of the topic and its increasing scientific visibility. The observed decline in average citations per year despite rising publication volume is consistent with citation lag as a common phenomenon in expanding fields where recently published works have not yet accumulated sufficient time within the citable window to garner proportional citation impact [15,24-26]. These growth indicators position Lactobacillus-based hypercholesterolemia research within the early developmental phase of scientific maturation, underscoring its conceptual novelty, clinical relevance,

and capacity to attract sustained multidisciplinary investigation in the coming decade. Publication trends is summarized in Table 1.

Table 1. Integrated Bibliometric Overview

Description	Results
Timespan	2015:2025
Sources (Journals, Books, etc)	95
Documents	191
Annual Growth Rate (%)	15.15
Document Average Age	4.25
Average Citations per Document	24
Keywords Plus	2767
Author's Keywords	664
Authors	1254
Authors of Single-Authored Documents	1
Co-Authors per Document	8.21
International Co-Authorships (%)	1.571

3.1.2. Global Research Distribution and Collaboration

Analysis of authorship, institutional affiliation, and country-level contributions as illustrated in Figure 2 identifies a geographically concentrated thus internationally networked research landscape. Research output is predominantly anchored in Asia, with Malaysia, Thailand, and China emerging as the primary national hubs, complemented by institutional contributors including Universiti Kebangsaan Malaysia, Chiang Mai University, and the Thailand Institute of Scientific and Technological Research (TISTR). While cross-national linkages exist, such as those connecting New Zealand and Saudi Arabia through Auckland University of Technology, and Brazil and the United Kingdom through UNESP, international co-authorship remains limited at 1.571%, indicating that most research output arises from internally concentrated, institution-level networks rather than global collaborative structures [27]. This regional concentration has direct implications for the clinical evidence base: findings derived predominantly from Asian populations may not fully capture the lipid profiles, dietary patterns, and gut microbiome compositions of Western, African, or Latin American cohorts, thereby limiting the generalizability of current evidence to more diverse clinical populations. Strengthening international research collaboration therefore represents both a structural priority for the field and a prerequisite for producing more globally applicable clinical guidance on Lactobacillus-based interventions.

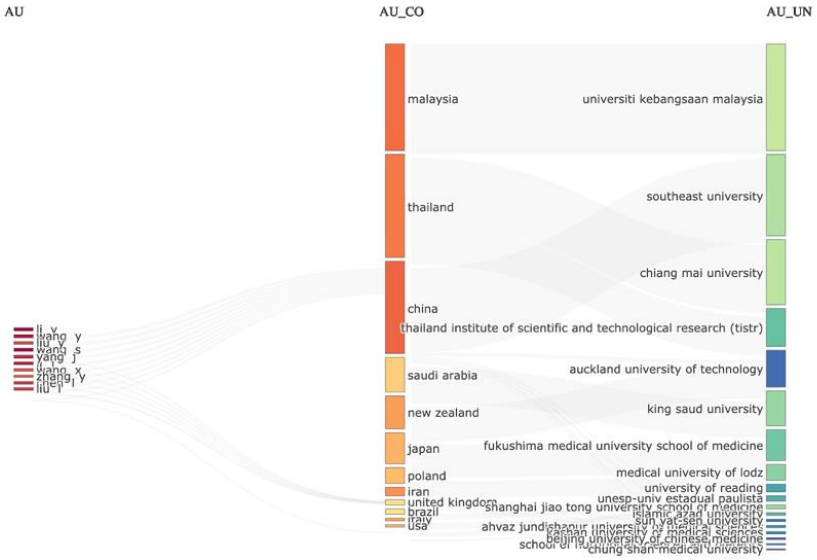


Figure 2. Three-Field Plot of Authors, Countries, and Affiliations

3.1.3. Thematic Evolution and Emerging Research

Co-occurrence, document coupling, and factorial analyses of author keywords and indexed terms reveal three converging thematic clusters that define the intellectual organization of this research domain. Co-occurrence analysis, as shown in Figure 3, anchored by large thematic clusters of *gut microbiota*, *probiotics*, and primary metabolic outcomes, with *Lactobacillus* and its key strains, particularly *L. plantarum* and *L. paracasei*, positioned as consistently interconnected nodes alongside lipid-related parameters such as *atherosclerosis*, *hyperlipidemia*, and *lipid profile* [28-31]. Document coupling analysis reinforce the methodological foundation of the field by encompassing strain-specific RCT designs, biochemical endpoint assessments, and demographic stratification. Factorial approach captures systemic metabolic and inflammatory regulation, linking gastrointestinal microbiome modulation with biomarkers such as cholesterol, triglycerides, C-reactive protein, and glycated hemoglobin. The emergence of metabolomics within these clusters signals a growing interest in elucidating the molecular signatures underlying probiotic-mediated lipid regulation. Critically, there is translational gap between mechanistic microbiota studies and clinical RCTs, a divide that the systematic review component of this study is well positioned to address. Collectively, these thematic patterns confirm that Lactobacillus-based hypercholesterolemia research is scientifically grounded and clinically oriented, yet remains in a phase of active maturation requiring more standardized, strain-specific, and internationally collaborative investigation.

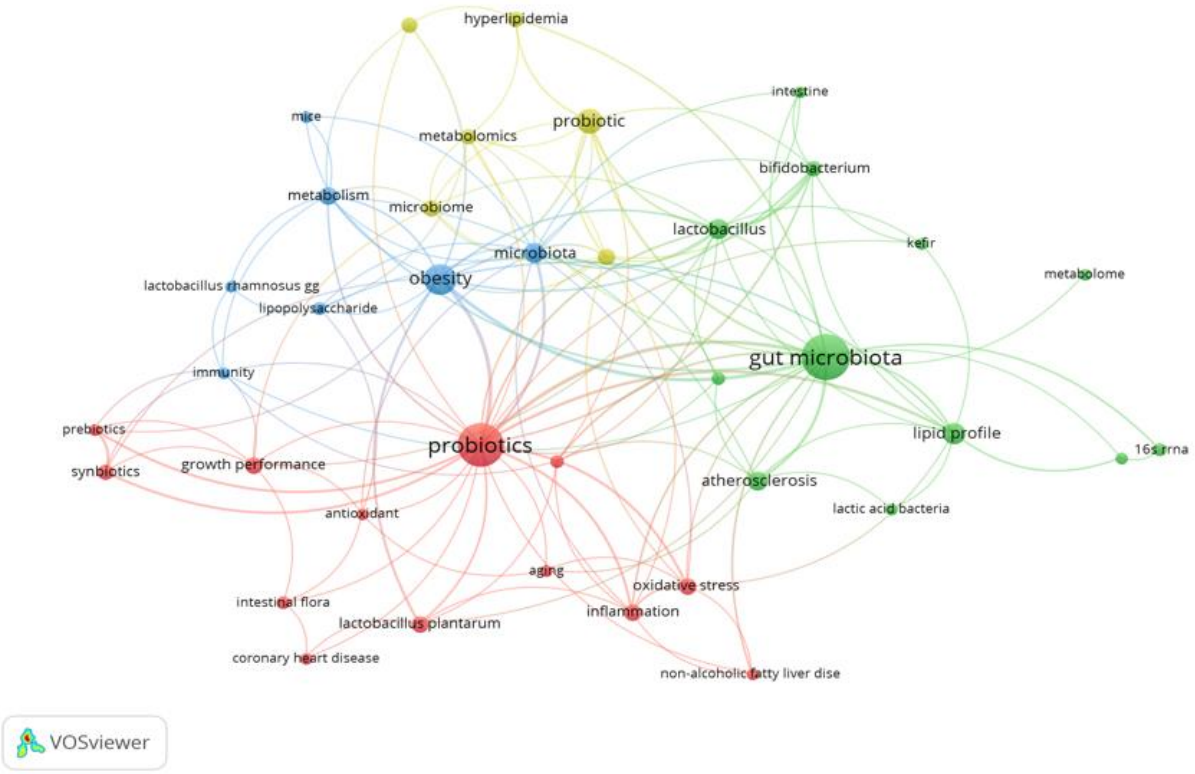


Figure 3. Co-Occurrence Network

3.2. Study Characteristics of Included Study on Systematic Reviews

The characteristics of the included papers (Table 2) indicate a varied and international study landscape, encompassing both Asian and European locations. Research is notably concentrated in Thailand, China, and South Korea. Substantial contributions were also recognized from Europe, particularly the United Kingdom and Germany, as well as from South America (Brazil). This global distribution indicates broad scientific interest in substantiating the cardiovascular benefits of Lactobacillus as a non-pharmacological approach to cholesterol management across diverse ethnic and dietary contexts. The research populations primarily consisted of persons aged 18 to 70 years

diagnosed with mild to moderate hypercholesterolemia or dyslipidemia. Sample sizes varied considerably across the trials, ranging from small-scale pilot studies with 16 to 30 individuals to larger clinical investigations involving over 100 people. This variation offers a comprehensive perspective, encompassing basic mechanistic viability to broader clinical effectiveness. Concerning probiotic interventions, *Lactocaseibacillus paracasei* (previously *Lactobacillus paracasei*) and *Lactobacillus plantarum* were identified as the most extensively studied species.

The supplementation period was generally uniform, typically 6 to 12 weeks. This period is regarded as a conventional clinical term adequate to notice significant changes in serum lipid profiles and possible alterations in the gut microbiota. The distribution modalities for these probiotics were varied, encompassing both pharmaceutical and food-based methodologies. Capsules were the predominant delivery method, favored for their capacity to deliver and stabilize, forming Unit (CFU) dosages that often ranged from 1.05×10^9 to 4×10^9 CFU per day. Moreover, numerous studies investigated functional food matrices, including fermented milk, yogurt, and soy products. The effectiveness of *Lactobacillus* in many media across various media is due to its adaptability as both a therapeutic supplement and a functional dietary element for enhancing lipid metabolism.

3.3. Risk of Bias Assessment

Assessment using the CASP checklist showed that all seven studies had a robust research design, with clear objectives and appropriate random selection of participants. Six studies used a double-blind design, while Jiang et al. [32] used a single-blind design. Most studies maintained high participant retention, with follow-up rates from 84% to 100%. Intention-to-treat analysis was used in six studies, while Kerlikowsky et al. [33] used a different analytical method. Four studies explicitly described allocation concealment procedures, while three did not provide sufficient detail. Baseline characteristics were generally comparable across groups, though minor differences emerged in three studies, including lower baseline LDL cholesterol, reduced diastolic blood pressure, and higher fasting blood glucose in the probiotic group. A key limitation was the lack of transparency regarding whether outcome assessors were blinded to group assignments. Six studies detailed their sample size determination, while Nuankham et al. [14], a pilot study, did not. Overall, these studies were assessed as moderate to high quality with low to moderate risk of bias, supporting the reliability of their findings.

3.4. Effect of Lactobacillus on Hypercholesterolemia

This systematic review synthesized evidence from seven randomized controlled trials to evaluate the cholesterol-lowering efficacy of Lactobacillus supplementation in individuals with mild to moderate hypercholesterolemia. The included studies examined various Lactobacillus strains, including *L. paracasei, L. plantarum, and L. acidophilus*, as well as combination formulations. Dosages ranged from 1.05×10^9 to 4×10^{10} CFU per day, administered for 6 to 12 weeks. Owing to considerable heterogeneity in intervention characteristics and study populations, a structured narrative synthesis with individual effect sizes was performed. Findings were considered supportive when at least 70% of studies reported consistent effects. Table 3 presents the impact of Lactobacillus supplementation on hypercholesterolemia, detailing outcomes such as LDL-C, HDL-C, triglycerides, and total cholesterol. The following subsections discuss the effects on each specific lipid parameter and atherosclerosis-related biomarker.

Table 2. Study characteristics included in systematic reviews

Reference	Country	Design	Population	N	Strain	Duration	CFU/dose	Frequency, Form	Comparator /control
[13]	Thailand	Randomized, double-blind, placebo-controlled clinical trial	Hypercholesterolemic subjects, aged 30–65 years	30 participants (Probiotics: 15; Placebo: 15)	*Lactobacillus paracasei* TISTR 2593	12 weeks	1 x 10^9 CFU per day	Once daily (at bedtime), Freeze-dried powder in capsules	Maltodextrin capsule (Placebo)
[34]	United Kingdom	Double-blind, randomized, placebo-controlled, parallel-group, pilot study	Adult (35–70 years)	Total analyzed: 16 (Active: 8; Placebo: 8)	*Lactobacillus plantarum* ECGC 13110402	6 weeks of treatment (followed by 3 weeks washout)	4 x 10^9 CFU per day	Once daily (after lunch), Capsular format (DR1 vegetable capsule)	Identically looking capsule containing corn starch (placebo)
[14]	Thailand	Single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study	Hypercholesterolemic adults, aged 30–65 years	22 participants (Probiotics: 12; Placebo: 10)	*Lactocaseibacillus paracasei sup. paracasei* TISTR 2593	90 days	1.05 x 10^9 CFU per day	Three capsules per day, Freeze-dried powder in capsules	Maltodextrin capsule (placebo)
[33]	Germany	Randomized, double-blinded, placebo-controlled clinical trial	Healthy adults with untreated elevated LDL-C, Mean age 53.6 years	86 participants (LP group: 43, Placebo group: 43)	Mixture of *Lactobacillus plantarum* CECT7527, CECT7528, and CECT7529	12 weeks	1.2 x 10^9 CFU per day	Once daily, Capsules	Placebo (maltodextrin)
[35]	Brazil	Randomized, double-blind, placebo-controlled clinical trial	Moderately hypercholesterolemic men, mean age 43.1 ± 9.3 years	30 participants (probiotics group: 15; placebo group:15)	*Enterococcus faecium* CRL 183 and *Lactobacillus helveticus* 416	6 weeks	10^9 CFU of each strain per day	Once daily (200 mL), Probiotic soy product (fermented)	Unfermented soy product (Placebo)
[32]	China	Randomized, single-blind, controlled intervention study	Dyslipidemia subjects, aged 18–70 years	109 participants (probiotics group: 54; control group: 55)	*Lactobacillus paracasei* N1115	12 weeks	1.1 x 10^8 CFU/g	Once daily, a Probiotic fermented milk product	Routine care (usual diet and physical activity) without probiotics
[36]	Thailand	Randomized double-blind controlled trial	Hypercholesterolemic healthy adults	64 completed (Probiotics: 31; Placebo: 33)	*Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Infloran®)	6 weeks	1 x 10^9 CFU of each strain	Three times daily, Capsule	Placebo capsule (identical in size and colour)

Table 3. Study characteristics included in systematic reviews

Ref	Outcome	Unit	Intervention group				Control group				95% CI	p-value	Direction
			Baseline	Post	Δ	Cohen's d	Baseline	Post	Δ	Cohen's d			
[13]	LDL-C	mg/dL	161.07 ± 22.25	144.13 ± 17.58	−16.94	−0.845	158.47 ± 18.00	159.00 ± 16.03	+0.53	+0.031	NR	0.022	S
	HDL-C	mg/dL	53.13 ± 11.13	56.67 ± 11.11	+3.54	+0.318	54.73 ± 11.37	51.93 ± 9.47	−2.80	−0.268	NR	0.224	NS
	TG	mg/dL	129.87 ± 52.87	128.80 ± 50.80	−1.07	−0.021	128.73 ± 47.97	127.67 ± 38.07	−1.06	−0.024	NR	0.945	NS
	Total CHOL	mg/dL	240.20 ± 23.32	226.53 ± 21.04	−13.67	−0.616	239.00 ± 18.23	236.47 ± 20.30	−2.53	−0.131	NR	0.197	NS
[34]	LDL-C	mmol/L	4.55 ± 1.10	4.00 ± 1.34	−0.55	−0.449	4.10 ± 0.92	4.60 ± 1.69	+0.50	+0.367	(0.57, 1.89)	0.001	S
	HDL	mmol/L	1.46 ± 0.41	1.24 ± 0.35	−0.22	−0.577	1.81 ± 0.56	1.79 ± 0.44	−0.02	−0.040	(0.03, 0.43)	0.03	S
	TG	mmol/L	1.49 ± 0.88	1.34 ± 0.71	−0.15	−0.188	1.13 ± 0.46	1.29 ± 0.67	+0.16	+0.278	(-0.21, 0.68)	0.28	NS
[14]	LDL-C	mg/dL	155.15 ± 27.20	137.63 ± 29.20	−17.52	−0.621	151.61 ± 34.61	163.00 ± 39.90	+11.39	+0.305	(-30.32, 2.08)	0.027	S
	HDL-C	mg/dL	53.35 ± 8.46	55.85 ± 10.83	+2.50	+0.257	52.48 ± 7.41	57.00 ± 10.90	+4.52	+0.485	(-2.37, 12.49)	0.870	NS
	TG	mg/dL	143.50 ± 19.31	151.21 ± 41.42	+7.71	+0.239	146.08 ± 36.56	157.14 ± 66.99	+11.06	+0.205	(-21.53, 22.71)	0.115	NS
	Total CHOL	mg/dL	233.50 ± 15.39	227.75 ± 33.45	−5.75	−0.221	231.48 ± 25.20	246.70 ± 40.42	+15.22	+0.452	(-18.06, 22.64)	0.876	NS
[33]	LDL-C	mg/dL	176.7 ± 18.0	164.7 ± 23.4	−12.0	−0.575	176.0 ± 15.6	170.8 ± 24.3	−5.2	−0.255	(-13.0, 1.1)	0.098	NS
	HDL-C	mg/dL	57.7 ± 14.6	57.0 ± 13.5	−0.7	−0.050	56.9 ± 16.3	57.1 ± 15.6	+0.2	+0.013	(-2.7, 3.5)	0.793	NS
	TG	mg/dL	116.5 ± 52.8	103.7 ± 42.1	−12.8	−0.268	109.1 ± 43.1	105.7 ± 57.6	−3.4	−0.067	(-23.4, 12.0)	0.523	NS
	Total CHOL	mg/dL	257.6 ± 26.6	241.9 ± 30.6	−15.7	−0.548	254.7 ± 23.7	248.9 ± 34.0	−5.8	−0.198	(-15.5, 1.5)	0,106	NS
[35]	LDL-C	mg/dL	153.2 ± 20.4	140.2 ± 22.1	−13.0	−0.611	149.6 ± 23.1	151.3 ± 22.5	+1.7	+0.075	NR	<0.05	S
	HDL-C	mg/dL	40.5 ± 8.2	41.8 ± 7.9	+1.3	+0.161	41.2 ± 7.5	40.8 ± 7.2	−0.4	−0.054	NR	>0.05	NS

[32]	TG	mg/dL	173.5 ± 65.4	161.4 ± 60.2	−12.1	−0.193	179.4 ± 70.1	182.1 ± 68.3	+2.7	+0.039	NR	>0.05	NS
	Total CHOL	mg/dL	228.4 ± 23.3	214.3 ± 25.1	−14.1	−0.582	226.7 ± 22.8	228.5 ± 21.6	+1.8	+0.081	NR	<0.05	S
	LDL-C	mmol/L	3.58 ± 0.81	3.46 ± 0.80	−0.12	−0.149	3.47 ± 0.84	3.57 ± 0.94	+0.10	+0.112	NR	0,046	S
	HDL-C	mmol/L	1.28 ± 0.36	1.23 ± 0.30	−0.05	−0.151	1.35 ± 0.40	1.31 ± 0.34	−0.04	−0.108	NR	0.334	NS
	TG	mmol/L	1.86 ± 0.96	1.76 ± 1.05	−0.10	−0.099	1.76 ± 0.95	1.67 ± 0.81	−0.09	−0.102	NR	0.548	NS
	Total CHOL	mmol/L	5.42 ± 0.98	5.23 ± 0.89	−0.19	−0.203	5.36 ± 0.86	5.39 ± 0.95	+0.03	+0.033	NR	0.038	S
[36]	LDL-C	mg/dL	158.1 ± 38.8	153.9 ± 44.3	−4.2	−0.101	159.4 ± 26.7	182.1 ± 39.3	+22.7	+0.676	-48.9, -7.5	<0.01	S
	HDL-C	mg/dL	56.5 ± 16.5	52.0 ± 10.2	−4.5	−0.328	60.7 ± 18.0	59.1 ± 16.0	−1.6	−0.094	-13.9,-0.3	0.04	S
	TG	mg/dL	175.9 ± 148.2	148.0 ± 97.4	−27.9	−0.222	151.0 ± 52.4	145.0 ± 55.6	−6.0	−0.111	-37.0, 41	0.91	NS
	Total CHOL	mg/dL	237.2 ± 31.7	212.7 ± 41.4	−24.5	−0.664	231.0 ± 25.2	252.8 ± 34.2	+21.8	+0.726	-59.0, -21.2	<0.001	S

Note: NR (not reported), S (significant), NS (not significant), Equation for d = [(Post − Baseline) / $\sqrt{[(SD^2_{pre} + SD^2_{post})/2]}$, negative value = decrease in rate, positive value = increase in rate, value ≈ 0 = minimal change (trivial), Interpretation |d|: <0.2 = trivial | 0.2–0.5 = small | 0.5–0.8 = medium | >0.8 = large.

3.4.1. Effect on Low-Density Lipoprotein (LDL-C)

This systematic review demonstrates a clinically meaningful reduction in LDL-C levels associated with Lactobacillus supplementation, as evidenced by multiple randomized controlled trials. Of the seven studies included, six reported statistically significant reductions in LDL-C within the intervention group, as further corroborated by the within-group effect sizes (Cohen's d) calculated for this review. The largest within-group effect on LDL-C was observed in Khongrum et al. [13], where *Lactobacillus paracasei* TISTR 2593 supplementation produced a Cohen's d of −0.845 (large effect), corresponding to a mean decrease of 16.94 mg/dL ($p = 0.022$) over 12 weeks. Notably, the placebo group showed a trivial effect (d = +0.031), underscoring the specificity of the intervention. Similarly, Nuankham et al. [14] demonstrated a medium-to-large effect (d = −0.621) with a 17.52 mg/dL reduction ($p = 0.027$), while the control group exhibited a small positive drift (d = +0.305), strengthening attribution of the reduction to the probiotic. Keleszade et al. [34] reported a small-to-medium effect (d = −0.449) corresponding to a 0.55 mmol/L decrease ($p = 0.001$; ~13.75% from baseline), while the placebo group showed a contrasting positive effect (d = +0.367), amplifying the net between-group difference. Cavallini et al. [35] documented a medium effect (d = −0.611) with a 13.0 mg/dL reduction ($p < 0.05$), against a trivial placebo change (d = +0.075). Kerlikowsky et al. [33] reported a medium effect size (d = −0.575) despite non-significance (−12.0 mg/dL, $p = 0.098$), likely due to limited statistical power and responder heterogeneity linked to baseline gut microbiome composition. Jiang et al. [32] showed a trivial-to-small effect (d = −0.149) but statistically significant reduction (−0.12 mmol/L, $p = 0.046$), consistent with the lower CFU dose employed. Rerksuppahol et al. [36] produced a small within-group effect (d = −0.101; −4.2 mg/dL) in the intervention arm, yet the control group exhibited a large positive effect (d = +0.676; +22.7 mg/dL), yielding a net treatment difference of approximately 26.9 mg/dL and demonstrating a strong protective role against spontaneous LDL-C rise in the pediatric cohort.

Based on another study, the supplementation of Lactobacillus has been consistently demonstrated to reduce LDL-C levels in humans through multiple interrelated mechanisms. One of the primary pathways involves bile salt deconjugation, whereby Lactobacillus strains enzymatically deconjugate bile acids in the intestinal lumen, thereby impairing cholesterol reabsorption and increasing its fecal excretion [39,40]. Concurrently, certain strains such as Lactobacillus fermentum have been shown to upregulate the production of short-chain fatty acids (SCFAs), particularly propionate and butyrate, which inhibit hepatic cholesterol synthesis through suppression of the mevalonate pathway [38]. Beyond these direct metabolic effects, synbiotic formulations incorporating Lactobacillus have been reported to facilitate the hepatic transport of cholesterol in the form of cholesteryl esters for subsequent hydrolysis, further contributing to the reduction of circulating plasma cholesterol levels [39]. Notably, the cholesterol-lowering efficacy of Lactobacillus appears to be potentiated when combined with prebiotics; for instance, the co-administration of Lactobacillus salivarius with fructooligosaccharides (FOS) yielded more pronounced reductions in LDL-C compared to probiotic supplementation alone, underscoring a synergistic interaction between the probiotic and its prebiotic substrate [40]. In addition to its lipid-lowering properties, Lactobacillus supplementation has been associated with broader systemic benefits, including reduced triglyceride levels, enhanced immune responses, and favorable modulation of gut microbiota composition [43,44], collectively positioning it as a multifaceted intervention for cardiometabolic health.

3.4.2. Impact on High-Density Lipoprotein (HDL-C)

The impact of Lactobacillus supplementation on HDL-C levels demonstrated variability across studies, with within-group Cohen's d values providing additional context beyond statistical significance. Keleszade et al. [34] observed a medium negative effect (d = −0.577) in the intervention group (−0.22 mmol/L, $p = 0.03$), while the placebo group showed only a trivial decline (d = −0.040). This outcome indicates that the probiotic intervention likely contributed to the reduction in HDL-C. Similarly, Rerksuppahol et al. [36] reported a small-to-medium decline (d = −0.328) in the intervention arm, compared to a trivial change in the placebo group (d = −0.094, $p = 0.04$), resulting in a net treatment difference of approximately 2.9 mg/dL. The remaining five studies reported trivial-to-small

and non-significant effects. For instance, Khongrum et al. [13] identified a small positive trend in the intervention group (d = +0.318) and a small negative trend in the placebo group (d = −0.268, p = 0.224). Nuankham et al. [14] found small positive trends in both groups (d = +0.257 and d = +0.485, p = 0.870). Kerlikowsky et al. [33] and Jiang et al. [32] reported near-zero effects on HDL-C in both groups (d values between −0.151 and +0.013). Cavallini et al. [35] observed a small positive intervention effect (d = +0.161) with a negligible placebo effect (d = −0.054, p > 0.05). The predominance of trivial-to-small HDL-C effects is consistent with previous evidence suggesting that Lactobacillus interventions primarily influence atherogenic lipoproteins rather than reverse cholesterol transport. Furthermore, Cavallini et al. [35] proposed that bile salt hydrolase (BSH) activity selectively affects LDL-related pathways without significantly altering HDL-mediated transport, which may provide a clinical advantage over pharmacological agents that reduce both lipoprotein fractions.

Another study revealed that the effect of Lactobacillus supplementation on HDL-C remains inconclusive, with existing evidence yielding inconsistent findings across studies. The majority of clinical investigations, including meta-analyses of RCTs, have reported that Lactobacillus supplementation does not significantly alter HDL-C levels, despite producing notable reductions in TC and LDL-C [42]. This null effect on HDL-C was similarly observed in an animal model involving hypercholesterolemia-induced pigs, where Lactobacillus supplementation failed to elicit any meaningful change in HDL-C concentrations [14]. In contrast, certain studies suggest that specific probiotic formulations may possess the capacity to elevate HDL-C levels; a synbiotic intervention combining probiotics with prebiotics demonstrated a significant increase in HDL-C after 12 weeks of supplementation in adults with dyslipidemia [43], and a comparable elevation was reported in healthy young individuals receiving Lactobacillus salivarius in combination with fructooligosaccharides (FOS) [40]. Nevertheless, these favorable outcomes are not universally replicated, as studies employing Lactobacillus plantarum strains [33] and multi-strain synbiotic preparations [44] failed to detect significant improvements in HDL-C, despite concurrent reductions in other lipid parameters. The divergence in findings across these studies is likely attributable to heterogeneity in study design, probiotic strain specificity, administered dosages, and duration of intervention, collectively highlighting the need for more standardized and strain-specific investigations to clarify the role of Lactobacillus in modulating HDL-C metabolism.

3.4.3. Effect on Triglycerides (TG)

Triglyceride responses were consistently trivial to small across all seven studies, as indicated by Cohen's d values and uniformly non-significant p-values (0.115–0.945). The largest intervention effect was reported by Rerksuppahol et al. [36] (d = −0.222, small; −27.9 mg/dL, p = 0.91), but this did not reach statistical significance due to substantial inter-individual variability (baseline SD = 148.2 mg/dL). Kerlikowsky et al. [33] observed a small intervention effect (d = −0.268; −12.8 mg/dL) compared to a trivial placebo decline (d = −0.067, p = 0.523). Keleszade et al. [34] and Cavallini et al. [35] reported small to trivial intervention effects (d = −0.188 and d = −0.193), alongside small positive placebo changes (d = +0.278 and d = +0.039). Khongrum et al. [13] and Jiang et al. [32] found near-zero effects in both groups (d between −0.024 and −0.102), while Nuankham et al. [14] observed small positive effects in both intervention (d = +0.239) and control (d = +0.205) arms, likely reflecting dietary variation at the study level unrelated to the intervention. These consistently small triglyceride effect sizes suggest that the primary metabolic targets of the tested strains are LDL-C and total cholesterol pathways. This finding aligns with the predominant role of bile acid deconjugation and modulation of intestinal cholesterol absorption in Lactobacillus-mediated lipid reduction, rather than VLDL-mediated endogenous triglyceride production [39,40].

Another study revealed that Lactobacillus supplementation has been shown to exert a meaningful reducing effect on TG levels, with both mechanistic and clinical evidence supporting this association. At the molecular level, the TG-lowering effect is thought to be mediated through the upregulation of key lipid metabolism-related genes, including peroxisome proliferator-activated receptor alpha (PPARα) and farnesoid X receptor (FXR), alongside an increase in plasma apolipoprotein A-V (ApoA-V) levels, which collectively promote enhanced TG clearance and fatty

acid oxidation [45]. Furthermore, Lactobacillus supplementation has been demonstrated to favorably modulate gut microbiota composition, which in turn exerts downstream regulatory effects on lipid metabolism and contributes to TG reduction [40,49]. These mechanistic insights are substantiated by robust clinical evidence; a systematic review and meta-analysis encompassing nine randomized controlled trials (RCTs) with a total of 598 participants confirmed that Lactobacillus supplementation significantly reduced TG levels, with the effect being particularly pronounced when administered as part of a normal dietary regimen [42]. Consistent with these findings, a clinical study involving hyperlipidemic patients reported that a mixed probiotic formulation containing Lactobacillus produced a significant decrease in serum TG levels following three months of supplementation [47], further reinforcing the therapeutic potential of Lactobacillus-based interventions in the management of hypertriglyceridemia.

3.4.4. Effect on Total Cholesterol

Reductions in total cholesterol (TC) closely paralleled the effect sizes observed for low-density lipoprotein cholesterol (LDL-C). Most intervention arms demonstrated medium within-group effects, whereas placebo groups generally exhibited only trivial changes. The most pronounced TC reduction in an intervention group was reported by Rerksuppahol et al. [36] ($d = -0.664$, medium; −24.5 mg/dL, $p < 0.001$). In contrast, the corresponding placebo group showed a large positive effect ($d = +0.726$; +21.8 mg/dL), representing the greatest divergence in the dataset and resulting in a net treatment difference of approximately 46.3 mg/dL over six weeks. Khongrum et al. [13] observed a medium intervention effect ($d = -0.616$; −13.67 mg/dL) compared to a trivial placebo change ($d = -0.131$, $p = 0.197$). Kerlikowsky et al. [33] and Cavallini et al. [35] reported similar medium effects ($d = -0.548$ and $d = -0.582$, respectively) with trivial placebo differences ($d = -0.198$ and $d = +0.081$, respectively). Jiang et al. [32] identified a small but statistically significant intervention effect ($d = -0.203$; −0.19 mmol/L, $p = 0.038$) and a negligible control change ($d = +0.033$). Nuankham et al. [14] reported a small intervention effect ($d = -0.221$) alongside a medium positive control drift ($d = +0.452$, $p = 0.876$), indicating considerable within-study variability. Keleszade et al. [34] did not provide total cholesterol data. Collectively, the TC effect size data demonstrate a consistent medium effect of Lactobacillus supplementation across studies. Placebo groups generally showed minimal spontaneous change or, as observed in [36], marked deterioration, which amplified the net therapeutic benefit attributable to the probiotic intervention.

3.4.5. Mechanisms of Cholesterol-Lowering Effects

Lactobacillus species reduce cholesterol through multiple mechanisms, as demonstrated by the studies reviewed. Cavallini et al. [35] and Jiang et al. [32] emphasized the role of Bile Salt Hydrolase (BSH) in cholesterol reduction. The BSH, also known as cholylglycine hydrolase (EC 3.5.1.24), is produced by various gut bacteria including probiotic genera such as Lactobacillus and Bifidobacterium, and is widely regarded as the primary mechanistic route through which microbiota mediate lipid modification. The enzyme catalyzes hydrolysis (deconjugation) of bile acids conjugated with glycine or taurine, releasing free bile acids and free amino acids [48], [49], [50]. In the liver, bile acids are first conjugated with glycine or taurine to increase their solubility prior to intestinal secretion [48], [51]. These conjugated bile acids are subsequently reabsorbed with high efficiency in the ileum via the apical sodium-dependent bile acid transporter (ASBT), forming the basis of enterohepatic recycling [50], [52]. This disruption of enterohepatic circulation compels the liver to synthesize new bile acids from cholesterol, thereby reducing serum cholesterol levels. However, direct measurements by Cavallini et al. [35] did not show a significant increase in total bile acid excretion, suggesting the involvement of compensatory mechanisms or complex alterations in bile acid metabolism.

Multiple studies confirm that Lactobacillus strains assimilate cholesterol from their environment, incorporating it into the bacterial cell membrane during growth and thereby sequestering cholesterol and reducing its availability for host absorption. It is supported by observed reductions in medium cholesterol content following incubation with Lactobacillus [53], [54] and by scanning electron micrographs showing cholesterol adhered to the bacterial cell surface, consistent

with physical association and possible membrane incorporation [55]. Cavallini et al. [35] observed trends toward increased coprostanol excretion in fecal neutral sterol measurements, although these findings did not achieve statistical significance. These results suggest that cholesterol assimilation and conversion may contribute to cholesterol reduction, but these mechanisms likely play a secondary role compared to others.

Jiang et al. [32] reported significant increases in apolipoprotein E (ApoE) levels ($p < 0.01$) following *L. paracasei* N1115 supplementation, indicating modulation of genes involved in cholesterol metabolism. ApoE facilitates the clearance of VLDL and LDL from plasma by promoting their interaction with hepatic receptors. The upregulation of ApoE suggests that probiotics may influence hepatic gene expression related to lipoprotein metabolism. The authors hypothesized that short-chain fatty acids (SCFAs), particularly butyrate produced by beneficial bacteria, may inhibit histone deacetylases and thereby affect cholesterol-related gene expression. However, direct measurements of SCFA levels did not reveal significant changes, indicating that this proposed mechanism warrants further investigation.

Park et al. [56] and Kerlikowsky et al. [33] conducted comprehensive microbiome analyses. Park et al. demonstrated that supplementation with *L. plantarum* Q180 reduced the abundance of *Eggerthella* spp., a genus associated with adverse lipid profiles. Conversely, Kerlikowsky et al. found that higher baseline levels of *Roseburia* spp., a butyrate-producing genus, were inversely correlated with LDL-C reduction. These findings suggest that a favorable baseline microbiome may enhance the efficacy of probiotic interventions. Overall, these results highlight the need to evaluate the entire gut microbiome rather than focusing solely on the administered probiotic strain.

Khongrum et al. [13] and Cavallini et al. [35] reported significant reductions in inflammatory markers, supporting the anti-inflammatory and antioxidant effects of probiotics. Khongrum et al. observed notable decreases in tumor necrosis factor-alpha (TNF-α) ($p < 0.01$) and malondialdehyde (MDA), a marker of lipid peroxidation ($p < 0.001$). These findings indicate that probiotics may indirectly reduce cholesterol by mitigating systemic inflammation. Inflammation contributes to dyslipidemia by promoting insulin resistance, altering hepatic lipid metabolism, and impairing endothelial function. Cavallini et al. also documented a 24.2% reduction ($p < 0.05$) in electronegative LDL, an atherogenic LDL variant. Reduced oxidative stress and LDL oxidation may improve cardiovascular outcomes beyond cholesterol-lowering alone.

3.4.6. Dose-Response Relationship and Optimal Treatment Duration

Analysis of dose-response relationships across studies provides critical insights for clinical application. High dosages ($\geq 4 \times 10^9$ CFU/day) consistently produce substantial reductions in LDL-C levels [5,9-10,12-13,15]. In contrast, lower dosages (e.g., 1.2×10^9 CFU/day) are linked to more variable outcomes [33]. These results suggest the existence of a threshold effect. However, the optimal dosage likely depends on the specific probiotic strain and individual patient characteristics. The duration of interventions ranged from 6 to 12 weeks across the studies, with the most pronounced effects observed after 12 weeks. Jiang et al. [32] reported intermediate LDL-C reductions at 6 weeks, which became more significant by 12 weeks. This pattern indicates a time-dependent effect, possibly attributable to gradual probiotic colonization and microbiome adaptation. Further long-term studies are required to determine whether these effects stabilize, continue to increase, or necessitate ongoing supplementation for sustained benefit.

3.4.7. Safety Profile and Tolerability

Evaluation of safety and tolerability is a critical component of therapeutic intervention assessment. A comprehensive analysis of seven studies found that Lactobacillus supplementation exhibited a favorable safety profile, with no serious adverse events reported. Jiang et al. [32] reported that none of the participants experienced illness or discomfort related to probiotic consumption. Nuankham et al. [14] found no significant changes in liver function biomarkers (ALT, AST, ALP, GGT) or vitamin D levels, indicating that prolonged probiotic use does not negatively impact hepatic function or fat-soluble vitamin metabolism.

Cavallini et al. [35] conducted comprehensive safety monitoring, including complete blood counts, renal function assessments, and blood pressure measurements. No clinically significant changes were observed in any safety parameter. Such a thorough evaluation is especially pertinent for individuals with hypercholesterolemia, who may present with additional cardiovascular risk factors or require concurrent pharmacological therapies.

The lack of significant gastrointestinal side effects is notable, given that such issues are frequently associated with probiotic supplementation. Park et al. [56] systematically assessed gastrointestinal symptoms using validated questionnaires and found no significant differences in abdominal pain, bloating, or stool consistency between probiotic and placebo groups. This favorable tolerability profile supports the practicality of prolonged probiotic use for cholesterol regulation.

3.5. Strengths and Limitations

This systematic review and bibliometric analysis identify numerous significant aspects that strengthen the validity of the findings of Lactobacillus supplementation. The study rigorously followed the PRISMA 2020 recommendations and employed a prospectively registered protocol on the OSF platform, ensuring transparency and reducing the likelihood of reporting bias. The use of a dual-analytical approach offers a distinctive, multi-faceted perspective on the biological effects of probiotics and the global progression of the study domain from 2010 to 2025. The trials included priployed high-quality randomized, double-blind, placebo-controlled designs, which are considered the gold standard for clinical data in lipid management research. The review encompasses several delivery matrices, including functional fermented foods, facilitating a comprehensive understanding of the impact of varied factors on probiotic stability and lipid-lowering effects. A notable methodological strength of the bibliometric component is the use of both Biblioshiny and VOSviewer, which enable extensive, high-resolution bibliometric visualization through minimal coding requirements, thereby facilitating a comprehensive and accessible mapping of the research landscape.

Despite these advantages, there are restrictions considered when analysing the findings. A significant methodological limitation of this review is the absence of a formal meta-analysis. Although meta-analysis would have provided more robust quantitative synthesis, several factors precluded its application in this study: (1) substantial heterogeneity in Lactobacillus strains (*L. paracasei, L. plantarum, L. acidophilus*, and mixed-strain formulations), each potentially exerting distinct mechanisms of action; (2) wide variability in dosing regimens ranging from 1.05×10^9 to 4×10^{10} CFU/day, which introduces dose-response heterogeneity; (3) differences in delivery matrices (capsules, fermented foods, synbiotic formulations) that may affect bioavailability and efficacy; (4) variability in intervention duration (6-12 weeks), which limits temporal comparability; and (5) heterogeneity in baseline lipid profiles and participant characteristics across studies.

In addition to these clinical constraints, the bibliometric component also presents evidence and process limitations that should be acknowledged. The integration of Scopus and PubMed records resulted in partial metadata loss due to inconsistencies in database formatting, particularly affecting cited references and source categories [57]. Furthermore, the dual use of Biblioshiny and VOSviewer may introduce methodological bias, as each platform employs distinct preprocessing rules and clustering algorithms, with VOSviewer relying exclusively on Scopus data. These disparities can influence network structures, thematic clusters, and citation patterns, meaning that some observed bibliometric trends may reflect software- or database-specific artifacts rather than intrinsic characteristics of the research landscape.

3.6. Implications for Practice and Policy

The observed LDL-C reductions of 10-15% across the majority of included studies provide preliminary evidence suggesting that Lactobacillus supplementation may warrant consideration as a potential adjunct approach for individuals with mild-to-moderate hypercholesterolemia. However, given the limited number of trials (n=7), substantial inter-study heterogeneity in strains and dosing, and lack of long-term follow-up data, these findings should be considered exploratory and

hypothesis-generating rather than definitive. Further large-scale, well-controlled trials are necessary before specific clinical recommendations can be made.

Among individuals receiving statin therapy who have not achieved LDL-C targets, probiotic supplementation may further reduce LDL-C without increasing the risk of statin-associated adverse effects. The distinct mechanisms of action, including statin inhibition of HMG-CoA reductase, bile acid sequestration, and probiotic modulation of the microbiome, suggest the possibility of additive effects. However, this hypothesis requires validation in dedicated combination therapy trials. The demonstrated reductions in ApoB, non-HDL-C, and oxidative stress markers suggest that probiotics may provide cardiovascular benefits beyond simple LDL-C lowering [5,9,13]. The reduction in electronegative LDL and inflammatory markers is particularly relevant, as these factors contribute to residual cardiovascular risk even when LDL-C is adequately controlled.

Correlation analyses by Kerlikowsky et al. [33] highlight the importance of baseline microbiome composition in determining the efficacy of probiotic interventions. As gut microbiome testing becomes more accessible, it may become feasible to identify individuals most likely to benefit from targeted probiotic therapies, thereby supporting a precision nutrition approach to cholesterol management. Given its favorable safety profile and moderate efficacy, *Lactobacillus* supplementation could be integrated into broader public health strategies aimed at preventing cardiovascular disease. The straightforward administration regimen and over-the-counter availability increase accessibility for diverse populations. However, standardization of probiotic products and regulation of strain-specific health claims are necessary to ensure consistent quality and efficacy.

3.7. Research Gaps and Future Directions

While current findings are promising, several critical gaps must be addressed before Lactobacillus supplementation can be integrated into evidence-based clinical practice. Dose-response relationships remain inadequately defined, as the tentative threshold of ≥4 × 10^9 CFU/day is derived from only seven heterogeneous trials. The absence of direct strain comparisons under standardized conditions prevents definitive conclusions regarding strain-specific efficacy. Most trials are limited to 12 weeks or less, leaving the long-term sustainability of lipid-lowering effects, potential for tolerance development, and outcomes following discontinuation uncharacterized. The field has not yet examined hard cardiovascular endpoints such as myocardial infarction, stroke, or cardiovascular mortality, and improvements in lipid profiles may not necessarily translate to reduced cardiovascular risk. Mechanistic understanding remains incomplete, necessitating quantitative assessments of bile acid excretion, short-chain fatty acid production, gut microbiome remodeling, and postprandial lipid dynamics, which are not captured by fasting triglyceride measurements. Generalizability is constrained by the overrepresentation of Asian cohorts; rigorous evaluation in Western, African, and Latin American populations is required, given known differences in baseline microbiome composition and lipid-related genetic factors. Additional research priorities include combination therapy trials with statins, standardization of manufacturing and regulatory frameworks, and cost-effectiveness analyses compared to established lipid-lowering strategies. Until these gaps are addressed through adequately powered and methodologically rigorous studies, clinical recommendations should remain provisional and clearly qualified.

4. CONCLUSION

This systematic review and bibliometric analysis provide initial evidence that Lactobacillus supplementation modestly improves cholesterol profiles, particularly low-density lipoprotein cholesterol (LDL-C) and total cholesterol. The limited number of included trials (n=7), substantial heterogeneity in strains, dosages, and study populations, and the absence of long-term safety and efficacy data preclude definitive clinical recommendations. Mechanistic studies suggest biological pathways involving bile salt metabolism, apolipoprotein modulation, and anti-inflammatory effects; however, these remain unconfirmed until validated by larger, standardized trials. The bibliometric

analysis reveals rapid global research expansion and identifies emerging themes linking probiotics, gut microbiota, and metabolic health. These findings highlight both the growing scientific interest in this field and the necessity for more rigorous, internationally coordinated studies to establish evidence-based clinical guidelines.

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