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# Clinical efficacy of probiotics in the treatment of alcoholic liver disease: a systematic review and meta-analysis

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**Objective:** Alcoholic liver disease (ALD) is a liver damage disease caused by long-term heavy drinking. Currently, there is no targeted pharmaceutical intervention available for the treatment of this disease. To address this, this paper evaluates the efficacy and safety of probiotic preparation in treating ALD through conducting a meta-analysis, and provides a valuable insight for clinical decision-making.

**Methods:** A systematic search was conducted across databases, including PubMed, Embase, Web of Science, Cochrane Library, CNKI, VIP, Wanfang, and CBM from the inception dates to October 15, 2023, to identify clinical randomized controlled trials on probiotic preparations in the treatment of ALD. After the literature underwent screening, data extraction, and quality assessment, RevMan 5.3 and Stata 14.2 were employed for data analysis and processing.

**Results:** A total of 9 randomized controlled trials fulfilled the inclusion criteria. The results of the meta-analysis showed that probiotic preparation could significantly improve the liver function of patients with alcoholic liver disease compared with the control group. Probiotic intervention led to a significant reduction in the levels of alanine aminotransferase (MD=-13.36,95%CI:-15.80,-10.91;  $P<0.00001$ ), aspartate aminotransferase (MD=-16.99,95%CI:-20.38,-13.59;  $P<0.00001$ ),  $\gamma$ -glutamyl transpeptidase (MD=-18.79,95% CI:-28.23,-9.34;  $P<0.0001$ ). Concurrently, the level of serum albumin (MD=0.19,95% CI:0.02,0.36;  $P=0.03$ ) was increased. Furthermore, probiotic intervention could also modulate the composition of intestinal flora in patients with alcoholic liver disease, leading to an augmentation in *Bifidobacteria* and a reduction in *Escherichia coli*. However, in patients with alcoholic liver disease, probiotic intervention showed no significant effects on total bilirubin (MD=-0.01,95% CI:-0.17,0.15;  $P=0.91$ ), tumor necrosis factor- $\alpha$  (MD=0.03,95% CI:-0.86,0.92;  $P=0.94$ ) and interleukin-6 (MD=-5.3,95% CI:-16.04,5.45;  $P=0.33$ ).

**Conclusion:** The meta-analysis indicates that probiotics can improve liver function in alcoholic liver disease, reduce inflammatory responses, regulate intestinal flora, which have potential value in the treatment of alcoholic liver disease.

**Systematic review registration:** <https://www.crd.york.ac.uk/prospero/>, identifier CRD42023472527.

#### KEYWORDS

alcoholic liver disease, probiotics, intestinal flora, inflammation, meta-analysis

## 1 Introduction

Alcoholic liver disease (ALD) is a chronic liver disease caused by prolonged and excessive alcohol consumption, leading to various manifestations such as alcoholic fatty liver, alcoholic hepatitis (AH), and alcoholic cirrhosis. In severe cases, it can progress to liver failure or even mortality (Singal et al., 2018). A study conducted in the United States revealed that the increase in cirrhosis mortality was primarily driven by alcoholic cirrhosis, especially among people aged 25 to 34 (Tapper and Parikh, 2018). ALD is considered the cause of nearly half of liver related deaths worldwide (Mellinger et al., 2018). According to the 2018 Global Alcohol Status Report released by the World Health Organization, the mortality rates of AH and cirrhosis are particularly high, with a mortality rate of up to 50% for severe acute AH (World Health Organization, 2018). Therefore, the issue of alcohol-related liver disease has garnered increasing global attention. Alcohol and its metabolites exert detrimental effects on the liver through mechanisms including direct injury and oxidative stress (Galicia-Moreno et al., 2016). Genetic, environmental and epigenetic factors influence the progression of ALD to more severe forms (Argemi et al., 2020). Current treatment strategies for ALD encompass active abstinence, nutritional support, vitamin supplementation, and other general measures, pharmacological interventions may involve the use of steroids, pentoxifylline, and antioxidants (Siddiqi et al., 2020). However, substantial clinical evidence remains insufficient (Singal et al., 2018).

Numerous studies have demonstrated a strong correlation between the pathogenesis of ALD and alterations in the intestinal microbiota (Llopis et al., 2016; Bajaj, 2019; Ranjbarian and Schnabl, 2023). Prolonged alcohol consumption disrupts the composition of the intestinal microbiota, leading to increased levels of intestinal endotoxin, compromised intestinal barrier function, and subsequent translocation of bacteria and endotoxins from the portal vein to the liver, ultimately resulting in hepatic inflammation (Bull-Otterston et al., 2013). As beneficial microorganisms for hosts, probiotics play a pivotal role in modulating the intestinal microbiota (Kaufmann et al., 2023).

Preclinical studies have shown that supplementing probiotics has a significant improvement effect on ALD (Hong et al., 2015; Tian et al., 2015; Li et al., 2021a). Probiotic supplementation enhances populations of beneficial bacteria, such as *Bifidobacteria* and *Enterococci*, within the intestines while suppressing the growth of gram-negative bacteria, thereby reducing intestinal endotoxemia (Kim et al., 2018; Huang et al., 2019).

However, there is currently no consensus on the clinical utility of probiotics in patients with ALD. Therefore, the objective of this study is to systematically review published data regarding the clinical efficacy of probiotics in patients with ALD to provide valuable insights for evidence-based decision-making concerning probiotic intervention in ALD.

## 2 Materials and methods

### 2.1 Overview

This study is conducted in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analysis) (Page et al., 2021) and the Cochrane working manual, this study has been registered on PROSPERO (registration number: CRD42023472527).

### 2.2 Retrieval strategy

Relevant studies were identified through a comprehensive search of electronic databases, including PubMed, Embase, Web of Science, Cochrane Library, CNKI, VIP, Wanfang, and CBM. The investigation was limited from the inception of each database to October 15, 2023, and the literature search was not restricted to languages. From the perspective of evidence-based medicine, we need to collect all the research evidence of this topic as comprehensively as possible to minimize bias. Therefore, we conducted a comprehensive search on the above eight databases, and each electronic database has its unique advantages. For example, PubMed is one of the largest

medical literature databases in the world, it covers many fields such as medicine, nursing and health care. Embase is a large biomedical database focused on drug research and pharmacology. Web of Science is a comprehensive academic literature database, which provides a global academic literature index and citation database in the fields of science, technology, medicine and social sciences. The Cochrane Library provides the latest clinical trial results and systematic reviews. In addition, within the limits of our resources, we also conducted searches of Chinese databases including CNKI, Wanfang, VIP and CBM. Subsequently, we conducted a meticulous review of the references cited in these articles to identify additional randomized controlled trials (RCTs). The search terms employed encompassed Medical Subject Headings (MeSH) terms and free words: “Alcoholic liver disease”, “Alcoholic fatty liver”, “Alcoholic hepatitis”, “Alcoholic liver fibrosis”, “Alcoholic cirrhosis”, “probiotics”, “probiotic”, “probiotic agent”, “random\* or placebo\* or blind\*”. Detailed search strategies are available in the Supplementary materials.

## 2.3 Inclusion and exclusion criteria

According to the PICOS principle, the inclusion criteria for articles consisted of the following: (1) inclusion of participants diagnosed with ALD, including alcoholic fatty liver disease, alcoholic hepatitis, alcoholic liver fibrosis, and alcoholic cirrhosis; (2) the intervention group was probiotic preparation. While the control group was treated with a placebo, other treatments, or no intervention; (3) including at least one of the following main indicators: alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT), total bilirubin (TB), albumin (Alb). Additionally, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and intestinal flora are secondary outcome indicators; (4) utilization of an RCT study. Articles were excluded if they fulfilled the following conditions: ALD complicated with other chronic liver diseases; incomplete data or no clear outcome indicators; unable to obtain the full text; repeated publication.

## 2.4 Literature screening and data extraction

The literature was independently screened, and data were extracted by 2 researchers per the established protocol for preliminary duplicate inspection. Any discrepancies during this process were resolved through discussion or, if necessary, by a third-party arbitrator. The extracted data encompassed essential information from the included literature (such as first author, publication year, region, and title), sample size, age distribution, specific interventions employed in both experimental and control groups, treatment duration, and relevant outcome indicators.

## 2.5 Risk of bias evaluation

The quality of studies were assessed by Cochrane risk of bias tool Review Manager 5.3 (Nordic Cochran aa). The evaluations include the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The included studies were evaluated to three degrees including low, unclear, and high risk of bias.

## 2.6 Statistical analysis

The statistical analysis was conducted using RevMan 5.3 and Stata 14.2 software packages. Continuous variables were described using Weighted Mean Difference (WMD) or Standard Mean Deviation (SMD), along with their corresponding 95% confidence intervals (CI). A significance level of  $\alpha=0.05$  was employed, considering results statistically significant when  $P<0.05$ . The  $I^2$  statistic was used to assess the heterogeneity within the model. If  $P>0.1$  or  $I^2<50\%$ , it indicates an absence of heterogeneity, leading to a fixed effect model for analysis; otherwise, a random effects model was applied. The funnel plot served as a tool to evaluate publication bias, while Begg's Test assessed the symmetry of said plot;  $P > 0.05$  indicated a symmetrical funnel plot and no publication bias among included studies. Subgroup and sensitivity analyses were performed to assess the study's robustness and explore potential sources of heterogeneity.

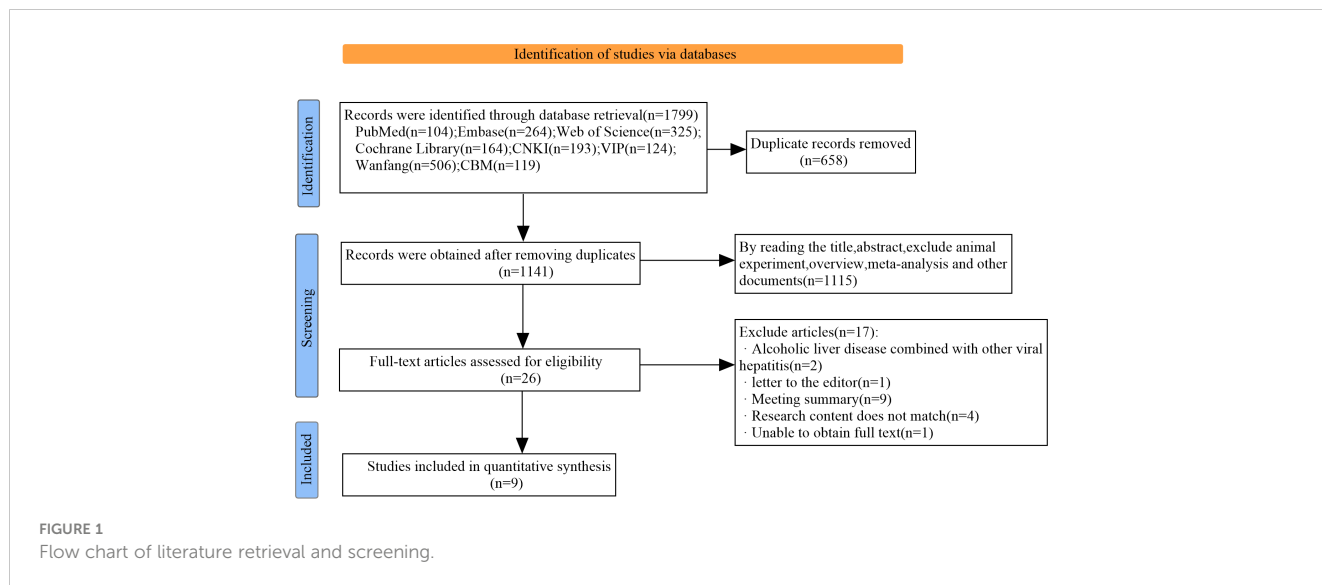
# 3 Results

## 3.1 Study selection

A total of 1799 articles were retrieved through a computerized search, and 1141 articles were obtained after eliminating 658 duplicate reports. Following the assessment of titles, abstracts and full-text reading, animal experiments, systematic reviews, meta-analyses, and irrelevant studies were excluded. Ultimately, 9 original studies (Gupta et al., 2022); (Han et al., 2015); (Kirpich et al., 2008); (Koga et al., 2013); (Li et al., 2021b); (Stadlbauer et al., 2008); (Vatsalya et al., 2023); (Zhang et al., 2011); (Zhu and Wu, 2019) were included in the analysis. The specific screening process is illustrated in Figure 1.

## 3.2 Characteristics of included literature

Table 1 presents the fundamental characteristics of the articles included, encompassing a total of 639 patients, with 355 in the experimental group and 284 in the control group, comprising 545 males and 94 females. Amongst the 9 original studies incorporated, 4 studies focused on alcoholic hepatitis and 2 studies on alcoholic cirrhosis; 1 study focused on alcoholic fatty liver disease, the other 2



studies did not clearly specify the stage of alcoholic liver disease in the participants.

suggests a greater risk of detection bias. All data were complete and selective report did not appear in all of the studies (Figures 2, 3).

### 3.3 Assessment of the quality of the included studies

Among all included articles, 7 documents reported the generation of random sequences. Only 1 document mentioned allocation concealment, this indicated that there was selectivity bias in the included studies. 6 documents explained the blinding of researchers and subjects. Only 2 documents mentioned blinding evaluators, this

### 3.4 Meta-analysis

#### 3.4.1 Liver function

The impact of probiotic intervention on ALT was assessed in 9 studies. A fixed-effects model was used to combine the trials because there was statistical homogeneity for this outcome ( $I^2 = 48\%$ ). The combined effect size was found to be  $-13.36$  (95% CI:  $-15.80, -10.91$ ;  $P < 0.00001$ ), demonstrating that the

TABLE 1 Basic characteristics of literature included in the literature.

First author (Year)	Place	Sample	Age	Sex (male: female)	Interventions		Duration (week)	Outcome
					Probiotics	control		
Gupta et al, 2022	Korea	44/45	50.8 ± 9.4	83:6	<i>Lactocaseibacillus rhamnosus</i> R0011 and <i>Lactobacillus helveticus</i> R0052	Placebo	1	①②③④⑤⑥
Han et al, 2015	Korea	60/57	52.7 ± 11.3	75:42	<i>Lactobacillus subtilis</i> / <i>Streptococcus faecium</i>	Placebo	1	①②③④⑤⑥
Koga et al, 2013	Japan	18/19	53.3 ± 13.3	30:7	<i>Lactobacillus casei</i> Shirota YIT 9029	Placebo	4	①②③④⑤⑦
Li et al, 2021a	China	112/46	50.98 ± 5.1	158:0	<i>Lactobacillus casei</i>	Placebo	8	①②③④⑤⑦
Vatsalya et al, 2023	USA	24/22	44.6 ± 10.7	26:20	<i>Lactobacillus rhamnosus</i> GG	Placebo	4	①②③⑤
Zhu and Wu, 2019	China	40/40	47.05 ± 5.12	66:14	Polyene phosphatidylcholine capsules+ <i>Clostridium Butyricum</i> Tablets	Polyene phosphatidylcholine capsules	8	①②④⑥⑦
Kirpich et al, 2008	Russia	13/13	-	26:0	<i>Bifidobacterium bifidum</i> and <i>Lactobacillus plantarum</i> 8PA3	Vitamin	1	①②③④
Stadlbauer et al, 2008	U.K.	12/8	53.5 ± 18.3	15:5	<i>Lactobacillus casei</i> Shirota	Standard treatment	4	①④⑤
Zhang et al, 2011	China	32/34	45.75 ± 1.29	66:0	<i>Bifidobacterium, lactob-acillus</i> and <i>enterococcus</i>	Standard treatment	1	①②③④

①ALT, ②AST, ③γ-GT, ④TB, ⑤ALB, ⑥TNF-α, ⑦IL-6.

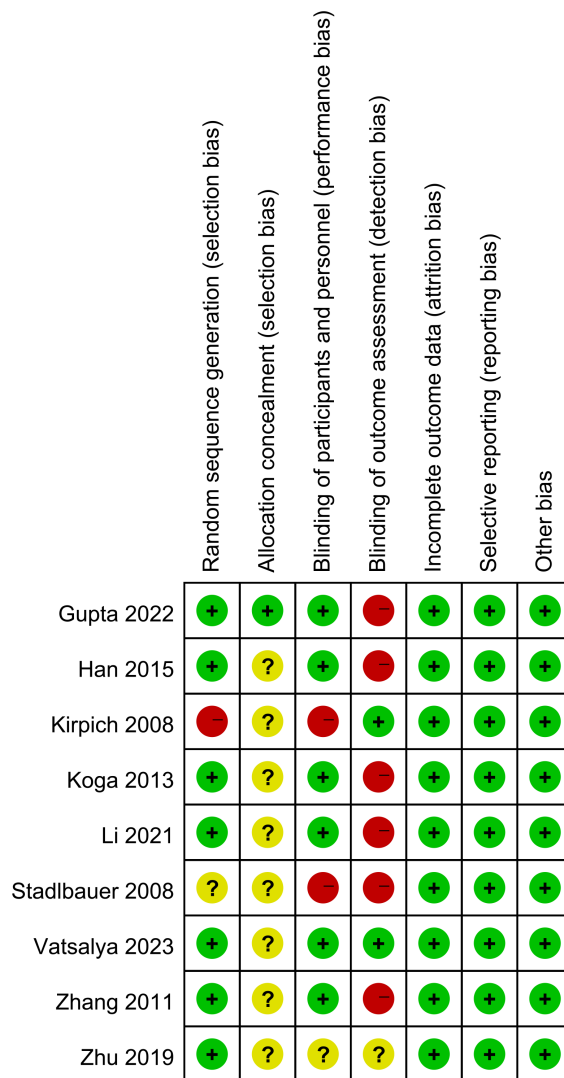


FIGURE 2 Risk of bias summary.

probiotic intervention group exhibited a significant reduction in ALT levels compared to the control group among ALD patients (Figure 4). Additionally, 8 studies investigated the impact of the probiotic intervention on AST. The fixed effects model was employed for meta-analysis with  $I^2 = 0\%$ . The AST levels of patients with ALD were significantly decreased by treatment

with probiotics (MD=-16.99, 95% CI: -20.38, -13.59;  $P < 0.00001$ ) (Figure 5). 6 studies reported on the impact of the probiotic intervention on  $\gamma$ -GT levels. Heterogeneity testing revealed an  $I^2 = 0\%$ , thus, a fixed-effects model was applied. The meta-analysis showed that compared to control group, the probiotics treatment significantly decreased the  $\gamma$ -GT levels (MD=-18.79, 95% CI: -28.23, -9.34;  $P < 0.0001$ ) (Figure 6). 9 studies examined the impact of the probiotic intervention on TB levels, however, substantial heterogeneity was observed with an  $I^2 = 75\%$  (Figure 7). We tried to conduct two subgroup analyzes based on differences in intervention time and stages of alcoholic liver disease, but neither could eliminate heterogeneity. 5 studies reported the effect of the probiotic intervention on Alb levels. Heterogeneity testing showed  $I^2 = 0\%$ ; therefore, a fixed-effects model was used to pool data. The results indicated that compared to the control group, probiotic intervention significantly increased serum albumin levels in patients with ALD (MD=0.19, 95% CI:0.02,0.36;  $P=0.03$ ) (Figure 8).

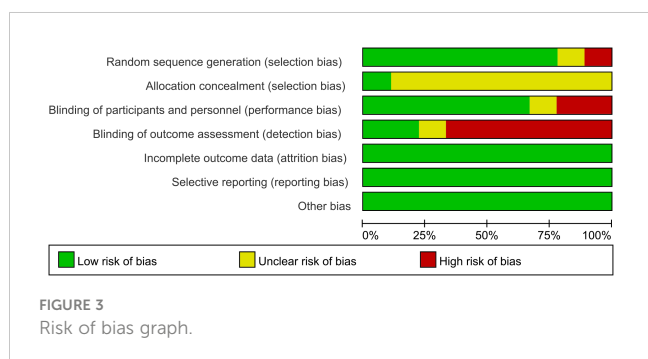


FIGURE 3 Risk of bias graph.

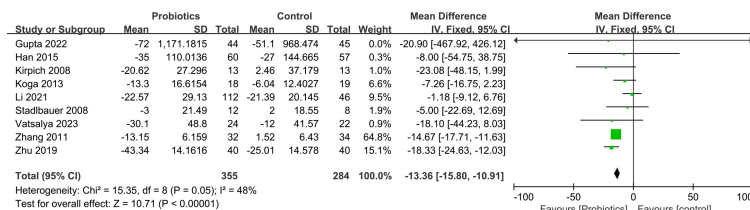


FIGURE 4  
Forest plots of serum ALT level.

### 3.4.2 Serum inflammatory factors

4 studies have reported on the impact of probiotic intervention on serum TNF- $\alpha$  levels in patients with ALD. The combined effect size was 0.03, (95% CI: -0.86, 0.92;  $P=0.94$ ), the heterogeneity test results indicate a substantial heterogeneity ( $I^2 = 94\%$ ). And we did not find significant changes in heterogeneity after a sensitivity analysis by sequentially excluding each study, which indicated the stability of the present random-effect model (Figure 9). 3 studies assessed the impact of probiotic intervention on serum IL-6 levels in ALD patients [MD=-5.30, (95% CI:-16.04,5.45),  $P=0.33$ ], and a sensitivity analysis suggested that the Li’s study was the source of heterogeneity, which was reduced to 0% after excluding this article (Figure 10).

### 3.5 Intestinal microbiota

Considering the different assessment methods of intestinal flora among different studies, we did not combine this part of the data. As shown in Table 2, 7 studies reported the changes in intestinal flora after probiotic intervention. In general, after probiotic treatment, the proportion of Gram-negative bacilli such as *Escherichia coli*

decreased, while the proportion of Gram-positive bacilli such as *Bifidobacterium* and *Lactobacillus* increased.

### 3.6 Publication bias and sensitivity analysis

Publication bias was tested using funnel plots and Egger’s regression test. The test results of ALT, AST,  $\gamma$ -GT, TB, Alb major outcome indicators showed that the  $p$  value of each major indicator was greater than 0.05, indicating that there was no significant publication bias (Figure 11). Sensitivity analysis was conducted on the major and demonstrated that even after systematically excluding individual studies for each indicator one by one, the integrated effect size remained within the 95% confidence interval of the original effect size. Consequently, these meta-analysis results can be considered relatively robust.

## 4 Discussion

This systematic review and meta-analysis aimed to investigate the efficacy of probiotic supplementation in individuals with ALD.

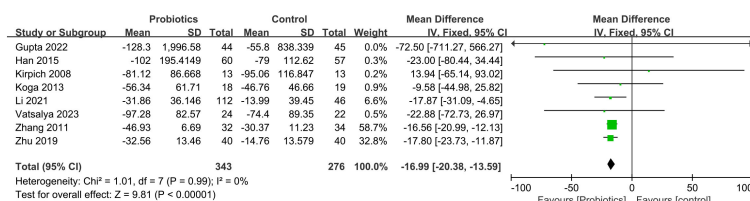


FIGURE 5  
Forest plots of serum AST level.

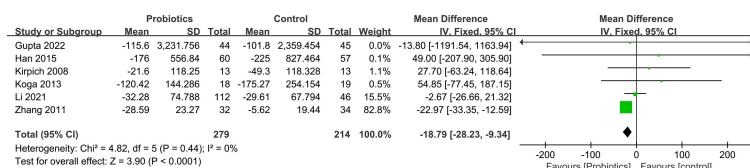


FIGURE 6  
Forest plots of serum  $\gamma$ -GT level.



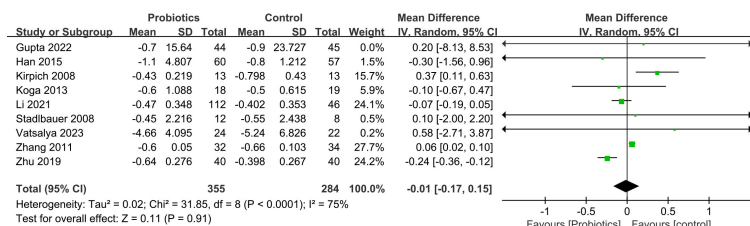


FIGURE 7  
Forest plots of serum TB level.

Through analysis of 9 randomized controlled trials, we obtained valuable insights into the definitive effectiveness of probiotic preparations in patients with ALD. Specifically, meta-analysis results showed that supplementation with probiotic preparations significantly reduced serum ALT, AST, and  $\gamma$ -GT levels in ALD patients, and these findings suggest that probiotics are effective in alleviating liver inflammation in ALD patients. Furthermore, serum Alb levels increased following probiotic intervention, indicating a substantial improvement in liver synthesis function. However, no statistically significant difference was observed in bilirubin levels between the control group and the probiotic treatment group. In the clinical trials incorporated within this study, the probiotic

intervention was administered for a duration ranging from 7 to 60 days. Given the short duration of the intervention included in the study, it is unlikely that bilirubin levels would have improved significantly in a short period of time. On the other hand, due to the different stages of alcoholic liver disease, different doses and types of probiotics taken, and a small number of included literature, there was significant heterogeneity in the results of TNF-a and IL-6. Therefore, in the future, we hope to have more studies to explore the impact of probiotics on the levels of inflammatory factors in ALD patients.

Research has demonstrated that long-term ethanol exposure can lead to various liver diseases (Gu et al., 2019). When alcohol is

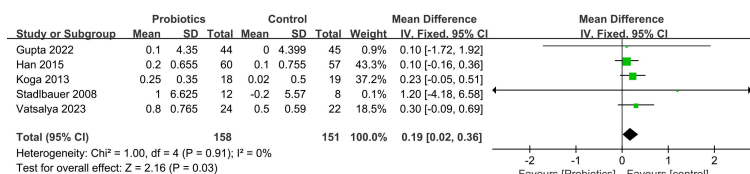


FIGURE 8  
Forest plots of serum Alb level.

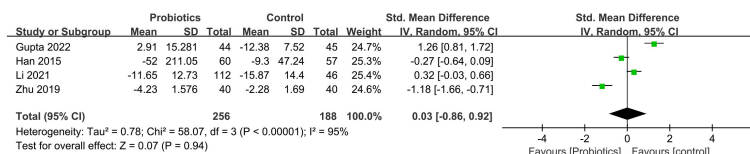


FIGURE 9  
Forest plots of serum TNF- α level.

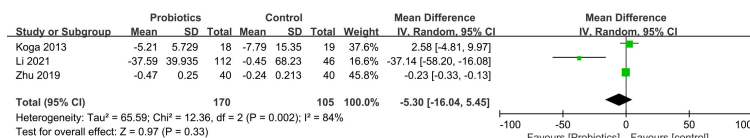


FIGURE 10  
Forest plots of serum IL-6 level.

TABLE 2 Changes in intestinal flora.

	Disease type	Probiotic type	Changes in intestinal flora after probiotic supplementation
Gupta et al, 2022	Alcoholic hepatitis	<i>Lacticaseibacillus rhamnosus</i> R0011 and <i>Lactobacillus helveticus</i> R0052	<i>Bacteroidetes</i> ↑, <i>Proteobacteria</i> and <i>Fusobacteria</i> ↓
Han et al, 2015	Alcoholic hepatitis	<i>Lactobacillus subtilis</i> / <i>Streptococcus faecium</i>	<i>Escherichia coli</i> ↓
Kirpich et al, 2008	Alcoholic hepatitis	<i>Bifidobacterium bifidum</i> and <i>Lactobacillus plantarum</i> 8PA3	<i>Bifidobacteria</i> and <i>Lactobacilli</i> ↑
Koga et al, 2013	Alcoholic cirrhosis	<i>Lactobacillus casei</i> Shirota YIT 9029	Obligate anerobic bacteria↑, <i>Enterobacteriaceae</i> ↓
Li et al, 2021a	Alcoholic fatty liver	<i>Lactobacillus casei</i>	<i>Lactobacillus</i> and <i>Bifidobacterium</i> ↑
Zhang et al, 2011	Alcoholic liver disease	<i>Bifidobacterium</i> , <i>lactobacillus</i> and <i>enterococcus</i>	<i>Bifidobacteria</i> , <i>Lactobacilli</i> and <i>enterococci</i> ↑
Zhu and Wu, 2019	Alcoholic liver disease	<i>Clostridium Butyricum</i>	<i>Bifidobacteria</i> , <i>Lactobacilli</i> ↑, <i>Escherichia coli</i> ↓

"↑" indicates an increase; "↓" indicates a decrease.

ingested, 90% of it is absorbed by the small intestine and transported to the liver through the portal vein, and the remaining 10% is excreted through sweat, breath, and urine (Holford, 1987; Cederbaum, 2012). Both preclinical studies and clinical evidence suggest that alcohol consumption disrupts the

composition and structure of the gut microbiome (Milosevic et al., 2019; Ranjbarian and Schnabl, 2023). Specifically, ethanol entering the intestine will cause an imbalance of the intestinal flora, increase the number of Gram-negative bacteria. In addition, alcohol will destroy the integrity of the intestinal mucosa and increase the intestinal permeability of macromolecules. Permeability, allowing endotoxins to pass from the intestine into the portal system (see Figure 12) (Chopyk and Grakoui, 2020). For instance, research conducted by Kirpich and his colleagues (Kirpich et al., 2008) demonstrated a significant reduction in *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* in the feces of individuals with alcoholic patients, while the *Escherichia coli* exhibited an increasing trend. The study of Fang and his colleagues (Fang et al., 2023) found that ethanol consumption promotes the growth of Gram-negative bacteria such as *Proteobacteria* in the intestine and reduces the relative abundance of *Firmicutes* and *Bacteroidetes*. On the other hand, after ethanol enters the liver, it is oxidized to acetaldehyde in liver cells and then metabolized to acetic acid under the catalysis of acetaldehyde dehydrogenase (Cederbaum, 2012). Acetaldehyde induces liver damage by promoting glutathione consumption, ROS toxicity, and lipid peroxidation. Therefore, ethanol metabolism can induce direct biochemical reactions in liver cells, including the production of cytotoxic metabolites, reactive oxygen species (ROS) Accumulation and lipid peroxidation (Lamas-Paz et al., 2018). Gut-derived microbial lipopolysaccharide (LPS), a constituent of the outer membrane of Gram-negative bacteria, is known to play a pivotal role in the pathogenesis of AH (Szabo, 2015). Alcohol disrupts intestinal barrier function, thereby facilitating the translocation of LPS from the intestinal lumen into the portal vein and subsequently into the liver. Chronic alcohol exposure has been reported to sensitize Kupffer cells in the liver to LPS through the upregulation of microRNA-155 (Szabo et al., 2010), where LPS binds to Toll-like receptor 4 (TLR-4), ultimately activates various proinflammatory cytokines such as

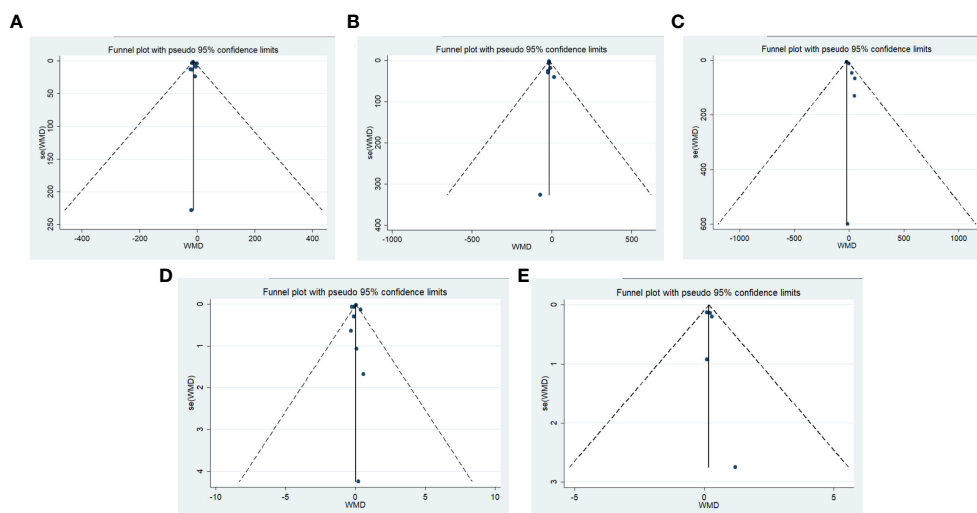
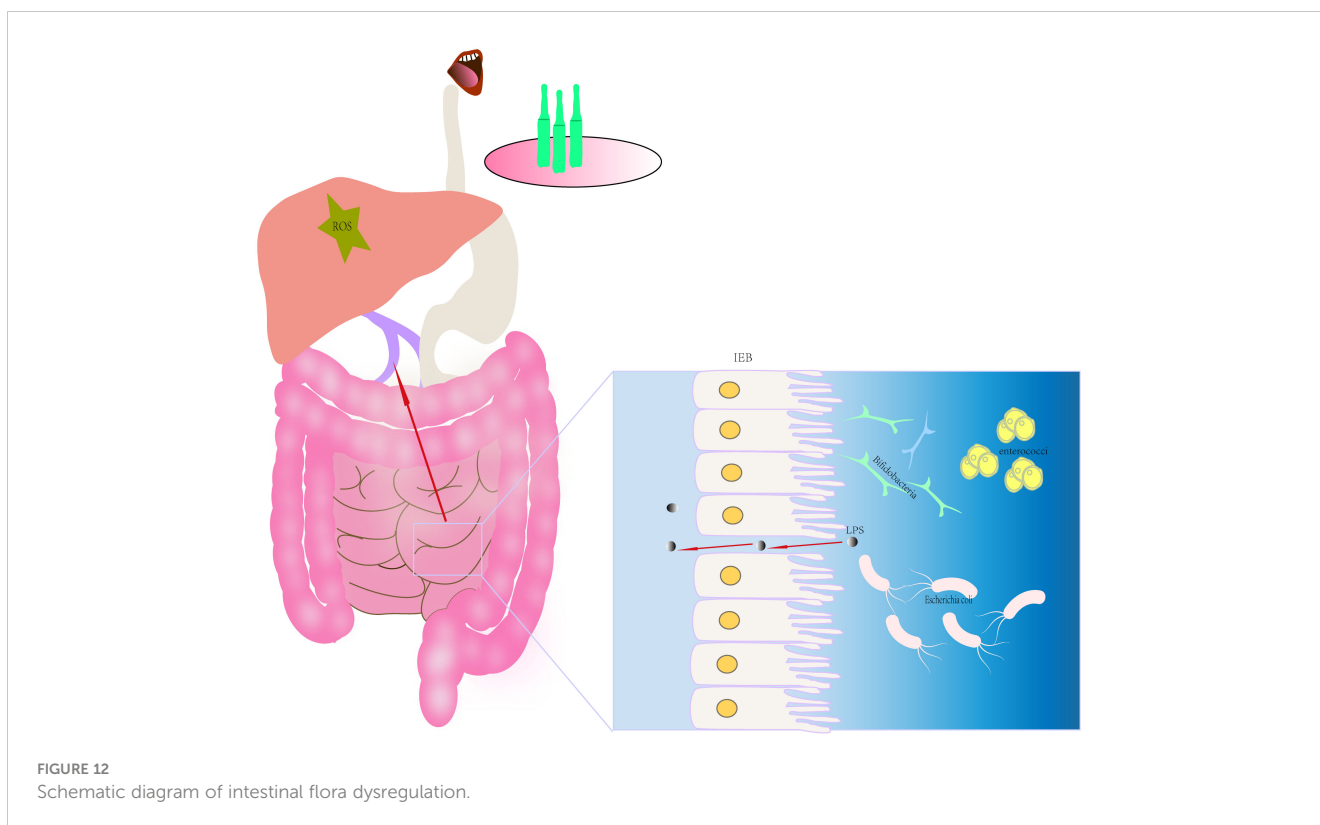


FIGURE 11 Publication bias funnel plot. (A) ALT, Egger's Test result  $P=0.56$ ; (B) AST, Egger's Test result  $P=0.70$ ; (C)  $\gamma$ -GT, Egger's Test result  $P=0.09$ ; (D) TB, Egger's Test result  $P=0.66$ ; (E) Alb, Egger's Test result  $P=0.53$ .





TNF- $\alpha$  (Tapper and Parikh, 2018). TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are important indicators reflecting the severity of inflammatory response and playing crucial roles in liver injury development. While TNF- $\alpha$  exerts direct cytotoxic effects, it can also cause microcirculatory disorders leading to hepatocyte necrosis, furthermore, it interacts with other inflammatory factors like IL-6 to further exacerbate liver damage (Kohn et al., 2002; Albano, 2008). It is worth noting that during liver injury, the levels of inflammatory cytokines increase and reach the intestine through circulation, disrupting the intestinal mucosal barrier. This phenomenon disrupts the balance of intestinal microbiota and forms a vicious cycle (Thurman et al., 1998).

The gut microbiome comprises a diverse array of bacterial strains and microorganisms that inhabit the stomach and intestinal tract (Jia et al., 2008), playing a crucial role in maintaining human homeostasis, metabolism, circulation, immunity, and hormone regulation (Qin et al., 2010; Schroeder and Bäckhed, 2016). The FAO (the United Nations Food and Agriculture Organization) and the WHO (the World Health Organization) defines probiotics as “live microorganisms that are beneficial to host health when ingested in moderate amounts” (Hill et al., 2014). Previous studies have demonstrated the potential role of probiotics in improving liver inflammation and regulating blood lipids in patients with non-alcoholic fatty liver disease (NAFLD) (Famouri et al., 2017; Ahn et al., 2019). Probiotics can effectively inhibit the occurrence of alcoholic liver disease, involving various potential mechanisms, including changes in gut microbiota, regulation of gut barrier function and immune response,

reduction of endotoxin levels, and bacterial translocation (Chang et al., 2013; Vitetta et al., 2017; Mishra et al., 2023). It has been reported that supplementation of probiotics can inhibit the growth of pathogenic gram-negative bacteria, enhance phagocytosis activity, promote IgA secretion, and thus enhance cellular immune function (Zhang et al., 2010). Probiotics inhibit liver endotoxin levels by regulating gut flora, thereby reducing the production of pro-inflammatory markers (IL-6, TNF- $\alpha$ , IFN- $\gamma$ , etc.) by down-regulating the expression of NF- $\kappa$ B (O’Sullivan, 2008). Recently, A meta-analysis based on animal studies has demonstrated that probiotic intervention can augment intestinal epithelial barrier (IEB) integrity, alleviate intestinal dysbiosis, and significantly ease liver function, blood lipids, inflammatory factors, and other indicators in ALD mice (Wang et al., 2022). Liu and his colleagues (Liu et al., 2023) have demonstrated that complex probiotics reduce LPS levels in the liver by upregulating mucus production and tight junction (TJ) protein expression, reversing acute alcohol-induced dysbiota and maintaining the integrity of the intestinal barrier.

Our analysis of the included original studies found that after probiotic intervention, the abundance of *Bifidobacteria* increased and *Proteus* decreased in the intestines of ALD patients, showing the potential role of probiotics treating ALD by regulating intestinal flora. However, due to the limited literature incorporating these indicators to date, we expect more high-quality research documents to support our findings in future investigations. Last but not least, all original studies emphasized strict abstinence from alcohol during the trial period. Even without probiotic treatment, liver function in the control group

improved to varying degrees after alcohol abstinence, highlighting that alcohol abstinence is a basic requirement for ALD patients.

## 5 Strengths and limitations

To the best of our knowledge, this study represents the first meta-analysis investigating the clinical efficacy of probiotics in the treatment of ALD. Our findings demonstrate that probiotic intervention effectively improves liver function, reduces inflammatory factors, and regulates intestinal flora in patients with ALD. Moreover, no serious adverse events were reported in any of the included studies, indicating a higher level of safety associated with probiotic preparations. However, despite conducting systematic reviews and gaining valuable insights from this meta-analysis, it is essential to acknowledge certain limitations. Firstly, the number of included studies is relatively small, particularly concerning the composition of intestinal flora and relevant outcome indicators for inflammatory factors after probiotic intervention. This limitation restricts statistical power in these areas and underscores the need for further research. Secondly, heterogeneity exists among studies due to variations in intervention programs and durations. Therefore, future research should prioritize conducting high-quality RCTs with larger sample sizes to strengthen our conclusions.

## 6 Conclusion

In conclusion, probiotics have shown a good therapeutic effect in patients with ALD. It is speculated that the possible mechanism is to regulate intestinal flora and reduce the production of endotoxin, thereby improving liver function and reducing the body's inflammatory response.

## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

## Author contributions

S-YX: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review &

editing. G-SW: Formal analysis, Investigation, Writing – original draft. CL: Formal analysis, Investigation, Writing – original draft. WM: Validation, Visualization, Writing – review & editing. H-RL: Validation, Visualization, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcimb.2024.1358063/full#supplementary-material>

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