

Probiotics in the treatment of metabolic-associated fatty liver disease in adult patients: A systematic review and meta-analysis

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Abstract

Aim: This meta-analysis of randomized controlled trials (RCTs) was performed to evaluate the effectiveness of probiotics in treating metabolic-associated fatty liver disease (MAFLD) in adult patients, focusing primarily on liver function, glucose levels, lipid metabolism, and inflammation.

Method: RCTs completed on or before November 30, 2024 were acquired from PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials databases. A meta-analysis of the therapeutic efficacy of probiotics on liver function, glucose and lipid metabolism, and inflammatory biomarkers was performed via RevMan 5.4 software. Two reviewers independently extracted studies and patient characteristics and evaluated the quality of the studies utilizing the Cochrane risk-of-bias tool. A meta-analysis was conducted using RevMan 5.4 software.

Results: A total of 18 RCTs involving 962 adult patients were included. According to the results of the meta-analysis, probiotic therapy may lower the levels of alanine aminotransferase [mean difference (MD): -9.09(-10.15, -8.03), $p < 0.00001$], aspartate aminotransferase [MD: -8.52(-9.48, -7.56), $p < 0.0001$], glutamyl transferase [MD: -5.57(-6.68, -4.47), $p < 0.00001$], total cholesterol [MD: -0.17(-0.32, -0.02), $p = 0.03$], fasting plasma glucose [MD: -0.47(-0.62, -0.33), $p < 0.00001$], and homeostasis model assessment of insulin resistance [MD: -0.65(-1.28, -0.03), $p = 0.04$] in patients with MAFLD compared with those in control individuals. Nonetheless, among MAFLD patients, there was no statistically significant increase in triglyceride levels, tumor necrosis factor- levels, or C-reactive protein levels.

Conclusion: There is promising evidence that probiotic supplementation can reduce liver enzyme levels and regulate glycometabolism and cholesterol metabolism in patients with MAFLD.

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) (formerly non-alcoholic fatty liver disease (NAFLD)) is a condition characterized by the accumulation of fat in the liver, typically in the absence of excessive alcohol consumption. The term MAFLD refers to a range of liver conditions that include simple steatosis, steatosis with inflammation, nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. MAFLD has become very common in the last few years and is now a major public health problem, which is strongly related to the increasing incidence of obesity, type 2 diabetes and metabolic syndrome. The prevalence of MAFLD is estimated to affect approximately 25% of the global population, with higher rates observed in individuals with metabolic syndrome and type 2 diabetes [1,2]. The pathophysiology of MAFLD is complex and involves multiple factors, such as dysregulation of lipid metabolism, insulin resistance, inflammation, and gut microbiota dysbiosis [3]. The gut microbiota has emerged as a critical player in the pathogenesis of MAFLD. Research indicates that gut dysbiosis, an imbalance in the gut microbial community, contributes significantly to the development and progression of MAFLD [4,5].

Probiotics are safe and beneficial in treating various gastrointestinal conditions, such as inflammatory bowel disease, irritable bowel syndrome, constipation, and hepatic encephalopathy [6-9]. Recent clinical trials and studies have demonstrated the efficacy of specific probiotic strains in improving liver function and reducing markers

of liver inflammation in patients with MAFLD [10-12]. Given that multiple clinical trials have shown that probiotic supplementation has therapeutic effects on MAFLD, we conducted this meta-analysis of clinical RCTs to evaluate its efficacy, aiming to provide evidence-based guidance for the clinical treatment of MAFLD in adult patients.

Materials and methods

The reporting format of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement revised in 2020 [13].

Registration of review protocol

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews; CRD42025634671).

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Eligibility criteria

The inclusion criteria included the following: (1) studies on the treatment of adult patients with metabolic-associated fatty liver disease with probiotics; (2) randomized controlled trials, cluster randomized trials, and crossover trials; (3) placebo or standard treatment as the control group; (4) patients with metabolic-associated fatty liver disease; (5) outcomes, including survival events (mortality), clinical events, patient-reported outcomes (such as improvement in symptoms or quality of life), side effects, and other indicators; (6) studies using similar or comparable outcome measures; and (7) publications in English.

The exclusion criteria were as follows: (1) studies not related to the treatment of metabolic-associated fatty liver disease with probiotics; (2) nonrandomized controlled trials; (3) studies without placebo or standard treatment as the control group; (4) patients who were under 18 years old; (5) patients with other liver diseases; (6) studies without clear outcome measures; (7) studies published in languages other than English; and (8) studies without full texts available.

Information sources

We conducted a comprehensive literature search of the MEDLINE and EMBASE databases and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to November 30, 2024. Only studies published in English were included.

Search strategy

((Probiotics OR probiotics supplement) AND ((Metabolic Associated Fatty Liver Disease) OR (MAFLD) OR (Metabolic Dysregulation-Associated Fatty Liver Disease) OR (Nonalcoholic Fatty Liver Disease) OR (NAFLD)))

Study selection

Two independent reviewers (Guo JT and Xu L) used a predefined relevance criterion form to screen the studies. After the titles and abstracts were read, duplicate studies and studies that did not meet the inclusion criteria were excluded. Full-text access to relevant literature was obtained, and studies were screened for inclusion. Discrepancies at any stage were resolved by discussion with a third reviewer (Bai X). The level of agreement during screening was evaluated using the kappa statistic, with an *a priori* threshold of 0.60 for an acceptable level of agreement.

Data extraction

The data were extracted after the full texts were read. Two independent reviewers (Guo JT and Xu L) extracted the data. A third independent reviewer (Bai X) reviewed the data and resolved any discrepancies.

Data information

The extracted data included the following information: authors and publication year; study population; case number; treatment duration; intervention; and outcomes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG), homeostasis model assessment of insulin resistance (HOMA-IR), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP).

Risk of bias in individual studies

Risks of bias in individual studies were assessed using the Cochrane risk of bias tool. This tool assesses the following six domains of bias: sequence generation (decided as low risk bias, high risk, or unclear

risk), allocation concealment (decided as low risk bias, high risk, or unclear risk), blinding of outcome assessment (decided as low risk bias, high risk, or unclear risk), incomplete outcome data (decided as low risk bias, high risk, or unclear risk), selective outcome reporting (decided as low risk bias, high risk, or unclear risk), and other types of bias (decided as low risk bias, high risk, or unclear risk). Two reviewers (Guo JT and Xu L) independently assessed study quality, and the assessments were verified by a third reviewer (Bai X).

Summary measures

For dichotomous data, summary statistics are expressed as odd ratios with 95% CIs for interpretation.

Synthesis of results

All analyses were conducted in Review Manager Version 5.4. A statistically significant difference was considered at $\alpha=0.05$. Statistical heterogeneity in the included studies was examined using I^2 statistics. If the result of the heterogeneity test was $P \geq 0.10$, a fixed effect model was used for the meta-analysis; if $P < 0.10$, the sources of heterogeneity were investigated. If no obvious clinical heterogeneity and no clear statistical heterogeneity was observed, a random effects model was used for the meta-analysis. If the degree of clinical heterogeneity was too high, the data synthesis was discontinued, and a single research analysis was used instead. Sensitivity analysis was performed on some of the results from the aggregate analysis.

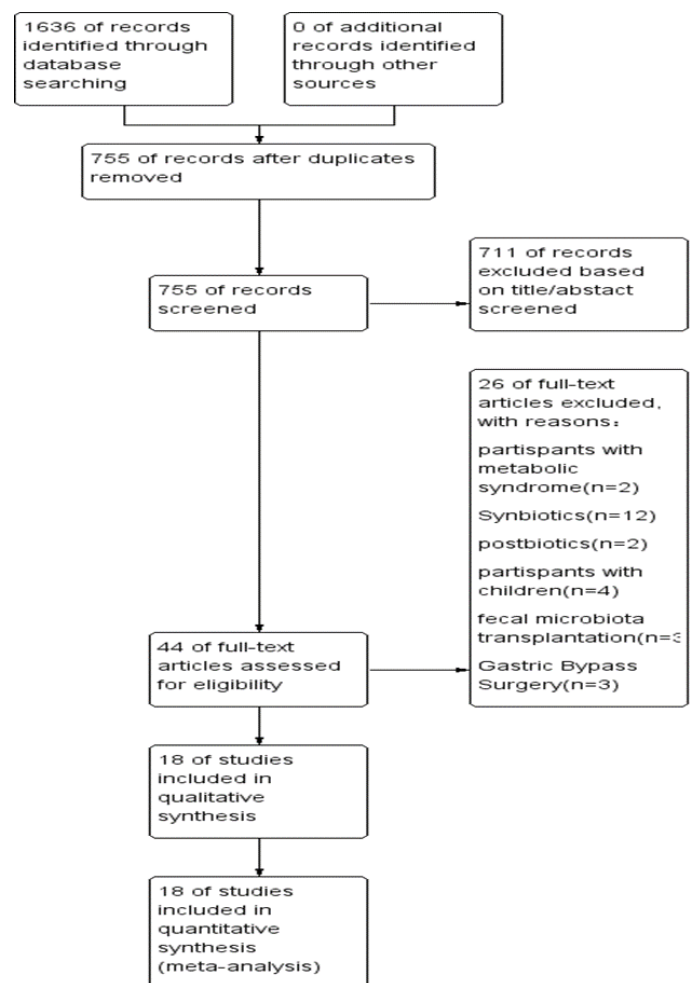


Figure 1. Flow chart of the retrieved studies

Assessment of publication bias

Potential publication bias was evaluated by funnel plot analysis.

Results

Study selection

A total of 1636 English-language publications were identified in the literature search. Of the identified publications, 881 articles that did not meet the inclusion criteria were eliminated. After the titles and abstracts were read, 711 articles were eliminated. Forty-four full-text articles published in English were retrieved. Of these, 12 articles were excluded because the interventions involved synbiotics, 2 because the interventions involved postbiotics, 3 because the interventions involved gastric bypass surgery, 3 because the interventions involved fecal microbiota transplantation, 4 because the participants were children, and 2 because the participants had metabolic syndrome. Ultimately, 18 RCTs fulfilled the inclusion criteria. Figure 1 shows the flow chart of the retrieved studies. The level of agreement between the 2 reviewers was acceptable ($\kappa = 0.67$).

Study characteristics

The screening process is illustrated in a flow chart (Figure 1). From electronic and manual searches of the three databases, we obtained 1,636 trials, 881 of which were duplicates. Among the 755 unduplicated articles, 711 were excluded on the basis of their title or abstract, leaving 44 reports for full manuscript review. Only 18 RCTs met our inclusion criteria [10-12,14-28]. The summarized characteristics of the 18 RCTs are shown in Table 1. The total number of patients was randomized into probiotic and control groups. Most of the studies were randomized, parallel-group, placebo-controlled trials. Additionally, many of the clinical trials were double-blind trials. The 18 trials were published in English between 2011 and 2024, with sample sizes ranging from 20 to 140.

Table 1. Characteristics of the studies included in the meta-analysis

Studies	Country	n	Intervention duration	Interventions (Probiotic strain(s))	Interventions (control group)	Outcomes
Aller 2011 [14]	Spain	14/14	12 w	Lactobacillus, <i>Streptococcus</i>	Placebo	HOMA-IR, TC, TG, ALT, AST
Wong 2013 [15]	Hong Kong	10/10	180 d	Lepicol probiotic	Nonplacebo	ALT, AST, BMI, IHTG,
Shavakhi 2013 [28]	Iran	31/32	180 d	Protexin	Placebo	ALT, AST, TC, TG, FBG
Sepideh 2016 [25]	Iran	21/21	8 w	Lactocare	Placebo	FBG, insulin, HOMA-IR, IL-6
Abdel Monem 2017 [17]	Egypt	15/15	4 w	Lactobacillus	Nonplacebo	ALT, AST
Manzhali 2017 [18]	Ukraine	38/37	12 w	Lactobacillus, Bifidobacterium, <i>Streptococcus</i>	Nonplacebo	ALT, AST, GGT, TC, TG
Kobyliak 2018 [19]	Ukraine	30/28	8 w	Multi strain probiotics	Placebo	FLI, liver stiffness, ALT, AST, GGT, TC, TG, TNF- α , IL-6
Ahn 2019 [20]	Korea	30/35	12 w	6 bacterial species	Placebo	IHF fraction, VFA, BMI, ALT, AST, TG, Insulin, IL-6, TNF- α , LPS, HOMA-IR
Duseja 2019 [21]	India	19/20	48 w	Multi strain probiotics	Placebo	ALT, AST, IL-6, TNF- α , Leptin, NAS score
Chong 2021 [22]	UK	19/16	10 w	<i>Streptococcus</i> , Bifidobacterium, Lactobacillus	Placebo	ALT, AST, TC, TG, LDL-c, HOMA-IR, CRP, NAFLD fibrosis risk score
Cai 2020 [26]	China	70/70	12 w	Bifidobacterium, Lactobacillus and Enterococcus	Placebo	ALT, AST, GGT, TBIL, TC, TG, LDL-c, HOMA-IR, NAS score,
Mohamad Nor 2021 [23]	Malaysia	17/22	180 d	Lactobacillus, Bifidobacterium	Placebo	ALT, AST, GGT, TC, TG, Steatosis score, Fibrosis score
Barcelos 2023 [24]	Brazil	23/23	24 w	probiotic mix	Placebo	FBG, Insulin, HOMA-IR, ALT, AST, GGT, TC, TG, BMI
Escouto 2023 [10]	Brazil	23/25	180 d	Lactobacillus acidophilus, Bifidobacterium lactis	Placebo	APRI score, NAFLD fibrosis score, ALT, AST, TNF- α , CRP, FBG, TC, TG, HOMA-IR, Insulin
Laue 2023 [11]	Germany	59/59	12 w	<i>L. fermentum</i> strains K7-Lb1, K8-Lb1 and K11-Lb3	Placebo	ALT, AST, GGT, CRP, FBG, TC, TG, HOMA-IR, liver steatosis grade
Aybo 2023 [27]	Malaysia	18/22	180 d	6 bacterial species	Placebo	ALT, AST, GGT, FBG, TC, TG,
Abd 2024 [16]	Egypt	25/25	12 w	Lact��l Fort	Nonplacebo	ALT, AST, fibrosis score
Lin 2024 [12]	Taiwan	15/11	60 d	TSF331, TSR332, and TSP05	Placebo	AST, ALT, UA, gut microbiota

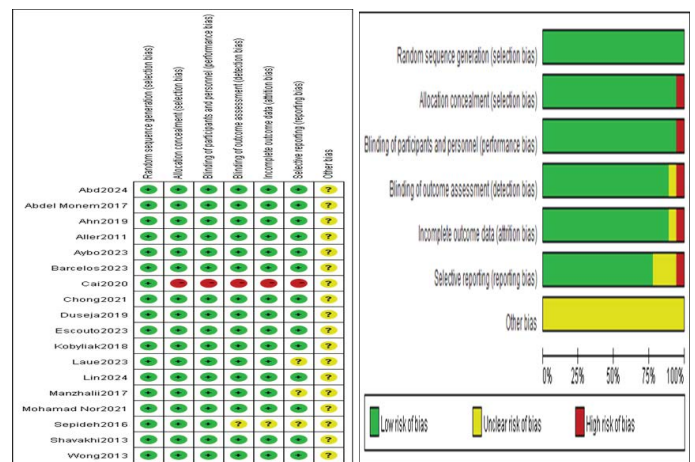


Figure 2. Risk of bias graph and risk of bias summary

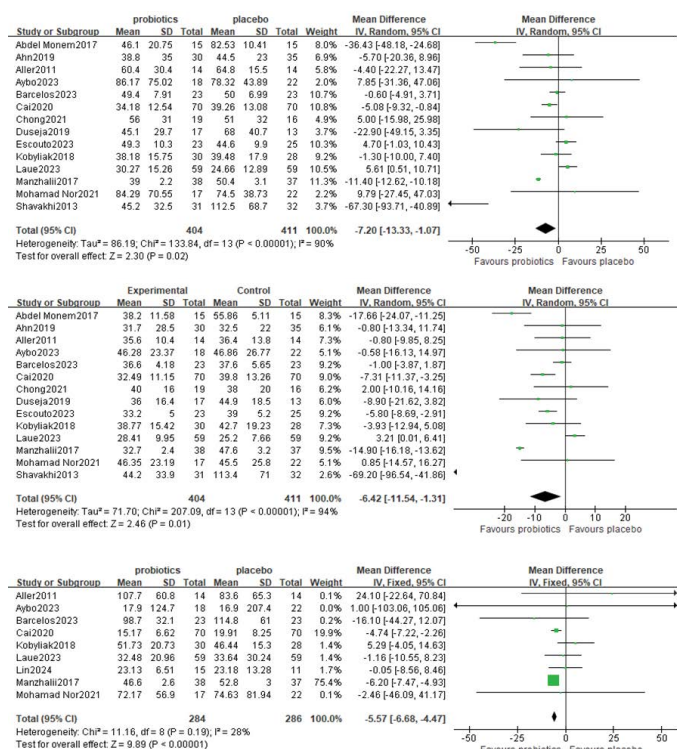
Risk of bias within studies

The risk of bias within the 18 studies included in this meta-analysis is summarized in Figure 2, showing the risk of bias graph and the risk of bias summary.

Synthesis of results

1. Effect on liver function

A meta-analysis of liver function was performed among studies that reported ALT, AST and GGT levels. A total of 14 RCTs involving 815 patients reported the pooled effect of probiotic supplementation on ALT levels. These trials showed heterogeneity in the consistency of the trial results (chi square=133.84, $p < 0.00001$; $I^2 = 90\%$); therefore, a random effects model was used for the statistical analysis. Overall, the



results of the meta-analysis suggested that probiotic regulation could reduce ALT in patients with MAFLD, as shown in Figure 3A [MD: -9.09 (-10.15, -8.03), $p < 0.00001$]. Sensitivity analysis revealed that removing an individual trial did not change the overall effect.

Fourteen studies, including a total of 815 participants, were used to examine the pooled effect of probiotic supplementation on AST levels. The trials showed heterogeneity in the consistency of the trial results (chi square=304.73, $p < 0.00001$; $I^2=96\%$); therefore, a random effects model was used for the statistical analysis. A meta-analysis revealed a significant beneficial effect of probiotics compared with the control group in decreasing the level of AST [MD: -8.52 (-9.48, -7.56), $p < 0.0001$] (Figure 3B).

Nine studies, including 570 participants, presented the pooled effect of probiotic supplementation on GGT levels. The trials showed heterogeneity in the consistency of the trial results (chi square=11.16, $p < 0.00001$; $I^2=28\%$); therefore, a random effects model was used for the statistical analysis. A meta-analysis revealed a significant beneficial effect of probiotics compared with the control group in decreasing the level of GGT [MD: -5.57 (-6.68, -4.47), $p < 0.0001$] (Figure 3C).

2. Effects on lipid metabolism

Twelve studies, including 706 participants, used TC levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 39.29, $P < 0.0001$; $I^2 = 72\%$). A meta-analysis revealed a beneficial effect of probiotics compared with the control group in decreasing the TC level [MD: -0.17 (-0.32, -0.02), $p = 0.03$] (Figure 4A).

Twelve studies, including 706 participants, used TG levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 32.59, $P < 0.0001$; $I^2 = 72\%$). A forest plot showing the results of the meta-analysis on TG is displayed in

Figure 4B, revealing no significant differences between the experimental and control groups [MD: -0.09 (-0.31, 0.13), $p = 0.41$].

3. Effects on glucose and HOMA-IR

Seven studies, including 380 participants, used FBG levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 41.07, $P < 0.00001$; $I^2 = 85\%$). A meta-analysis revealed a significant beneficial effect of probiotics compared with the control group in decreasing the level of FBG [MD: -0.47 (-0.62, -0.33), $p < 0.00001$] (Figure 5A).

Eight studies, including 522 participants, used the HOMA-IA levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 84.91, $P < 0.00001$; $I^2 = 92\%$); therefore, a random effects model was used for the statistical analysis. A meta-analysis revealed a beneficial effect of probiotics compared with the control group in decreasing the level of HOMA-IR [MD: -0.65 (-1.28, -0.03), $p = 0.04$] (Figure 5B).

4. Effect on inflammation biomarkers

Four studies, including 201 participants, used TNF- α levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 32.59, $P = 0.08$; $I^2 = 56\%$). A forest plot showing the results of the meta-analysis of TNF- α is displayed in Figure 6A, revealing no significant differences between the experimental and control groups [MD: -0.59 (-1.24, 0.06), $p = 0.07$] (Figure 6A).

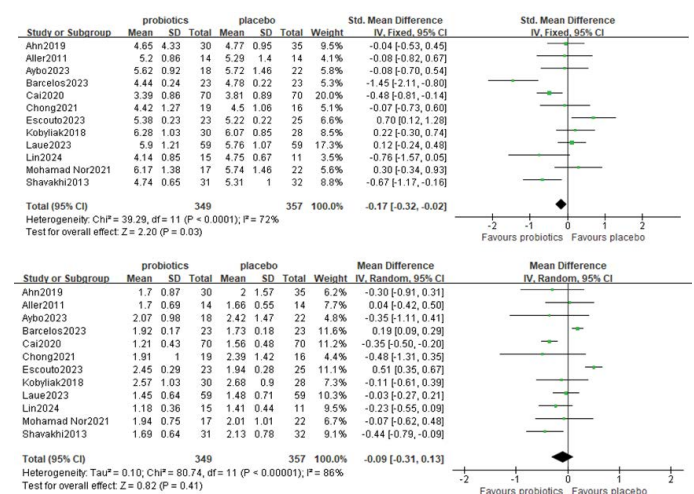


Figure 4. Forest plot comparing TC and TG levels in lipid metabolism

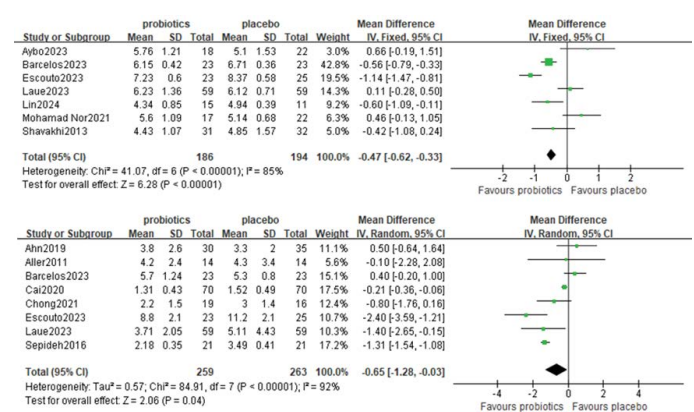


Figure 5. Forest plot comparing FBG and HOMA-IR levels

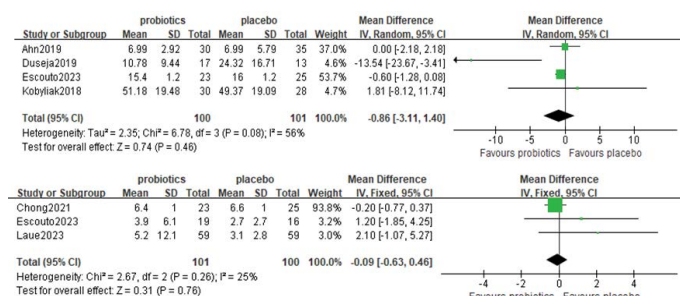


Figure 6. Forest plot comparing TNF-a and CRP levels

Three studies, including 201 participants, used CRP levels to measure outcomes. The trials showed heterogeneity in the consistency of the trial results (chi-square = 2.67, $P=0.26$; $I^2 = 25\%$). A forest plot showing the results of the meta-analysis of CRP is displayed in Figure 6B, revealing no significant differences between the experimental and control groups [MD: 0.28 (-0.94, 1.50), $p=0.65$] (Figure 6B).

Publication bias

Funnel plot analysis of the 14 RCTs of ALT levels revealed an asymmetric distribution indicating the presence of publication bias (Figure 7).

Discussion

Summary of evidence

This study performed a systematic review and quantitative analysis of the scientific literature to assess the therapeutic effectiveness of probiotic interventions in MAFLD. The meta-analysis incorporated data from 18 RCTs, involving 962 participants, with a focus on adult populations. This study evaluated the impact of probiotic supplementation on hepatic enzyme profiles, glycemic and lipid metabolic parameters, and systemic inflammatory markers in MAFLD patients. The synthesized evidence demonstrated that probiotic administration significantly reduced total cholesterol levels; improved hepatic enzyme levels; and increased the levels of glucose metabolism indicators, such as ALT, AST, GGT, FBG and HOMA-IR, compared with those in placebo controls. Nevertheless, there appears to be little effect of probiotic supplementation on TG and inflammatory biomarkers (CRP and TNF-a).

Abnormalities in the gut-liver axis, including intestinal microecology imbalance, intestinal bacterial overgrowth, increased intestinal permeability, or intestinal leakage, play a role in the occurrence and development of MAFLD [29]. Probiotic supplementation for patients with MAFLD is aimed at restoring the normal gut microbiota, thereby reducing liver inflammation. This may be the rationale for treating MAFLD with probiotics. Increases in the serum levels of hepatic enzymes, such as AST, ALT, ALP, and GGT, are indicative of liver damage.

The progression of MAFLD, which leads to elevated hepatic enzymes, aligns with the 'two-hit theory', where fat accumulation serves as the initial factor ('first hit'), and subsequent liver injury from necroinflammation and oxidative stress constitutes the 'second hit' [30]. The "multiple-hit" pathological hypothesis has been widely recognized in recent years [31,32]. Studies demonstrate the efficacy of microbial therapy in reducing hepatic enzymes in individuals with NAFLD. Treatment with probiotics specifically lowered levels of ALT, AST and GGT, with GGT recognized as a highly sensitive marker for liver damage and a novel indicator of inflammation and oxidative stress [33].

In this review, we found that probiotics were closely associated with a decrease in AST, ALT, and GGT levels, suggesting that probiotic supplementation in NAFLD patients may have protective effects on liver function by regulating the composition and metabolism of the gut microbiota. This conclusion is consistent with previous meta-analyses by Loman [34] and Wang [35].

A key factor in the pathogenesis of MAFLD is insulin resistance [36], which contributes to the progression of hepatic steatosis to more severe forms of liver disease, including NASH and cirrhosis. The intricate link between NAFLD and DM is well documented, with insulin resistance and hyperinsulinism serving as hallmark features of NAFLD. Studies have reported elevated fasting insulin levels in NAFLD patients, even in nondiabetic individuals [37].

HOMA-IR, a key indicator of insulin resistance, is particularly useful in evaluating NAFLD among diabetic patients [38,39] and has been identified as an independent predictor for advanced liver fibrosis in NAFLD patients [40]. Further-more, the FBG levels, another indicator of glycemic control, are significantly greater in individuals with NAFLD [41,42]. This study demonstrated that therapy with probiotics can significantly reduce insulin and FBG levels, highlighting the potential of these interventions in improving insulin resistance in the NAFLD population.

The pathophysiology of MAFLD involves complex interactions between lipid metabolism and various metabolic disturbances, including insulin resistance and dyslipidemia. Dyslipidemia, characterized by elevated serum TG and LDL-C levels, along with reduced HDL levels, is closely linked to MAFLD and its comorbidities [43,44]. The gut microbiota plays a vital role in lipid metabolism, a process influenced by microbiota-derived metabolites such as short-chain fatty acids and lipopolysaccharides [45,46]. Probiotics affect lipid profiles through various mechanisms, including modulation of the gut microbiota composition, enhancement of intestinal barrier function, and regulation of systemic inflammation. Clinical studies have demonstrated that probiotic supplementation can lead to significant reductions in total cholesterol, triglycerides, and LDL-C while increasing HDL-C levels in hyperlipidemic patients [47]. In this review, we found that probiotics were closely associated with a decrease in TC, suggesting that probiotic supplementation in MAFLD patients may have protective effects on cholesterol metabolism. However, we noticed that the TG levels were not significantly different between MAFLD patients and controls.

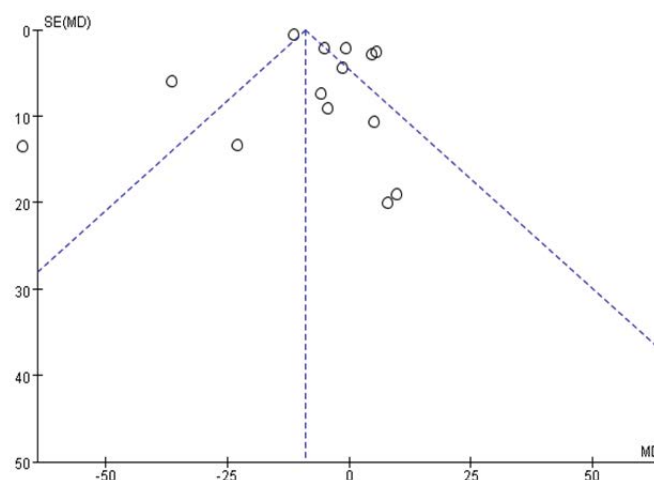


Figure 7. Funnel plot analysis comparing ALT levels

The inflammatory response in MAFLD is driven primarily by oxidative stress and dysregulated lipid metabolism, which can activate proinflammatory pathways. Elevated levels of inflammatory markers, such as CRP and TNF- α , have been linked with NAFLD [48]. Previous studies have explored the beneficial effects of probiotics on inflammatory markers [49,50]. A previous systematic review and meta-analysis highlighted the beneficial effects of probiotics on liver function and inflammation in individuals with nonalcoholic fatty liver disease [51]; however, in our study, probiotic treatment had no significant effect on CRP or TNF- α . The effects of probiotics on these markers have yet to be elucidated.

Limitations

Because meta-analysis involves secondary research, the evidence is influenced by the quality of the included studies. There are several limitations in our meta-analysis that should be mentioned. First, the quality of some studies included was low. More high-quality, multicenter, high-standard RCTs are needed in the future. Second, we searched for unpublished articles in English but were unable to identify all relevant unpublished data for inclusion. Publication bias was also evident through a funnel plot analysis. Third, since we searched for articles published only in English, reporting bias may exist.

Conclusion

Our meta-analysis revealed that probiotic consumption among adult patients with MAFLD has a beneficial effect on metabolic indicators by significantly reducing the levels of ALT, AST, GGT, TC, FBG and HOMA-IR. However, this intervention had no statistically significant effect on TC, CRP or TNF- α levels. There is promising evidence that probiotic supplementation can reduce liver enzyme levels and regulate glycometabolism and cholesterol metabolism in patients with MAFLD. Since some of the RCTs included in our meta-analysis were poorly reported and of low quality, the results should be interpreted with caution. More multicenter, high-quality RCTs are needed to evaluate the therapeutic effects of probiotics in adult patients with MAFLD.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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