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Research Paper

Meta-analysis of the effects of probiotics on hyperlipidemia

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ABSTRACT

Background: The potential role of probiotics in mitigating hyperlipidemia has garnered increasing evidence, yet the specific mechanisms warrant further investigation.
Objective: This study aimed to examine the alterations in short-chain fatty acids (SCFAs), a hypothesized lipid-lowering mechanism of probiotics, in animal models and to evaluate the lipid-lowering effects of probiotics on hyperlipidemic animal models through a meta-analysis of preclinical experiments. Methods: A comprehensive search of PubMed, Web of Science, EMBASE, Cochrane Library and Google Scholar up to June 2024 yielded nine studies that met the inclusion criteria (INPLASY registration number: No. CRD42024559937).
Result: The analysis revealed that mice receiving probiotics exhibited a significant increase in SCFA levels compared with control mice (acetic acid: standard mean difference [SMD] = 1.26, 95% confidence interval [CI] 0.80 to 1.72, $P < 0.00001$, $I^2 = 28\%$; propionic acid: SMD = 1.99, 95% CI 1.47 to 2.51; butyric acid: SMD = 0.66, 95% CI 0.04 to 1.28, $P = 0.04$, $I^2 = 22\%$; acetate: SMD = 4.5, 95% CI 3.57 to 5.42, $P < 0.00001$, $I^2 = 48\%$; propionate: SMD = 0.76, 95% CI 0.37 to 1.15, $P = 0.0002$, $I^2 = 44\%$; butyrate: SMD = 2.8, 95% CI 2.18 to 3.41, $P < 0.00001$, $I^2 = 26\%$). Additionally, probiotic consumption reduced markers of oxidation and inflammation as well as liver damage enzymes.
Conclusion: The findings from this meta-analysis suggest that probiotics can enhance SCFA content in the body, decrease lipid levels in animals, improve oxidative stress and inflammation, reduce liver damage, and effectively alleviate hyperlipidemia.

1. Introduction

Hyperlipidemia is characterized by an abnormal elevation of total cholesterol (TC) or triglycerides (TG) in human serum, leading to metabolic disorders (Havel and Rapaport, 1995; X. Liang et al., 2020). Furthermore, hyperlipidemia is associated with several long-term chronic diseases, including hypertension and cardiovascular disease (Y. Zhang et al., 2010). With approximately 78 million individuals affected by hyperlipidemia globally in 2022 due to unhealthy diets and sedentary lifestyles, it has emerged as a significant public health concern (L.-Y. Ma et al., 2020). Current pharmacological treatments for hyperlipidemia have limitations and side effects. For instance, statins, fibrates, and ezetimibe may cause liver and gastrointestinal damage and could potentially increase the risk of sudden death (Farnier and Davignon, 1998; Filippatos and Mikhailidis, 2009).

The pharmacological agents currently available for the management of hyperlipidemia are associated with various adverse effects. Statins, which are employed to lower low-density lipoprotein cholesterol (LDL-C), have been linked to hepatotoxicity (Farnier and Davignon, 1998). Fibrates, which primarily target TG, have been shown to increase the risk of sudden cardiac events in patients (Fazio and Linton, 2004). Ezetimibe, a medication that inhibits intestinal lipid absorption, may cause gastrointestinal damage and contribute to metabolic disorders (Filippatos and Mikhailidis, 2009). In contrast, probiotics present a promising alternative devoid of significant side effects, demonstrating substantial potential for lipid reduction. Studies have demonstrated that certain probiotics and their metabolites can effectively enhance cholesterol breakdown while inhibiting cholesterol synthesis in the

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human body (Jiang et al., 2021; Markowiak-Kopeć and Śliżewska, 2020). *Lactobacilli* can regulate TC and LDL-C, while increasing the concentration of high-density lipoprotein (HDL-C) in mice on a cholesterol-rich diet (J. Wang et al., 2012). In addition, *Lactobacillus salivarius* AP-32, *L. rhamnosus* bv-77, and *Bifidobacterium animalis* CP-9 are reported in reducing serum TC and LDL-C levels in dyslipidemic obesity children (Chen et al., 2022; Ejtahed et al., 2011).

The primary lipid-lowering mechanisms of probiotics encompass: (1) the production of bile salt hydrolase, which enhances cholesterol excretion; (2) the modulation of immune regulation and the intestinal barrier through signaling molecules; and (3) the promotion of cholesterol catabolism and the inhibition of cholesterol synthesis in the body via key intestinal metabolites, specifically SCFAs(Markowiak-Kopeć and Śliżewska, 2020; Patel et al., 2010). Contemporary research indicates that the regulation of lipids by probiotics through SCFAs is the most prominent and efficacious lipid-lowering mechanism (Markowiak-Kopeć and Śliżewska, 2020). A lipid-lowering mechanism associated with probiotics entails the modulation of the gut microbiota to enhance the prevalence of beneficial microorganisms, including *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, which are known to ferment significant quantities of SCFAs (Hold et al., 2003). Empirical evidence suggests that the proliferation of lactic acid bacteria leads to elevated levels of SCFAs, particularly butyrate, within the human body. This increase in SCFAs is correlated with a rise in anti-inflammatory factors, a reduction in pro-inflammatory factors, and the stabilization of blood lipid levels (Moens et al., 2019). Oral administration of *Lactobacillus plantarum* in elderly individuals has been demonstrated to effectively elevate propionic acid and acetate levels, thereby mitigating the risk of hyperlipidemia (L. Wang et al., 2014). Additionally, another study reported that healthy adults consuming probiotics exhibited an increase in butyric acid levels, accompanied by a rise in plasma antioxidants and a reduction in lipid concentrations (Pérez-Burillo et al., 2020). However, some studies have indicated that the regulation of SCFAs by probiotics does not achieve lipid-lowering effects through the modulation of inflammatory factors, liver damage, or antioxidant parameters such as tumour necrosis factor-alpha (TNF-α) and superoxide dismutase (MDA) (Y. Li et al., 2023; Y. Liang et al., 2018). Numerous studies have demonstrated that probiotics modulate the gut microbiota and influence metabolite production, potentially aiding in the treatment of hyperlipidemia and the maintenance of human health. However, the evidence concerning the role of short-chain fatty acids in stabilizing lipid metabolism disorders in hyperlipidemia, particularly through their effects on inflammation, liver enzymes, and oxidative biomarkers, remains limited and ambiguous. Consequently, further research is required to elucidate their efficacy and underlying mechanisms of action.

To the best of our knowledge, this meta-analysis represents the inaugural quantitative evaluation of the potential impact of probiotics on alterations in SCFAs within animal experiments. Furthermore, we specifically examined the associations between SCFAs and lipid levels, inflammation, liver enzymes, and oxidative biomarkers in animal models of hyperlipidemia. The study population was restricted to hyperlipidemic mouse models, with probiotics serving as the intervention. Major indicators assessed included acetic acid, propionic acid, butyric acid, acetate, propionate, butyrate, along with minor indicators assessed included superoxide dismutases (SOD), MDA, aspartate aminotransferase (AST), alanine aminotransferase (ALT), TNF-α, Interleukin Iβ (IL-Iβ), TC, TG, HDL-C, LDL-C.

2. Methods

2.1. Literature search strategy

This meta-analysis received a registration number from the International Registry for Systems Evaluation (INPLASY registration number: No. CRD42024559937). Data for the meta-analysis were retrieved from PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (http://isiknowledge.com/), Embase (https://www.embase.com/) and Cochrane Library (https://www.cochranelibrary.com/) up to June 2024. Google Scholar was also utilized to supplement the literature search. The key search terms included 'probiotic', 'hyperlipidemia', 'fatty acids, volatile', with free word terms retrieved from MeSH such as 'probiotics', 'yeast dried', 'yeasts', 'yogurt', 'Lactobacillus', 'Bifidobacterium', 'fermented product', 'fermented dairy product', 'Probiotics', 'cultured milk products', 'Hyperlipemia', 'Hyperlipemias', 'Hyperlipidemia', 'Lipidemia', 'Lipidemias', 'Lipemia', 'Lipemias', 'SCFA', 'Acid, Short-Chain Fatty', 'Fatty Acid, Short-Chain', 'Volatile Fatty Acids', 'Volatile Fatty Acid', 'Acid, Volatile Fatty', 'Short Chain Fatty Acid', 'Fatty Acid, Volatile', 'Fatty Acids, Short Chain', 'SCFAs', 'Fatty Acids, Short-Chain'. See Appendix S1 for more detailed search details.

2.2. Data criteria

Data Inclusion Criteria: All included preclinical studies met the following screening criteria: (1) The experimental animals were limited to mice to reduce experimental bias; (2) the studies were in animal vivo; (3) a control group without probiotic intervention was recorded; (4) probiotics were administered; and (5) the studies were published articles in Chinese or English; (6) at least two indicators of SCFA content were reported.

Data exclusion criteria: (1) Non-mouse in vivo experiments (human experiments and in vitro fermentation); (2) no control group; (3) no drugs with chemical components other than probiotics in the experimental group; (4) no direct experimental data of SCFA. The PICO (participants, intervention, comparison, and outcomes) criteria are shown in Table 1 utilized to formulate the research question.

2.3. Data extraction

Duplicates were manually removed using EndNote ×9 and the remaining preclinical studies were excluded or included according to established inclusion criteria. Two independent researchers conducted the qualification assessment and data recording of all literature, with discrepancies resolved through discussion or consultation with a third independent researcher. All data were normalised as Mean ± SD. Primary graphic data from bar charts and line charts were extracted by GetData Graph Digitizer version 2.26.

The data extracted included: experimental design (experimental period, sample size, probiotic dose); preclinical data (age, strain, modelling method); primary outcomes: acetic acid level, propionic acid level, butyric acid level, acetate level, propionate level, and butyrate level; secondary outcomes: hepatic Oxidative Parameters, including SOD and MDA; liver enzyme, including AST and ALT; serum inflammatory factors, including TNF-α and IL-1β; serum lipid, including TC, TG, HDL-C, LDL-C.

2.4. Criteria for evaluating literature quality

Following modification to the standards developed by Macleod et al. (Macleod et al., 2005; Macleod, O'Collins, Howells and Donnan, 2004), criteria were summarised as follows: (1) publication was peer-reviewed;

Table 1
PICO inclusion and exclusion criteria.

Parameters	Inclusion and exclusion criteria
Participants	Mouse model with hyperlipemia
Intervention	Probiotics
Comparison	A control group without intervention
Outcomes	Acetic acid, propionic acid, butyric acid, acetate, propionate, butyrate, SOD, MDA, AST, ALT, TNF-α, IL-Iβ, TC, TG, HDL-C, LDL-

(2) sample size calculation was provided; (3) environmental conditions such as temperature and humidity were controlled; (4) samples were randomly assigned to groups; (5) detailed probiotic strain information was displayed; (6) probiotic treatment was blinded; (7) main outcome measurements were masked; (8) at least two indicators of SCFA content were reported; (9) compliance with animal experimental ethics was ensured; and (10) conflict of interest was declared by the authors. One point was awarded for each criterion met, with a maximum score of ten.

2.5. Meta-data analysis

Data were analysed using Review Manager version 5.4. A p-value <0.05 was considered statistically significant. The effect size was calculated using Classical pairwise: experimental group (animal model of hyperlipidemia taking probiotics) - control group (Sztuka and Jasińska-Stroschein, 2017). This meta-analysis used Cochrane Q for quantitative assessment of heterogeneity and random-effects models were used to compensate for heterogeneity when heterogeneity exceeded 50%. Cochrane's Q is calculated as a weighted sum of squares of the difference between the effects of a single study and the combined effects of multiple studies. The effect size was determined by the standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity of the included data was assessed using I^2. In addition, we removed each study and re-evaluated pooled effect estimates to perform sensitivity analysis to determine if any single study unduly influenced the overall results.

3. Results

3.1. Search process and characteristics of included documents

In this study, online libraries such as PubMed, Web of Science, EMBASE, Cochrane Library and Google Scholar were searched up to June 2024. A total of 273 articles were collected by searching keywords in an online database, and another 3 articles were supplemented by manual search. After the removal of duplicates, the remaining 184 articles were carefully reviewed through their titles and abstracts, leading to the exclusion of 85 irrelevant articles. After excluding non-experimental studies and articles with no quantifiable results, nine preclinical studies remained available for further data extraction and meta-analysis. The detailed article selection process is shown in Fig. 1.

The preclinical experiments involved different types of rodents, including Wistar rats, Sprague-Dawley (SD) rats, Charles Foster rats, and C57BL/6 mice. In total, 80 rodents were divided into two groups: the first group was a probiotic treatment group with 114 mice, and the second group was a control group with 66 mice. Due to variations in rodent species and probiotic strains, the treatment duration ranged from 4 to 10 weeks. All literature detailing the characteristics and specific ingredients involved in the probiotics is summarised in Table 2.

3.2. Risk of bias

All preclinical studies were published after peer review. All literature described the strain information of probiotics and controlled the temperature and humidity of the environment, but no literature calculated the sample size and did not use blind methods for probiotic therapy and SCFA determination. The authors of two articles did not submit a conflict of interest statement, and the specific article risk scores and descriptions are shown in Table 3.

3.3. Meta-analysis results of the effects of probiotics on SCFAs in animal models

Nine experiments involving mice included 114 mice in the probiotic treatment group and 66 mice in the control group. As shown in Fig. 2(a)–(f), the SCFAs in the probiotic mice were significantly different from those in the control mice. Among them, acetic acid, propionic acid, acetate, propionate, and butyrate analyses are based on a fixed-effect model due to low heterogeneity. Moreover, SCFAs are measured in different ways in each experiment (acetic acid scores: SMD = 1.26, 95% CI, 0.8 to 1.72, $P < 0.00001$, $I^2 = 28\%$; propionic acid scores: SMD = 1.99; 95% CI, 1.47 to 2.51; $P < 0.00001$; $I^2 = 0\%$; acetate scores: SMD = 4.5, 95% CI, 3.57 to 5.42, $P < 0.00001$, $I^2 = 48\%$; propionate scores: SMD = 0.76; 95% CI, 0.37 to 1.15; $P = 0.0002$; $I^2 = 44\%$; butyrate scores: SMD = 2.8; 95% CI, 2.18 to 3.41; $P < 0.00001$; $I^2 = 26\%$). Due to high heterogeneity of butyric acid, a random-effects model is adopted (butyric acid scores: SMD = 0.66; 95% CI, 0.04 to 1.28; $P = 0.04$; $I^2 = 22\%$). The above results indicate that probiotic intervention can significantly improve SCFA levels in the body, including acetic acid, propionic acid, butyric acid, acetate, propionate and butyrate levels. The original images without removing heterogeneity are shown in Appendix S1.

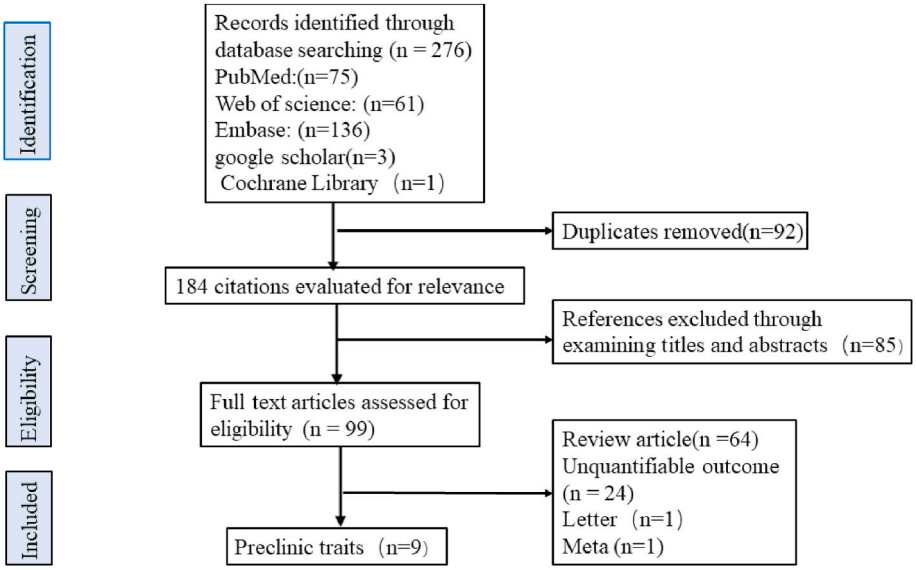

Fig. 1. Flow diagram of preclinic article screening process.

Table 2
Information of included studies, including author and year, country, model, intervention, duration, measurements, main finding.

Author and Year	Country	Model	Intervention	Duration	Measurements	Main finding
Caiqing Yao et al., 2020 (Yao et al., 2020)	China	HFD-Induced hyperlipidemia in Wistar rats	*Lactobacillus plantarum* LIP-1 (n = 10), 2.0×10^9 CFU/mL/da Microcapsuled *Lactobacillus plantarum* LIP-1 (n = 10), 2.0×10^9 CFU/mL/day	7 weeks	Lactic acid, Acetic acid, Propionic acid, Butyric acid, TG, TC, HDL-C, LDL-C, SOD, GSH-Px, MDA, AST, ALT, ALT/AST	*Lactobacillus plantarum* LIP-1 can effectively reduce various lipid indexes in hyperlipidemia animal models, and its microencapsulation can increase the activity and therapeutic efficiency of LIP-1 in the digestive system.
Micaelle Oliveira De Luna Freire et al., 2021 (de Luna Freire et al., 2021)	Brazil	HFD-Induced hyperlipidemia in Male Wistar rats (100 days of age)	*L. fermentum* 139&*L. fermentum* 263 & *L. fermentum* 296 (n = 6), 3.0×10^9 CFU/mL/day	4 weeks	Acetic Acid, Propionic Acid, TG, TC, HDL-C, LDL-C, SOD, MDA, CAT, GST, CRR, TNF-α, IL-6, IL-1β, IL-10	*L. fermentum* preparation reduces blood lipids in hyperlipidemia mice by regulating in vivo inflammation and oxides in the heart and colon of hyperlipidemia mice.
Jing Yan et al., 2022(C. Wang et al., 2022)	China	HFD-Induced hyperlipidemia in C57BL/6 mice (5 weeks of age)	*Bacillus* sp. DU-106 (GDMCC 60621) and *Lactobacillus plantarum* (GDMCC 1.2685) fermented rice buckwheat (n = 10), 5×10^9 CFU/mL/day	8 weeks	Acetic Acid, Propionic Acid, Isobutyric Acid, Butyric Acid, Isovaleric Acid, Valeric Acid, Caproic Acid, Total SCFAS, TG, TC, HDL-C, LDL-C, SOD, GSH-Px, MDA, AST, ALT, SREBP-1c, HMGCR, SREBP-2, PPAR-A, CPT-1A, LXR, TNF-α, IL-1β, IL-6	Fermented rice buckwheat has a good lipid-lowering effect, and its main mechanism is to achieve changes in lipid metabolism by regulating various inflammatory indicators and intestinal microorganisms in animal models. Active substances are crucial in the process of lipid metabolism.
Lingshuang Yang et al., 2021 (Yang et al., 2021)	China	HFD-Induced hyperlipidemia in SD male rats (5 weeks of age)	*E. faecium* strain 132 (n = 6), 1×10^9 CFU/(mL/100 g/day) *L. paracasei* strain 201 (n = 6), 1×10^9 CFU/(mL/100 g/day)	6 weeks	Acetic acid, Propionic acid, Isobutyric acid, Butyric acid, Isovaleric acid、Valeric acid, TG, TC, HDL-C, LDL-C, ALT, AST, IL-1β, IL-6 and TNF-α	Oral administration of *E. faecium* strain 132 and *L. paracasei* strain 201 can reduce cholesterol in animal models by regulating the dominant microbes in the gut as well as activity, while improving fatty liver and lipid metabolism.
Chaudhari Archana Somabhai et al., 2016 (Somabhai et al., 2016)	India	20%Fructose-Induced hyperlipidemia in Charles foster rats	*Escherichiacoli Nissle* 1917 (n = 6), 1×10^9 CFU/week *Escherichiacoli Nissle* 1917 (PQQ) (n = 6), 1×10^9 CFU/mL/week *Escherichiacoli Nissle* 1917(PQQ-glf) (n = 6), 1×10^9 CFU/mL/week *Escherichiacoli Nissle* 1917 (PQQ-glf-mtlK) (n = 6), 1×10^9 CFU/mL/week *Escherichiacoli Nissle* 1917 (pqq-fdh) (n = 6), 1×10^9 CFU/mL/week	2 months	Acetic Acid, Propionic Acid, Butyric Acid, TG, TC, HDL-C, LDL-C, VLDL, SOD, MDA, CAT, GSH, ALP, AST, ALT, Urea, Creatinine of Serum, FBG	Probiotic *Escherichiacoli Nissle* 1917 can alleviate fructose-induced fatty liver degeneration by producing PQQ and fructose-metabolizing enzymes in mice. This study demonstrates the potential of probiotic *Escherichiacoli Nissle* 1917in alleviating fructose-induced fatty liver degeneration.
Micaelle Oliveira De Luna Freire et al., 2023 (de Luna Freire et al., 2023)	Brazil	HFD-Induced hyperlipidemia in male Wistar rats	*L. fermentum* 139, *L. fermentum* 263, and *L. fermentum* 296 strains (n = 6), 3×10^9 CFU/mL/day	4 weeks	Acetate, Propionate, Succinate, TG, TC, HDL-C, LDL-C, TBARS, SOD, MDA, CAT, GST, Sulfhydryls, Creatinine, Urea, ALT, AST, TNF-A, 1L-6, IL-1B, IL-10	In female rats fed with HFD, it was found that administration of *Lactobacillus ferment* alleviated dyslipidemia levels, inflammation and oxidative stress index in colon, liver, heart and kidney by examination of lesions at various sites.
Lei Tian et al., 2023 (Tian et al., 2022)	China	HFD-Induced hyperlipidemia in SD rats (8 weeks of age)	L. plantarum N-1 group (n = 8), 3×10^9 CFU/mL/day	4 weeks	Acetate, Propionate, Isobutyrate, Butyrate, Isovalerate、Valerate, TG, TC, HDL-C, LDL-C	*L. plantarum* N-1 can effectively reduce blood lipids in hyperlipidemia rats, the most obvious effect is LDL-C. This may be because probiotics improve the content of SCFA especially butyrate and valerate in the body and inhibit HMG-CoA enzyme activity
Xiaolong Wang et al., 2022 (X. L. Wang et al., 2022)	China	HFD-Induced hyperlipidemia in male C57BL/6 mice (6 weeks of age)	*T. sinense mycelium* (n = 8), 3×10^9 CFU/mL/day	4 weeks	Acetate, Propionate, Butyrate, SOD, MDA, GSH-Px, Valerate, Total SCFAs, TG, TC, HDL-C, LDL-C, TNF-α, IL-1β, IL-6	*T. sinense* supplementation has a protective effect on HFD-induced obesity and hyperlipidemia. TSP may alleviate hyperlipidemia by altering intestinal flora, reducing inflammatory response, and regulating gene expression of lipid metabolism in liver
Ashish K. Singh et al., 2014 (Singh et al., 2014)	India	EtOH-Induced hyperlipidemia in Charles Foster male rats	*Escherichia coli Nissle* 1917 (n = 6), 10^8 CFU/mL/day *Escherichia coli Nissle* 1917–2 (n = 6), 10^8 CFU/mL/day *Escherichia coli Nissle* 1917–3 (n = 6), 10^8 CFU/mL/day *Escherichia coli Nissle* 1917–4 (n = 6), 10^8 CFU/mL/day	10 weeks	Acetate, Propionate, Butyrate, TG, TC, HDL-C, LDL-C, SOD, MDA, GSH	Probiotics also increase the levels of PQQ and SCFA in vivo to alleviate oxidative damage in liver and the whole body, which may be related to changes in mRNA expression of liver lipid metabolism gen

Abbreviations: HFD: High fat diet, EtoH: Ethyl alcohol, FBG: fasting blood glucose, HOMAIR: Homeostatic model assessment for insulin resistance, GSH-Px: Glutathione peroxidase, PQQ: Pyrro-quinoline quinone, CAT: Catalase, GST: Glutathione S-Transferase, CRR: Complete remission rate, IL-10: Interleukin-10, IL-6: Interleukin-6, VLDL: very low-density lipoprotein.

Table 3
Risk of bias assessment for the included preclinic experiments.

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	Score
Yao	2020	✓		✓	✓	✓			✓	✓	✓	7
de Luna Freire	2021	✓		✓		✓			✓	✓	✓	6
Yang	2021	✓		✓	✓	✓			✓	✓	✓	7
Somabhai	2016	✓		✓	✓	✓			✓	✓	✓	7
de Luna Freire	2023	✓		✓	✓	✓			✓	✓	✓	7
Tian	2022	✓		✓	✓	✓			✓			5
Yan	2022	✓		✓	✓	✓			✓		✓	7
Singh	2024	✓		✓	✓	✓			✓	✓		6
Wang	2022	✓		✓	✓	✓			✓		✓	6

Explanation:(1) publication was peer-reviewed; (2) sample size calculation was provided; (3) environmental conditions such as temperature and humidity were controlled; (4) samples were randomly assigned to groups; (5) detailed probiotic strain information was displayed; (6) probiotic treatment was blinded; (7) main outcome measurements were masked; (8) at least two indicators of SCFA content were reported; (9) compliance with animal experimental ethics was ensured; and (10) conflict of interest was declared by the authors. One point was awarded for each criterion met, with a maximum score of ten.

3.4. Meta-analysis results of the effects of probiotics on blood lipids in animal models

Serum lipid including TC level, TG level, LDL-C level, and HDL-C level in preclinical trials were all analysed using a fixed-effect model. As shown in Fig. 3(a)–(d), there were significant differences in TC, TG, and LDL-C between mice treated with probiotics for hyperlipidemia and those in the control group (TC scores: SMD = −2.68, 95% CI, −3.37 to −2.00, P < 0.00001, I^2 = 0%; TG scores: SMD = −1.83; 95% CI, −2.45 to −1.21; P < 0.00001; I^2 = 0%; LDL-C scores: SMD = −4.24, 95% CI, −5.22 to −3.25, P < 0.00001, I^2 = 0%). There was no significant difference in HDL-C between mice with hyperlipidemia treated with probiotics and those in the control group (HDL-C scores: SMD = 0.45, 95% CI, −0.04 to 0.94, P = 0.07, I^2 = 35%). The results showed that treatment with probiotics could reduce TC, TG and LDL-C in mice but had no significant effect on HDL-C. The original images without removing heterogeneity are shown in Appendix S1.

3.5. Meta-analysis on the effects of probiotics on oxides parameters, inflammatory factors and liver enzymes in animal models

As shown in Fig. 4(a)–(b), a random-effects model was used for the oxides SOD and MDA in mouse liver due to high heterogeneity. There was a significant difference in MDA levels between hyperlipidemic mice treated with probiotics and those in the control group (MDA scores: SMD = −1.28, 95% CI, −2.16 to −0.41, P < 0.00001, I^2 = 54%), but there was no significant difference in SOD levels between mice treated with probiotics and those in the control group (SOD scores: SMD = 0.7, 95% CI, −0.06 to 1.47, P = 0.07, I^2 = 56%).

As shown in Fig. 4(c)–(d), the inflammatory cytokines TNF-α and IL-Iβ in mouse serum were analysed using a fixed-effect model. As shown in Fig. 4(c)–(d), there were significant differences in TNF-α and IL-Iβ levels between hyperlipidemic mice treated with probiotics and those in the control group (TNF-α score: SMD = −0.79, 95%CI, −1.46 to −0.12, P = 0.02, I^2 = 29%; IL-Iβ score: SMD = −3.56, 95% CI, −4.71 to −2.41, P < 0.00001, I^2 = 24%).

As shown in Fig. 4(e)–(f), the liver enzymes AST and ALT in mice were analysed using a fixed-effect model. There were significant differences in AST and ALT levels between hyperlipidemic mice treated with probiotics and those in the control group (AST score: SMD = −2.09, 95%CI, −2.63 to −1.55, P < 0.00001, I^2 = 3%; ALT score: SMD = −1.06, 95% CI, −1.50 to −0.61, P < 0.00001, I^2 = 19%).

The results indicated that probiotics could reduce MDA, TNF-α, IL-Iβ, AST and ALT levels but had no significant effect on SOD. The original images without removing heterogeneity are shown in Appendix S1.

4. Discussion

To the best of our knowledge, this meta-analysis demonstrated significant changes in SCFAs (acetic acid, propionic acid, butyric acid, acetate, propionate, butyrate) in hyperlipidemic mice treated with probiotics for the first time. The mice treated with probiotics showed significant reductions in TC, TG, and LDL-C compared with the control group. Regarding the effects of probiotics on biochemical markers in mice, we observed improvements and changes in inflammatory factors (TNF-α, IL-1β), oxidative stress-related biomarkers (MDA), and liver enzymes (AST, ALT). However, due to the limited number of human clinical trials, further high-quality randomized controlled trials are necessary to enhance confidence in these estimates. The study's limitations, including the duration of some trials, as well as variability in strains, dosages, and strains of mice, may affect the generalizability of the results. Therefore, additional subgroup analyses are required to ensure the reliability of the findings. Furthermore, the long-term lipid-lowering effects of probiotic supplementation and the identification of the most effective lipid-lowering strains and combinations of probiotics are specific areas that warrant further investigation.

Although the specific mechanism by which probiotics treat hyperlipidemia needs further discussion, most evidence suggests that probiotics can regulate lipids by altering the composition of gut microbes and increasing the number of bacteria producing SCFAs(LeBlanc et al., 2017; Wa et al., 2019). In an animal study, the administration of mixed *Lactobacillus plantarum* resulted in elevated levels of acetic acid and butyric acid in mice with dyslipidemia, concomitantly reducing hepatic fat accumulation and significantly lowering lipid levels (H. Li et al., 2020). Additionally, *Lactobacillus sakei* MJM60958 was observed to increase the concentrations of lactic acid and acetic acid in the gastrointestinal tract, effectively decreasing TG levels in dyslipidemic mice (Nguyen et al., 2022). *Enterococcus faecalis* AG5, a probiotic known for its production of propionic acid, demonstrated an inhibitory effect on cholesterol. In vitro fermentation experiments further confirmed that *Enterococcus faecalis* exhibits strong cholesterol assimilation capabilities have the ability to regulate human blood lipids (Mishra et al., 2019). The augmented intake of probiotics and SCFAs has been acknowledged as an efficacious strategy for ameliorating chronic inflammatory pathways, oxidative stress, and hepatic damage (X.-l. Zhang et al., 2017; Y. Zhang et al., 2010). In an animal model study, the administration of mixed probiotics resulted in an elevated content of SCFAs and mitigated inflammation and liver damage induced by a high-fat diet. Notably, there was a significant reduction in the levels of TNF-α and ALT (Al-Muzafar and Amin, 2017). *Clostridium butyricum* was administered to mice exhibiting abnormal oxidation indices and inflammation, resulting

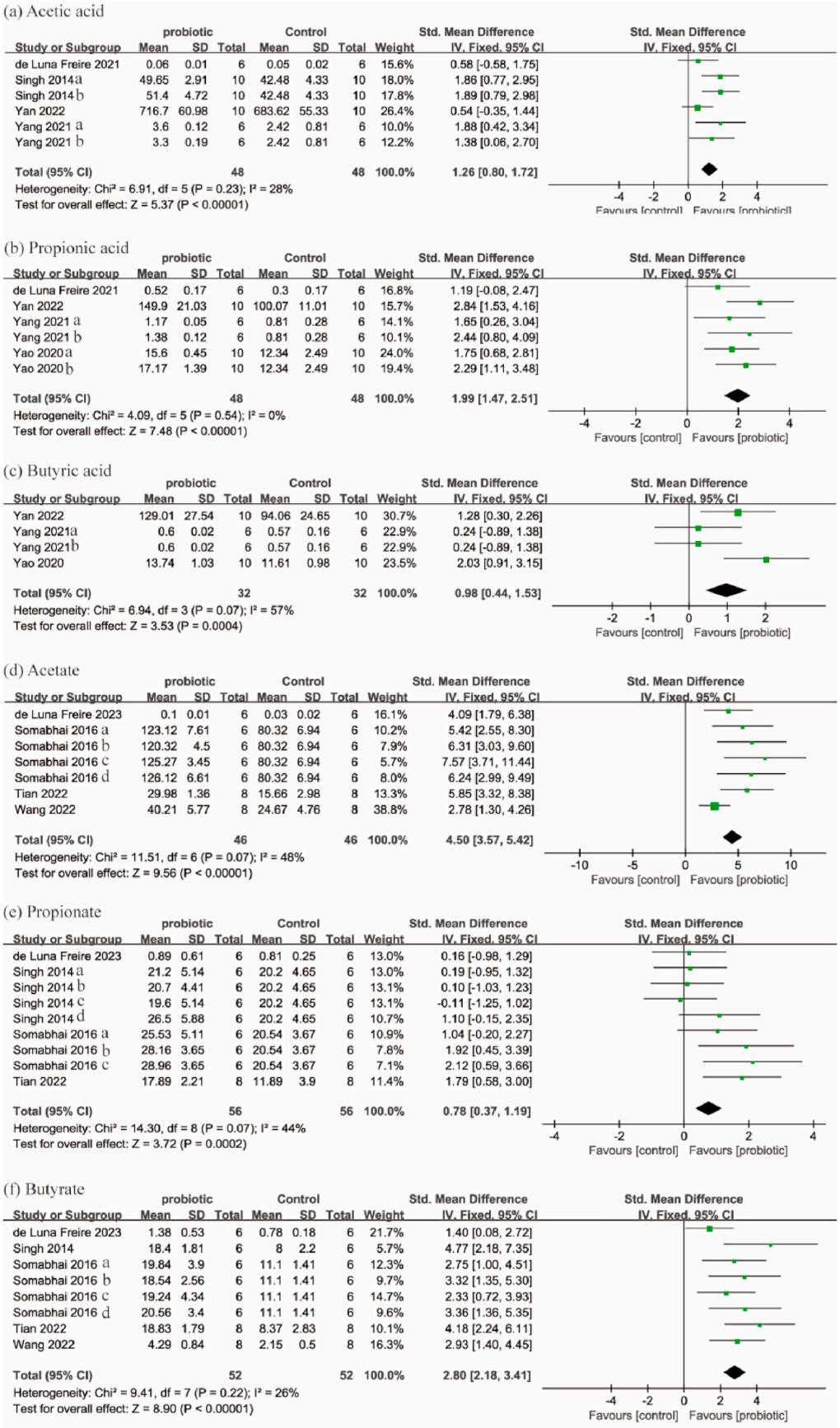

Fig. 2. Forest plot of standardized mean diference (Std. Mean Diference) and 95% confidence intervals (Cl) for the effect of probiotic administration on short-chain fatty acid: (a) acetic acid; (b) propionic acid; (c) butyric acid; (d) acetate; (e)propionate; (f) butyrate. The size of the squares represents the statistical weight of each study, and the rhomboid represent the overall results from all studies.

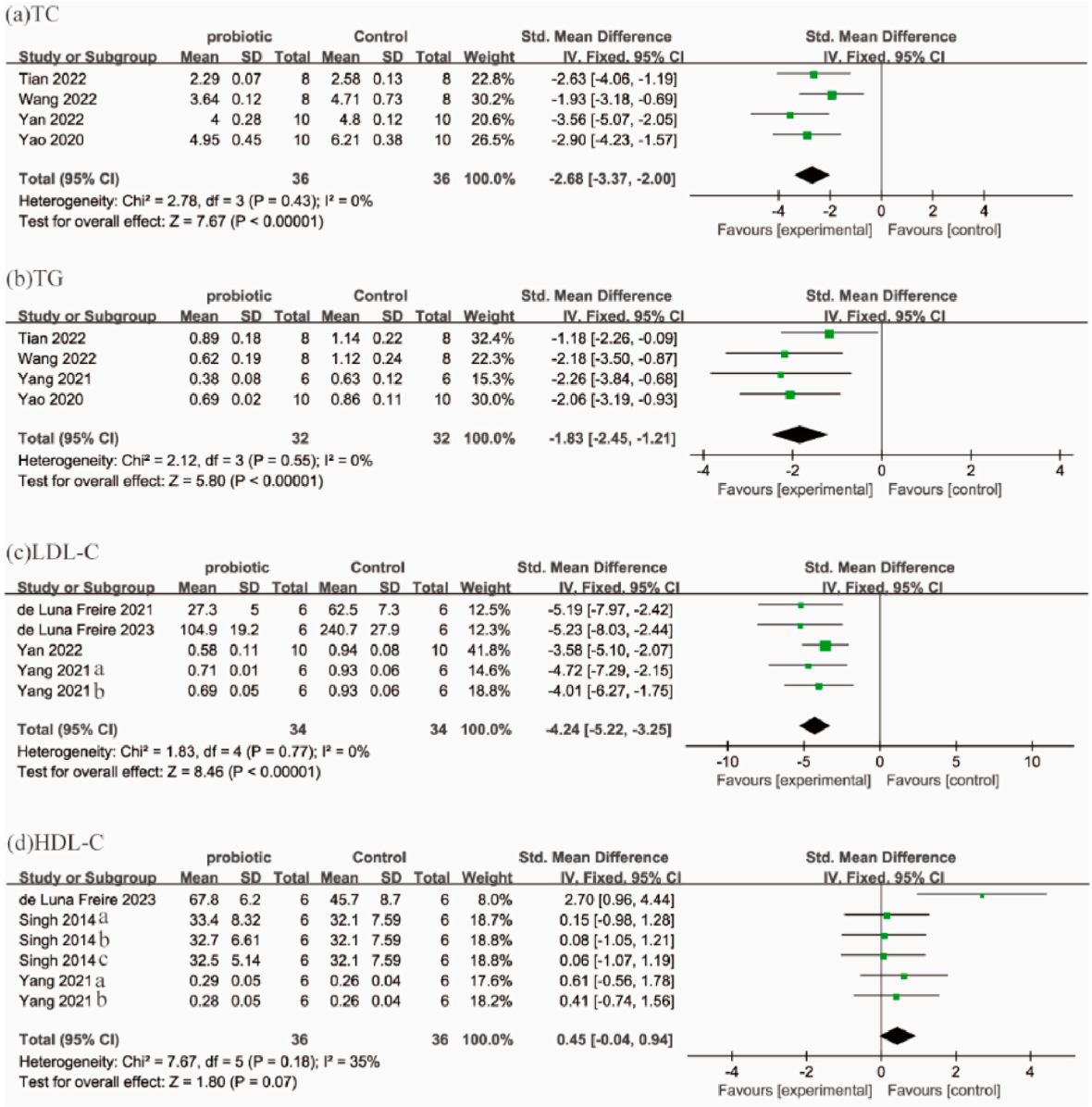

Fig. 3. Forest plot for the effects of probiotics and placebo on lipid parameters in an animal model of hyperlipidemia in preclinical experiments: (a)TC; (b) TG; (c) LDL-C; (d)HDL-C. The size of the squares represents the statistical weight of each study, and the rhomboid represent the overall results from all studies.

in a significant increase in intestinal antioxidant butyrate levels, alongside notable reductions in ALT, AST, and MDA levels (J. Liu et al., 2017). In a separate animal study, the administration of probiotics similarly elevated butyrate concentrations in mice, which effectively mitigated liver damage and oxidative stress, thereby preventing the progression of liver disease (Endo et al., 2013). In the meta-analysis, we observed that after consumption of probiotics, the serum lipids (TC, TG, LDL-C) in hyperlipidemic mice were significantly decreased, while the content of SCFAs, markers of oxidation (liver MDA), markers of inflammation (TNF-α, IL-1β), and markers of liver damage (AST, ALT) were increased in the body. We therefore infer that probiotic supplements may regulate lipids by significantly increasing SCFAs in hyperlipidemic mice, thereby reducing chronic inflammation, oxidative stress, and liver damage.

Most of the literature included in this meta-review supported the positive effects of probiotics on animal models of hyperlipidemia and suggested that an increase in SCFAs played a positive role. Regulation of intestinal microbial composition and related metabolites to reduce blood lipids is one of the mechanisms by which probiotics lower lipids. Therefore, probiotics may increase the content of SCFAs through regulation of SCFA-producing microbes to achieve lipid lowering, anti-inflammatory and immune improvement (Y. Cheng et al., 2022; Jia et al., 2021). Notably, this analysis found that the contents of acetic acid, propionic acid, butyric acid, acetate, propionate and butyrate in mice treated with probiotics increased compared with those in the control group (Fig. 2(a)–(f)). In contrast, compared with control mice, the levels of TC, TG, and LDL-C were significantly reduced in the blood lipids of mice treated with probiotics, except that HDL-C levels did not change (Fig. 3(a)–(d)). This suggests that the increase in SCFAs really has a positive mitigating effect on hyperlipidemia. Previous experiments have shown that acetic acid can reduce TG and LDL-C in rats with high cholesterol by inhibiting liver lipogenesis and increasing bile acid excretion (Fushimi et al., 2006). Propionic acid can be well absorbed into the blood and enter the metabolic pathway to regulate intestinal hormones to improve insulin resistance and reduce TC and TG in blood lipids by inhibiting cholesterol production (Mishra and Ghosh, 2020; Nie et al., 2019). An increase in butyric acid can prevent liver degeneration, obesity and lower TG (X. Li et al., 2022). Acetic acid, butyrate

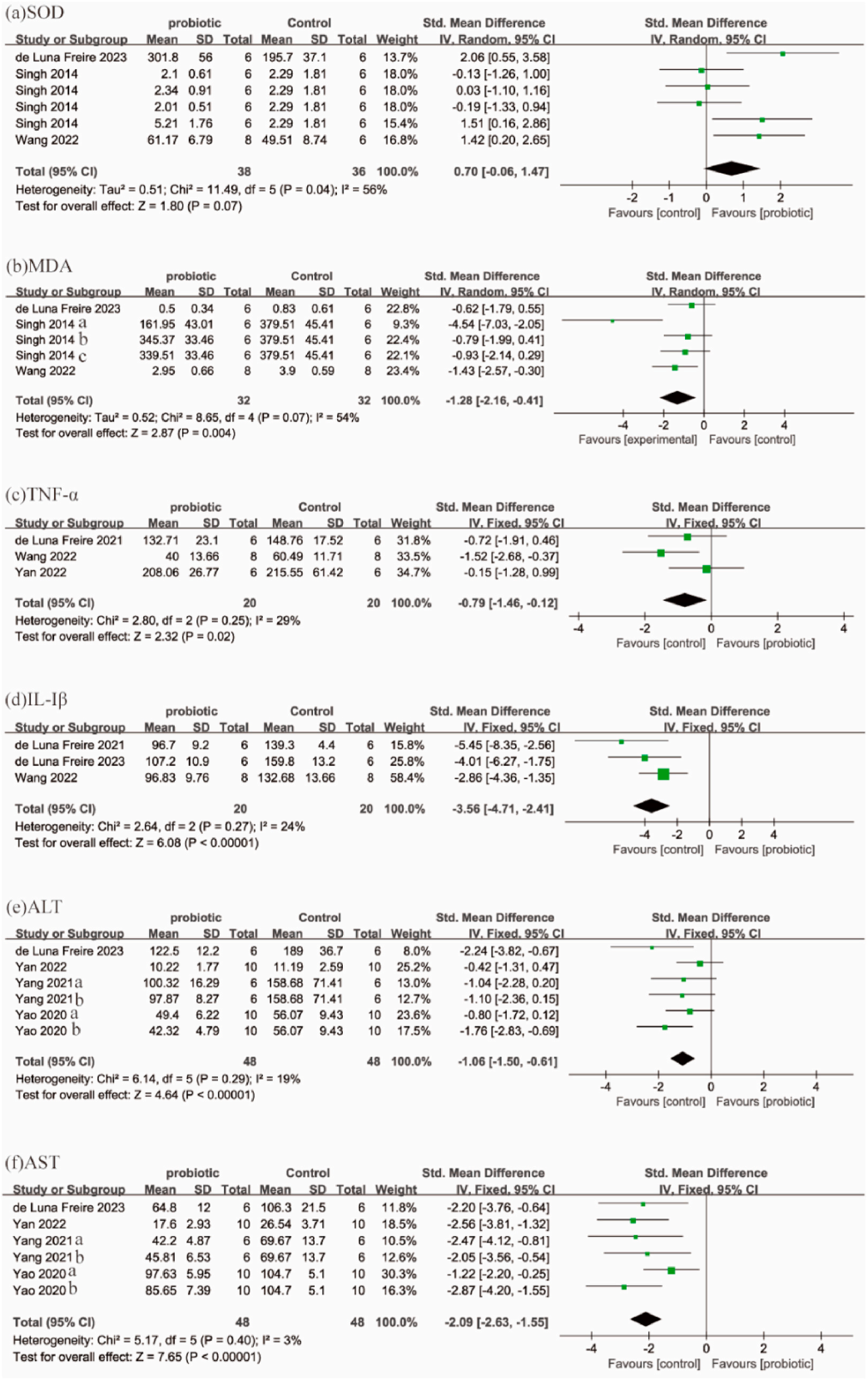

Fig. 4. Forest plot for the effects of probiotics and placebo on hepatic oxidative parameters, inflammatory factors and liver function in an animal model of hyperlipidemia in preclinical experiments: (a)SOD; (b) MDA; (c) TNF-α; (d) IL-1β; (e)AST; (f)ALT. The size of the squares represents the statistical weight of each study, and the rhomboid represent the overall results from all studies.

and propionic acid are converted into acetate, butyrate and propionate forms during metabolism; both are metabolised as short-chain fatty acids (Darzi et al., 2011). Acetate helps maintain an acidic gut environment, effectively preventing pathogen proliferation (LeBlanc et al., 2017). Propionate is effective in anti-inflammatory activities, anti-cancer properties and lowering cholesterol levels while stimulating the release of peptide YY and glucagon-like peptide-1 (GLP-1), which can reduce appetite (Ganesh et al., 2018; Markowiak-Kopeć and Śliżewska, 2020). As a mediator between the brain and gut, butyrate plays an important role in brain-gut axis interactions, protecting the gut while resisting neurodegenerative diseases (H. Ma et al., 2023; McMurdie et al., 2022). It is noteworthy that the analysis also indicated that probiotics had no significant impact on HDL-C levels in hyperlipidemic mice (Fig. 3(d)). This observation can be attributed to the primary function of HDL-C, which is to facilitate reverse cholesterol transport—a process predominantly regulated by the liver and small intestine (Assmann and Gotto Jr, 2004). Conversely, the primary effects of probiotics are localized within the gastrointestinal tract. Furthermore, HDL-C levels are influenced by a combination of genetic factors, dietary habits, physical activity, and body fat distribution, areas in which probiotics exert minimal influence (Waldman et al., 2014).

SCFAs are formed by microbial fermentation in the gut. Microbes convert complex cell wall components and mucins into sugars, which are then fermented to form SCFAs(Nagpal et al., 2018; Zhuang et al., 2019). Therefore, the content of SCFAs is closely related to changes in gut microbes (Dang and Marsland, 2019; Joseph et al., 2019). Probiotics, as one of the recognised methods for maintaining intestinal stability, can alter the dominant bacteria in the human colon model system and regulate metabolite SCFA production. The articles included in this analysis also examined changes in the gut microbiota of hyperlipidemic mice after consumption of probiotics. A preclinical study (C. Wang et al., 2022) found that consumption of probiotics in hyperlipidemic mice significantly increased the number of recognised SCFA-producing microbes such as *Lactobacillus*, *Blautia*, and *Bacteroides*. Previous study found that mice supplemented with probiotics had increased levels of short-chain fat-producing lactic acid bacteria, which have a positive effect on strengthening the intestinal barrier, maintaining immunity and lowering blood lipids (Thananimit et al., 2022). More detailed information about the potential mechanisms by which gut microbes increase SCFA to reduce lipids, inflammatory factors, and oxidative stress in the body is shown in Fig. 5. Therefore, future analyses and trials should conduct more comprehensive gut microbiome and metabolite detection to elucidate the specific mechanisms by which probiotics affect SCFAs and hyperlipidemia in patients.

Oxidative stress, increased pro-inflammatory factors, and liver damage are crucial in the exacerbation of hyperlipidemia (C. Li et al., 2014; Miri et al., 2012). In this meta-analysis, we observed that the oxidative marker MDA in hyperlipidemia mice decreased significantly after probiotic intervention compared with control mice (Fig. 4(a)–(b)). There is evidence that SCFAs can regulate oxidative stress, possibly by increasing oxidoreductase activity. Previous studies have demonstrated that butyrate has the ability to enhance glutathione reductase activity and regulate catalase activity (Ebert et al., 2003; Yano et al., 1989). In this analysis, it was observed that probiotics had no significant effect on SOD levels in hyperlipidemic mice (Fig. 4(b)). This lack of effect may be attributed to the fact that SOD is predominantly produced by mitochondria, the cytoplasm, and the nucleus within cells, and its activity is primarily localized at the cellular level. Consequently, its regulation may not be directly influenced by intestinal microbiota. Additionally, individual variability and the brief duration of the intervention may have contributed to the difficulty in detecting substantial changes in SOD levels (Okado-Matsumoto and Fridovich, 2001). As shown in Fig. 4 (c)–(d), it was demonstrated that the inflammatory factors TNF-α and IL-1β in hyperlipidemia mice were significantly decreased after

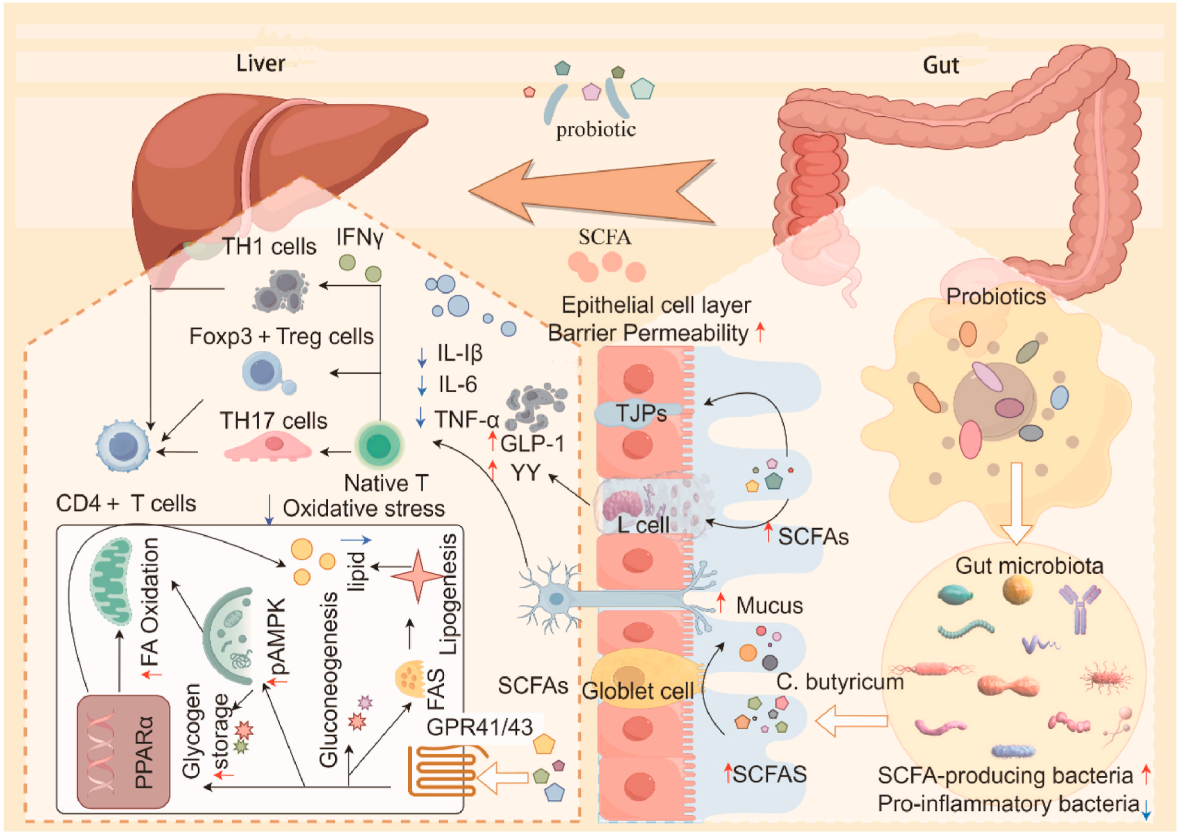

Fig. 5. Potential mechanisms by which probiotics increase SCFA to reduce lipids, inflammatory factors and oxidative stress (The figure was drawn by Figdraw). Abbreviations: TJPs, tight junction protein; T-reg: regulatory T-cell; FOXP3: forkhead box P3; GLP-1: glucagon like peptide-1; FA: fatty acid; PYY: peptide YY.

probiotic intervention compared with control mice. There is evidence that SCFAs can play an anti-inflammatory role; butyric acid, for example, inhibits the inflammatory cytokine TNF-α by activating GPR41 in macrophages, and oral butyric acid reduces inflammation in humans by down-regulating NF-κB and IL-1β(T. Li et al., 2015; P. Liu et al., 2021). Acetic acid can activate the GPCR pathway to inhibit LPS-induced TNF-α secretion (Masui et al., 2013). In this meta-study, it was demonstrated that the liver function indicators AST and ALT in hyperlipidemia mice were significantly decreased after probiotic intervention compared with control mice (Fig. 4(e)–(f)). In 2022, an experiment proved that SCFA can improve the metabolic function of the liver through FFAR3, and its use of metabolomics proved that promoting the production of intestinal SCFAs can effectively reduce liver fibrosis (Visekruna and Luu, 2021; C. Wang et al., 2022).

The aim of our research was to show the effects of probiotics on SCFAs in preclinical trials including acetic acid, propionic acid, butyric acid, acetate, propionate and butyrate. The possible positive effects of increased SCFA on oxidative stress, pro-inflammatory factors, and liver damage were also investigated in animal models. This meta-analysis provides new evidence to examine the role of probiotics in regulating gut microbiota to increase SCFA in alleviating hyperlipidemia in hyperlipidemic animal models.

5. Conclusion

Preclinical studies have shown that probiotics can effectively increase the content of short-chain fatty acids (acetic acid, propionic acid, butyric acid, acetate, propionate, butyrate) and reduce the level of blood lipid in hyperlipidemia mice, but has no significant effect on HDL-C. In addition, probiotic supplementation alleviated complications such as oxidative stress, inflammation and liver damage caused by hyperlipidemia by effectively reducing MDA, TNF-α, IL-Iβ, AST and ALT levels, but had no significant effect on SOD. However, due to the limited number of human clinical trials, this analysis can only provide some references for the study of probiotics lipid-lowering effects based on preclinical experiments, and further analysis of human randomized controlled trials is needed.

CRediT authorship contribution statement

Yuanyue Yao: conceived research, collected data, analysed data, drafted the manuscript. **Qing Hong:** conceived research, analysed data, drafted the manuscript, securing funding. **Siqi Ding:** collected data. **Jie Cui:** collected data. **Wenhui Li:** collected data. **Jian Zhang:** collected data. **Ye Sun:** collected data. **Yiyang Yu:** collected data. **Mingzhou Yu:** collected data. **Li Mi:** collected data. **Yinzhu Wang:** collected data. **Jinchi Jiang:** conceived research, writing–review & editing, securing funding. **Yonghong Hu:** conceived research, writing–review & editing, securing funding.

Declaration of competing interest

Yuanyue Yao, Qing Hong, Siqi Ding, Jie Cui, Wenhui Li, Jian Zhang, Ye Sun, Yiyang Yu, Mingzhou Yu, Li Mi, Yinzhu Wang, Jinchi Jiang and Yonghong Hu declare that they have no conflict of interest or financial conflicts to disclose, and manuscript is approved by all authors for publication. I would like to declare on behalf of my coauthors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crfs.2024.100885.

Data availability

Data will be made available on request.

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