


# Efficacy of traditional Chinese medicine combined with Silibinin on nonalcoholic fatty liver disease

## A meta-analysis and systematic review

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### Abstract

**Background:** The efficacy and safety of traditional Chinese medicine (TCM) combined with Silibinin in the treatment of nonalcoholic fatty liver disease (NAFLD) are still inconclusive. This meta-analysis intends to evaluate to explore the clinical efficacy and quality assessment of traditional Chinese medicine in combination with Silymarin in the treatment of NAFLD, aiming to provide evidence-based data analysis for researchers and clinical practitioners involved in TCM research for NAFLD, with the hope of facilitating wider adoption and application.

**Methods:** In this meta-analysis, we searched PubMed, Embase, Cochrane Library, CNKI, Wanfang, CQVIP and CBM databases from the establishment of the databases to Oct 2023. The study proposed to include studies that reported combination of TCM with Silibinin and Silibinin alone in the treatment of NAFLD, excluding studies for which full text was not available or for which data extraction was not possible; studies using animal studies; reviews and systematic reviews. All data were processed by STATA15.1 statistical software.

**Results:** 16 randomized controlled trials (RCTs) were included in this meta-analysis. The sample size ranged from 48 to 120, with a total of 1335 patients, including 669 in the Combined treatment group and 384 in the Silibinin group. The findings indicated that the total effective rate of combined treatment group was significantly higher than that of Silibinin alone. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglycerides (TG), and gamma glutamyl transpeptidase (GGT) of combined treatment group were all significantly lower than that of western medicine alone. Additionally, after treating NAFLD with a combination of TCM and Silibinin, the TCM syndrome score were significantly lower than those observed with Silibinin alone.

**Conclusion:** Traditional Chinese medicine in conjunction with Silibinin capsules has shown significant efficacy in the treatment of NAFLD, improving clinical symptoms, blood lipid levels, and liver function. Furthermore, it is essential to engage in multi-omics research, investigate iron death, and explore the gut microbiota as potential observational indicators for the diagnosis and inclusion criteria. Conducting more high-quality clinical experiments is necessary to further validate these findings.

**Abbreviations:** ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyl transpeptidase, NAFLD = non-alcoholic fatty liver disease, RCTs = randomized controlled trials, RR = relative risk, TC = total cholesterol, TCM = Traditional Chinese medicine, TG = triglycerides, WMD = weighted mean differences.

**Keywords:** efficacy, meta-analysis and systematic review, nonalcoholic fatty liver disease, Silibinin, traditional Chinese medicine

## 1. Introduction

nonalcoholic fatty liver disease (NAFLD) is a prevalent clinical manifestation of metabolic syndrome, primarily distinguished by the accumulation of excessive fat in the liver, defined as more than 5% fat content.<sup>[1,2]</sup> Importantly, NAFLD occurs

independently of autoimmune factors, drug-induced effects, viral hepatitis, or a history of excessive alcohol consumption.<sup>[3]</sup> NAFLD can progress from nonalcoholic simple fatty liver to nonalcoholic steatohepatitis, liver fibrosis, and even advance to liver cirrhosis and hepatocellular carcinoma.<sup>[4]</sup> Cirrhosis is

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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a late-stage organ failure of the liver that often requires a liver transplant, and liver cancer typically develops decades after cirrhosis or chronic hepatitis B infection. Both of these conditions are common causes of liver disease-related deaths in patients.<sup>[5,6]</sup> According to statistics, the global prevalence of NAFLD in the general population has reached 25%, with rates among Asian populations ranging from 15% to 40%.<sup>[7]</sup>

Research has shown that insulin resistance and genetic susceptibility play a role in the development of this disease.<sup>[8]</sup> Insulin resistance can promote the accumulation of lipids in the liver, causing the initial impact on the liver. The accumulated lipids can further trigger events such as inflammation and oxidative stress, leading to cellular toxicity and damaging liver function, constituting the ‘two-hit’ theory recognized by many scholars in the pathogenesis of nonalcoholic fatty liver disease.<sup>[9]</sup> At present, Silibinin capsules are commonly used in clinical treatment for nonalcoholic fatty liver disease. They can eliminate reactive oxygen species within liver cells, facilitate detoxification, and subsequently promote liver function recovery. However, using them as a standalone treatment may not achieve the desired therapeutic effect. The pathogenesis of NAFLD is complex,

and the disease progression is extensive. While there has been some progress in drug therapy, there is still no specific medication approved for the treatment of NAFLD. Traditional Chinese medicine (TCM) has gained increasing attention in the treatment of NAFLD, as it offers a unique advantage with its multi-component and multi-target effects in liver disease therapy. In recent years, multiple studies have indicated that a combination of traditional Chinese and Western medicine in treating NAFLD is more effective than Western medicine alone in improving abnormal liver function, reducing blood lipids, and enhancing insulin resistance, among other aspects.<sup>[10,11]</sup> Based on this, our study includes randomized controlled trials of traditional Chinese medicine in combination with Silymarin capsules for the treatment of NAFLD in accordance with the standards. We intend to use meta-analysis and systematic evaluation to explore the clinical efficacy and quality assessment of traditional Chinese medicine in combination with Silymarin in the treatment of NAFLD. This research aims to provide evidence-based data analysis for researchers and clinical practitioners involved in TCM research for NAFLD, with the hope of facilitating wider adoption and application.

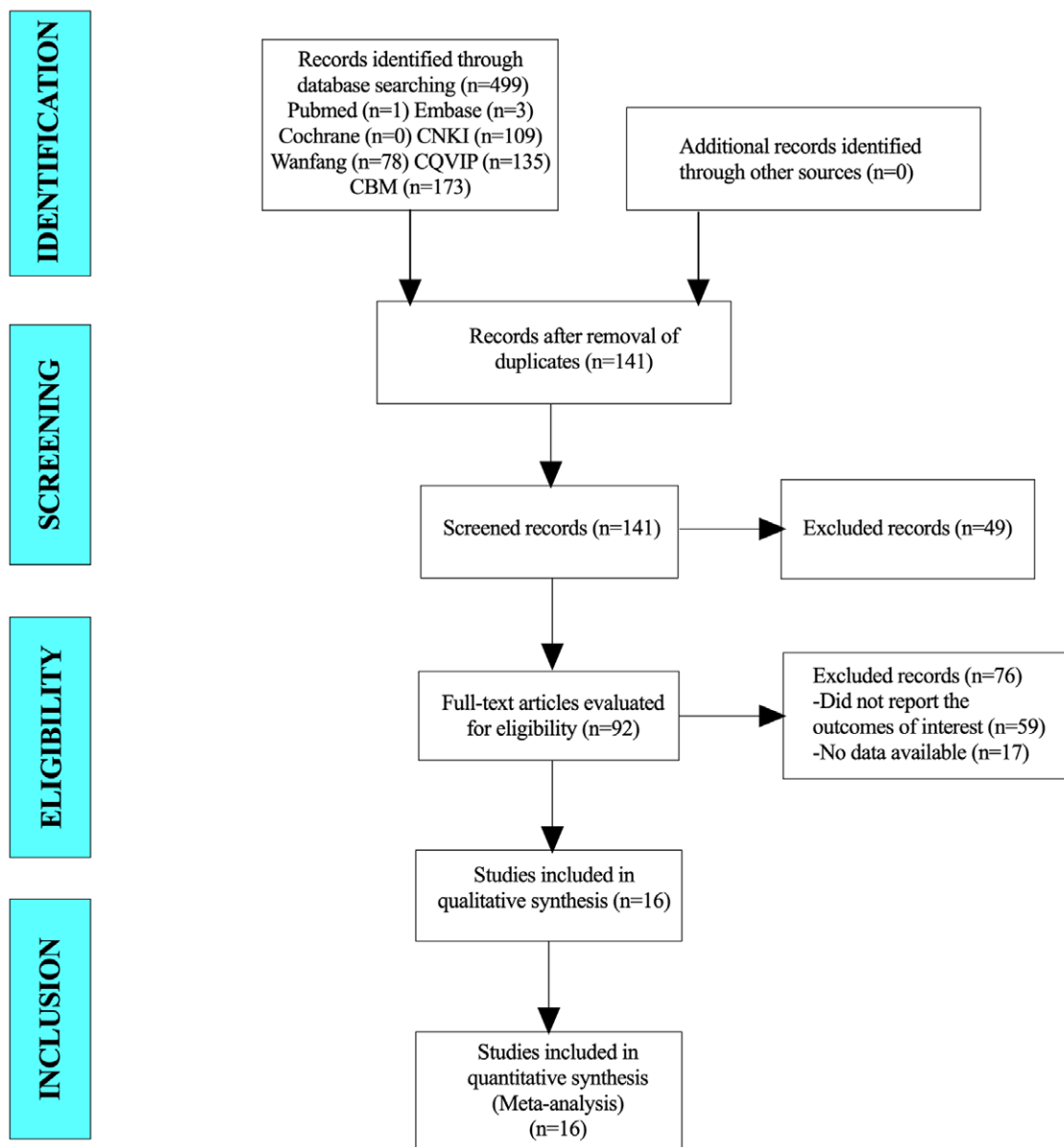


Figure 1. Flow diagram for selection of studies.

**Table 1**

**Baseline characteristics and quality assessment of the included studies.**

| Author                             | Yr   | Study design | Sample size              |               |               | Sex (male/female)        |               |               | Age                      |               |               | Duration of disease (yr) |   |                    | Measurements             |               |                          |
|------------------------------------|------|--------------|--------------------------|---------------|---------------|--------------------------|---------------|---------------|--------------------------|---------------|---------------|--------------------------|---|--------------------|--------------------------|---------------|--------------------------|
|                                    |      |              | Combined treatment group | Control group | Control group | Combined treatment group | Control group | Control group | Combined treatment group | Control group | Control group | Combined treatment group | Control group   | Control group      | Combined treatment group | Control group |                          |
|                                    |      |              |                          |               |               |                          |               |               |                          |               |               |                          |   |                    |                          |               | Combined treatment group |
| Háizher <sup>[15]</sup>            | 2019 | RCT          | 54                       | 54            | 28/26         | 41.4 ± 11.5              | 41.9 ± 11.3   | 2.3 ± 0.7     | 2.5 ± 0.7                | 2.5 ± 0.7     | 2.3 ± 0.7     | 2.5 ± 0.7                | Baogan Jiangzhi Decoction + Silibinin Capsules            | Silibinin Capsules | Silibinin Capsules       |               |                          |
| Zhang et al <sup>[16]</sup>        | 2020 | RCT          | 30                       | 30            | 23/7          | 48.5 ± 9.4               | 50.2 ± 7.2    | 3.3 ± 1.2     | 3.1 ± 1.0                | 3.1 ± 1.0     | 3.3 ± 1.2     | 3.1 ± 1.0                | Baogan Jiedu Decoction + Silibinin Capsules               | Silibinin          | Silibinin                |               |                          |
| Hui and Wei <sup>[17]</sup>        | 2018 | RCT          | 50                       | 50            | 24/26         | 45.9 ± 12.0              | 44.6 ± 11.7   | /             | /                        | /             | /             | /                        | Danshao Shugan Granules + Silibinin Capsules              | Silibinin          | Silibinin                |               |                          |
| Xiaofeng et al <sup>[18]</sup>     | 2016 | RCT          | 40                       | 40            | 31/9          | 44.9                     | 45.2          | 1             | 1                        | 1             | 1             | 1                        | Gan Zhi Ping Granule + Silibinin Capsules                 | Silibinin          | Silibinin                |               |                          |
| Ying et al <sup>[19]</sup>         | 2018 | RCT          | 25                       | 25            | 14/11         | 34.5 ± 6.6               | 33.8 ± 7.0    | 5.2 ± 1.6     | 5.3 ± 2.0                | 5.3 ± 2.0     | 5.2 ± 1.6     | 5.3 ± 2.0                | Huanglian Jiedu Decoction + Silibinin Capsules            | Silibinin          | Silibinin                |               |                          |
| Jie et al <sup>[20]</sup>          | 2010 | RCT          | 33                       | 32            | 18/14         | 36.8 ± 11.7              | 38.3 ± 12.8   | /             | /                        | /             | /             | /                        | Jianpi Shugan Granules + Silibinin Capsules               | Silibinin          | Silibinin                |               |                          |
| Nan et al <sup>[21]</sup>          | 2015 | RCT          | 42                       | 42            | 20/22         | 36.7 ± 8.6               | 37.3 ± 11.7   | /             | /                        | /             | /             | /                        | Jianpi Shugan Granules + Silibinin Capsules               | Silibinin          | Silibinin                |               |                          |
| Zhang et al <sup>[22]</sup>        | 2018 | RCT          | 46                       | 46            | 8/38          | 52.9 ± 9.4               | 53.0 ± 9.4    | 4.5 ± 1.9     | 4.4 ± 2.0                | 4.4 ± 2.0     | 4.5 ± 1.9     | 4.4 ± 2.0                | Jiangzhi Ligan Decoction + Silibinin Capsules             | Silibinin          | Silibinin                |               |                          |
| Shi <sup>[23]</sup>                | 2023 | RCT          | 40                       | 40            | 30/10         | 40.2 ± 3.1               | 41.3 ± 2.8    | 1.3 ± 0.2     | 1.4 ± 0.1                | 1.4 ± 0.1     | 1.3 ± 0.2     | 1.4 ± 0.1                | Qinggan Huashi Huoxue Decoction + Silibinin Capsules      | Silibinin          | Silibinin                |               |                          |
| Qi et al <sup>[24]</sup>           | 2015 | RCT          | 45                       | 45            | 31/14         | 47.8 ± 9.6               | 43.6 ± 12.0   | 1.4 ± 1.2     | 1.7 ± 1.3                | 1.7 ± 1.3     | 1.4 ± 1.2     | 1.7 ± 1.3                | Shugan Jianpi Decoction + Silibinin Capsules              | Silibinin          | Silibinin                |               |                          |
| Lin and Qing <sup>[25]</sup>       | 2017 | RCT          | 24                       | 24            | 12/12         | 45–65                    | 44–66         | /             | /                        | /             | /             | /                        | Self-Proposed TCM Prescription + Silibinin Capsules       | Silibinin          | Silibinin                |               |                          |
| Panyu et al <sup>[26]</sup>        | 2021 | RCT          | 54                       | 54            | 26/28         | 53.2 ± 8.3               | 52.8 ± 8.7    | 1.5 ± 0.2     | 1.5 ± 0.2                | 1.5 ± 0.2     | 1.5 ± 0.2     | 1.5 ± 0.2                | Xiaozhi Hugan Decoction + Silibinin Capsules              | Silibinin          | Silibinin                |               |                          |
| Yue et al <sup>[27]</sup>          | 2015 | RCT          | 35                       | 35            | 30/5          | 18–56                    | 20–54         | /             | /                        | /             | /             | /                        | Xingqi Huatan Method + Silibinin Capsules                 | Silibinin          | Silibinin                |               |                          |
| Yan and Jie <sup>[28]</sup>        | 2019 | RCT          | 56                       | 54            | 45/11         | 25–65                    | 20–66         | /             | /                        | /             | /             | /                        | Quzhi Prescription + Silibinin Capsules                   | Silibinin          | Silibinin                |               |                          |
| Shuan-Shuang et al <sup>[29]</sup> | 2022 | RCT          | 60                       | 60            | 36/24         | 47.4 ± 11.8              | 46.7 ± 12.2   | 2.0 ± 1.2     | 2.2 ± 1.2                | 2.2 ± 1.2     | 2.0 ± 1.2     | 2.2 ± 1.2                | Self-Proposed Xiaopi Huatan Granules + Silibinin Capsules | Silibinin          | Silibinin                |               |                          |
| Kajjie et al <sup>[30]</sup>       | 2021 | RCT          | 35                       | 35            | 23/12         | 42.4 ± 4.6               | 43.2 ± 5.1    | 4.1 ± 1.7     | 4.2 ± 1.9                | 4.2 ± 1.9     | 4.1 ± 1.7     | 4.2 ± 1.9                | Self-Proposed TCM Prescription + Silibinin Capsules       | Silibinin          | Silibinin                |               |                          |

RCT = randomized controlled trial, TCM = traditional Chinese medicine.

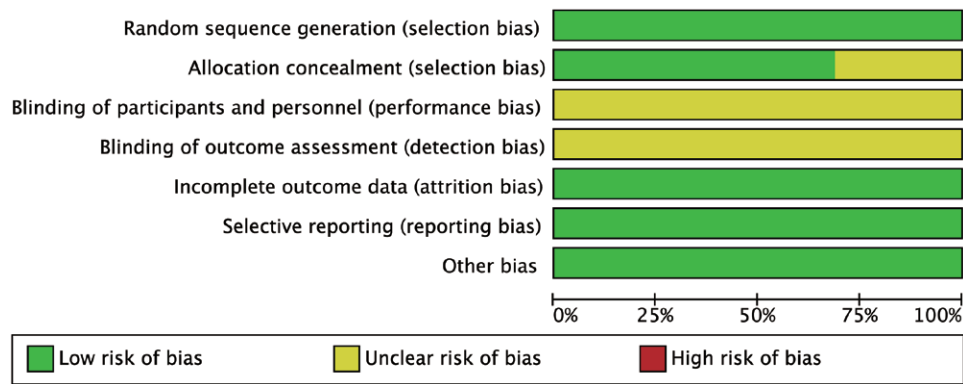


Figure 2. Risk of bias graph.

## 2. Methods

### 2.1. Literature inclusion and exclusion criteria

Inclusion criteria:

- 1) Subjects: patients with schizophrenia
- 2) Interventions: Combination of TCM and Silibinin in the treatment of NAFLD
- 3) Control: Silibinin alone
- 4) Outcome indicators: Total effective rate, changes in the levels of triglycerides (TG), total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT) and TCM syndrome score.
- 5) Study design: Randomized controlled trial (RCT)

Exclusion criteria:

Duplicate publications; studies for which full text was not available or for which data extraction was not possible; studies using animal studies; reviews and systematic reviews.

### 3. Search strategy

In this meta-analysis, we searched PubMed, Embase, Cochrane Library, CNKI, Wanfang, CQVIP and CBM databases from the establishment of the databases to Aug 2023. The mesh terms used were: “nonalcoholic Fatty Liver Disease” AND “Chinese medicine” “Chinese traditional medicine” “traditional Chinese medicine” “Integrated traditional Chinese and western medicine” “Combination of traditional Chinese and western medicine” AND “Silibinin” AND “Randomized Controlled Trial” “Randomized.” Specific search strategies in English are as follows: ((nonalcoholic Fatty Liver Disease[Title/Abstract]) AND (((((Chinese medicine[Title/Abstract]) OR (Chinese traditional medicine[Title/Abstract])) OR (traditional Chinese medicine[Title/Abstract])) OR (Integrated traditional Chinese[Title/Abstract] AND western medicine[Title/Abstract])) OR (Combination of traditional Chinese[Title/Abstract] AND western medicine[Title/Abstract]))) AND (Randomized[Title/Abstract]))

### 4. Literature screening and data extraction

Two researchers conducted the search for information, the screening of information and the capture of information respectively. Any questions or disagreements were made after consultation with a third party. Information was collected by author, year, study design, number of cases and outcome indicators.

### 5. Literature quality assessment

Two researchers carried out separate independent evaluations of the quality of the literature, using the Review manager 5.3<sup>[12]</sup>

software risk assessment tool to evaluate the included literature according to random sequence generation, allocation concealment, blinding, whether research results were blinded to review, completeness of outcome data, using the Cochrane Risk Assessment Scale, and gender, selection of reported research outcomes, other biases, etc, and in cases of disagreement, through discussion or consultation with third parties. The Meta-analysis was performed in accordance with the relevant items in the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) statement.<sup>[13]</sup>

### 6. Data synthesis and statistical analysis

Data were analyzed using STATA 15.1.<sup>[14]</sup> Weighted Mean differences (WMD) with 95%CI were used as continuous variables.  $I^2$  was used to evaluate cell heterogeneity. If the test for heterogeneity was  $P \geq .1$  and  $I^2 \leq 50\%$ , homogeneity between studies was indicated and the studies were analyzed together using a fixed effects model; if  $P < .1$  and  $I^2 > 50\%$ , significant heterogeneity between this group was indicated; if there was a difference, the source of the difference was identified using sensitivity analysis (We did a sensitivity analysis to exclude each of these trials one by one, and then did a combined analysis of the remaining trials). If the differences were still large, the random-effects model was used or the results of the combined study were discarded in favor of descriptive analysis. Publication bias was analyzed using funnel plots.

## 7. Results

### 7.1. Literature search results

A total of 499 articles were collected for this study. After excluding duplicate trials, 141 patients were included in this study. A total of 92 articles were identified after reading their titles and abstracts. Finally, 16 studies were included in the meta-analysis (Fig. 1).

### 8. Baseline characteristics and quality assessment of the included studies

16 RCT studies were included in this meta-analysis. The sample size ranged from 48 to 120, with a total of 1335 patients, including 669 in the Combined treatment group and 384 in the Silibinin group. The age distribution of patients in the combined treatment group was 18 to 65, and the age distribution of patients in the control group was 20 to 66, suggesting that the ages were comparable (Table 1). The quality assessment results of the 16 RCTs are shown in Figures 2–3. The findings showed that all studies included in this review described the formation

of random sequences. Eleven articles described “Allocation concealment,” but none described whether blinding was used.

**8.1. Results of meta-analysis**

**8.1.1. Total effective rate.** Fourteen studies were conducted to compare the total effective rate of TCM combined with Silibinin and Silibinin alone in the treatment of NAFLD. As

no significant heterogeneity was observed ( $I^2=0.0\%$ ,  $P = .526$ ), a fixed-effect model was employed for the meta-analysis. The findings indicated that the total effective rate of combined treatment group was significantly higher than that of Silibinin alone ( $RR = 1.25$ ,  $95\% CI: 1.19$  to  $1.32$ ,  $P = .000$ ) (Fig. 4).

**8.1.2. TC levels.** Fourteen studies conducted comparisons of TC levels in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 87.3\%$ ,  $P = .000$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the TC levels were significantly lower than those observed with Silibinin alone ( $WMD = -0.38$ ,  $95\% CI: -0.53$  to  $-0.23$ ,  $P = .000$ ) (Fig. 5).

**8.1.3. TG levels.** Twelve studies conducted comparisons of TG levels in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 86.1\%$ ,  $P = .000$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the TG levels were significantly lower than those observed with Silibinin alone ( $WMD = -0.38$ ,  $95\% CI: -0.48$  to  $-0.27$ ,  $P = .000$ ) (Fig. 6).

**8.1.4. ALT levels.** Fifteen studies conducted comparisons of ALT levels in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 68.0\%$ ,  $P = .000$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the ALT levels were significantly lower than those observed with Silibinin alone ( $WMD = -9.06$ ,  $95\% CI: -11.25$  to  $-6.87$ ,  $P = .000$ ) (Fig. 7).

**8.1.5. AST levels.** Fifteen studies conducted comparisons of AST levels in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 68.0\%$ ,  $P = .000$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the AST levels were significantly lower than those observed with Silibinin alone ( $WMD = -9.06$ ,  $95\% CI: -11.25$  to  $-6.87$ ,  $P = .000$ ) (Fig. 8).

**8.1.6. GGT levels.** Seven studies conducted comparisons of GGT levels in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 92.7\%$ ,  $P = .000$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the GGT levels were significantly lower than those observed with Silibinin alone ( $WMD = -11.15$ ,  $95\% CI: -17.39$  to  $-4.92$ ,  $P = .000$ ) (Fig. 9).

**8.1.7. TCM syndrome score.** Four studies conducted comparisons of TCM syndrome score in the treatment of NAFLD with TCM in combination with Silibinin versus Silibinin alone. Since there was significant heterogeneity ( $I^2 = 75.4\%$ ,  $P = .007$ ), a random-effect model was used for the meta-analysis. The summarized results indicated that after treating NAFLD with a combination of TCM and Silibinin, the TCM syndrome score were significantly lower than those observed with Silibinin alone ( $WMD = -3.49$ ,  $95\% CI: -4.74$  to  $-2.24$ ,  $P = .000$ ) (Fig. 10).

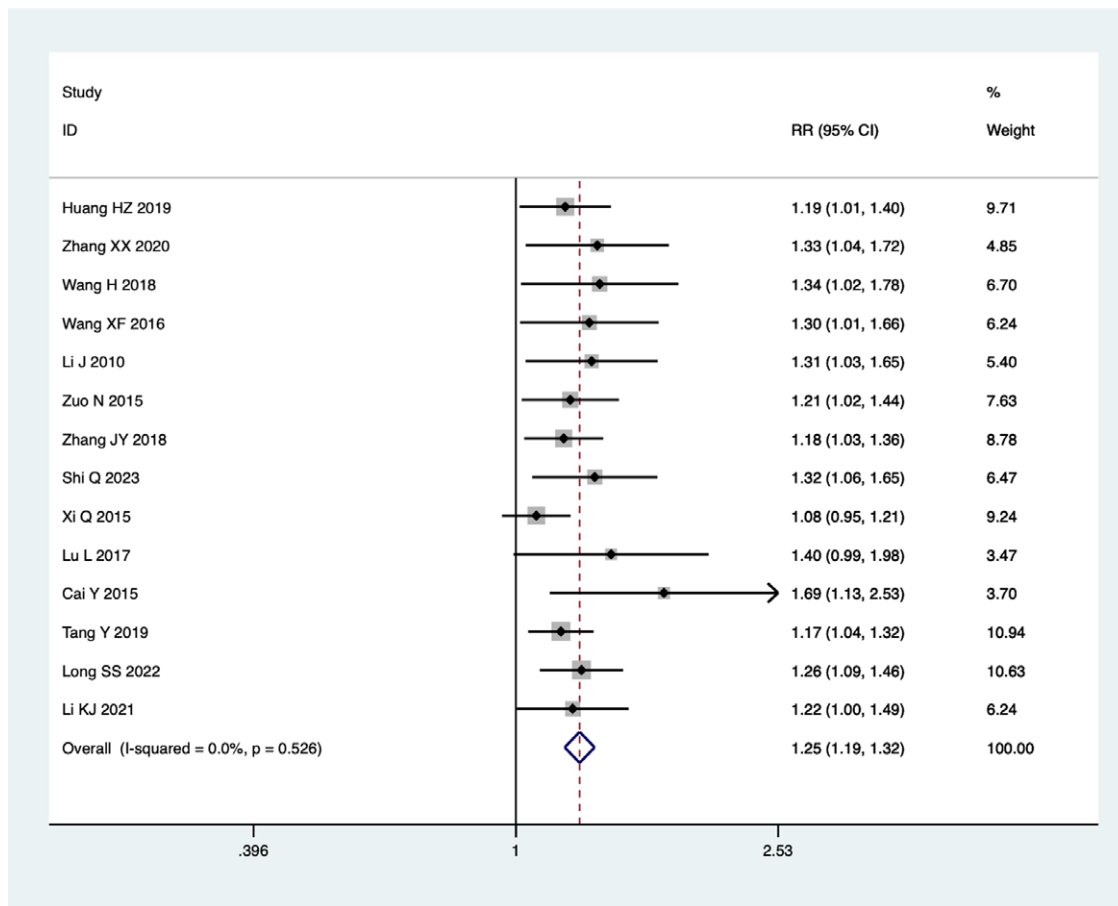
**8.2. Sensitivity analysis**

We did a sensitivity analysis to exclude each of these trials one by one, and then did a combined analysis of the remaining trials.

|               | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|---|---|---|---|--|--------------------------------------|------------|
| Cai Y 2015    | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Huang HZ 2019 | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Li J 2010     | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Li KJ 2021    | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Liu JJ 2021   | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Liu Y 2018    | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Long SS 2022  | +   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Lu L 2017     | +   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Shi Q 2023    | +   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Tang Y 2019   | +   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Wang H 2018   | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Wang XF 2016  | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Xi Q 2015     | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Zhang JY 2018 | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Zhang XX 2020 | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Zuo N 2015    | +   | ?                                       | ?   | ?   | +  | +                                    | +          |

Figure 3. Risk of bias summary.





**Figure 4.** Comparing the differences in total effective rate between combined treatment group and Silibinin group in the treatment of NAFLD. NAFLD = non-alcoholic fatty liver disease.

By doing a Meta-analysis, we found that all the Meta-analyses did not have much effect on the results of the Meta-analysis, indicating that the results of the Meta-analysis were stable and reliable.

### 8.3. Publication bias

The funnel plot drawn in this study is as follows, and it can be seen that the funnel diagram is basically symmetrical. The *P* value obtained by Egger test was .524, indicating that no significant publication bias was found in this paper (Fig. 11).

## 9. Discussion

According to the clinical symptoms and characteristics of patients, NAFLD can be classified within the realm of TCM as conditions related to “fat-dampness,” “hypochondriac pain,” “accumulation,” and “liver stagnation.” Its pathological location is the liver, with pathological factors such as phlegm-dampness, damp-heat, qi stagnation, and blood stasis. These various pathological factors can intersect, leading to a complex presentation that may include both deficiency and excess conditions. It can be differentiated into pattern types such as liver depression with spleen deficiency, phlegm-dampness obstruction, damp-heat retention, or phlegm-blood stasis intermingling, among others. For clinical treatment of NAFLD with concurrent liver damage, the main therapeutic

approach involves behavioral interventions, liver protection, and managing enzymes, while also focusing on blood sugar and lipid control.<sup>[31]</sup> Silibinin capsules have antioxidative and anti-inflammatory properties. They work by inhibiting the generation of fatty acids, reducing the accumulation of lipids and peroxidation in the liver. Moreover, they improve mitochondrial function and enhance lipid exchange between the interior and exterior of cells, thereby alleviating cellular lipid stress. These actions have been shown to be clinically effective and safe.<sup>[32]</sup>

This study summarizes clinical randomized controlled trials of TCM in combination with Silibinin for the treatment of NAFLD. By employing various software for analysis, assessing bias risks, and evaluating evidence quality, it aims to provide evidence-based medicine data for the combined treatment of NAFLD using both traditional Chinese and Western medicine. The results indicate that, regardless of treatment duration, administration methods, medication forms, or geographical distribution, the total effective rate of TCM in combination with Silibinin is significantly superior to the control group, with statistically significant differences. This suggests a clinical advantage for TCM in conjunction with Silibinin. TCM offers the advantage of targeting multiple mechanisms, making it an important source for the development of new approaches and drugs for NAFLD. However, due to the lack of repetition in the TCM methods used in the included literature, it is unclear which specific TCM approach is superior.

In terms of observed indicators, it was found that liver function markers (ALT, AST, GGT), lipid metabolism markers

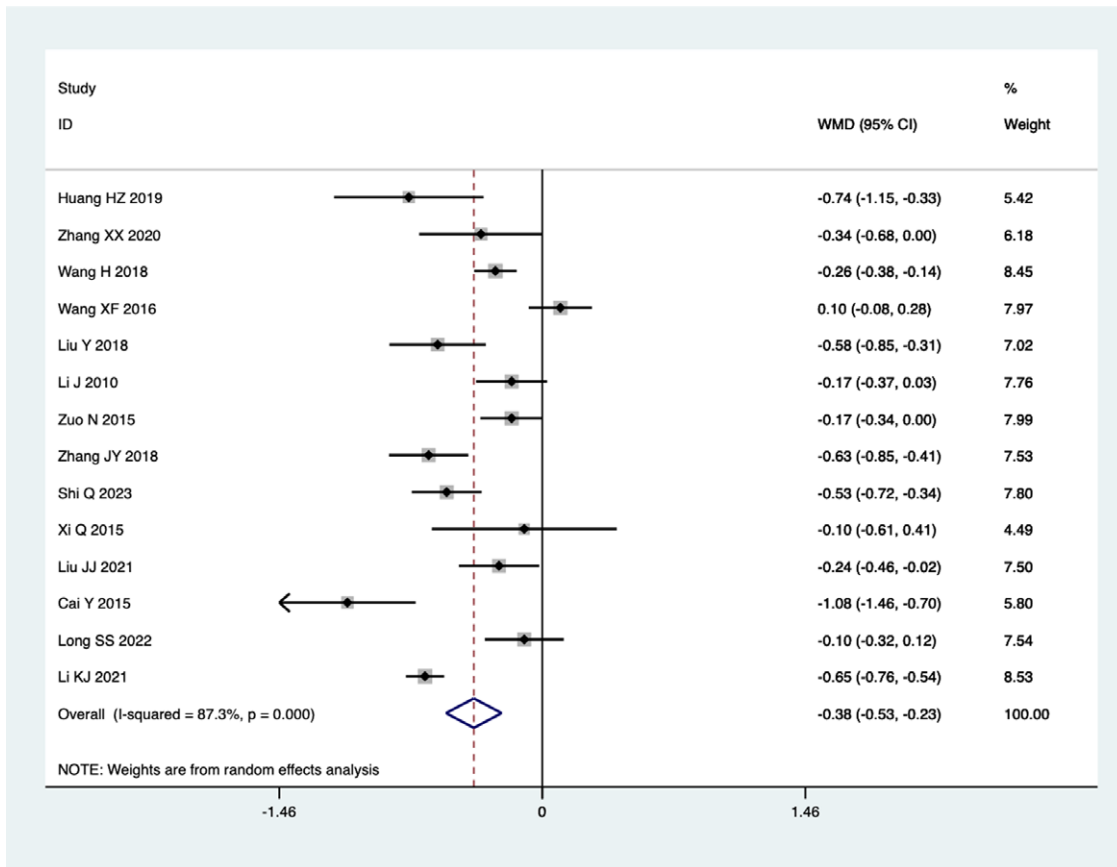


Figure 5. TC levels in the combined treatment group and the Silibinin group after treating NAFLD. NAFLD = non-alcoholic fatty liver disease.

(TG, TC), and TCM syndrome scores showed more significant improvements in the combined treatment of traditional Chinese and Western medicine. In fact, during the data collection process for this study, it was noted that some researchers used fasting insulin, insulin index, leptin, adiponectin, and other parameters as observed indicators. However, due to limited available data, these parameters were eventually excluded from this study. NAFLD is closely associated with metabolic syndrome, type 2 diabetes, cardiovascular diseases, and colorectal tumors. Therefore, we need more evidence to support the inclusion of additional observational indicators. Mass spectrometry-based multi-omics studies are gaining popularity, and it is promising to obtain biomarkers for NAFLD from genomics, transcriptomics, proteomics, and metabolomics. The “gut-liver axis” has been shown to be of great significance in NAFLD, and iron death, closely related to lipid peroxidation, has also been implicated in the pathophysiology of NAFLD.<sup>[33]</sup> Therefore, utilizing multi-omics, iron death, or studying the gut microbiota associated with NAFLD as observational indicators can help elucidate the mechanisms of traditional Chinese medicine in the context of NAFLD.

This study has certain limitations: Traditional Chinese medicine prescription and medication lacked standardization. Included literature primarily used classic formulas, clinical experience, or research on commercially available patent medicines as the basis for interventions. The diversity in intervention measures, along with variations in herbal flavors and dosages in traditional Chinese medicine compound components, made it challenging to compare results and interpret them consistently, which reduced the comparability

between trials. Lack of follow-up records. None of the 16 RCTs included in this study had any follow-up data, preventing a deeper understanding of the prognosis of NAFLD when treated with traditional Chinese medicine in conjunction with Silymarin capsules.

### 10. Conclusion

Traditional Chinese medicine in conjunction with Silibinin capsules has shown significant efficacy in the treatment of NAFLD, improving clinical symptoms, blood lipid levels, and liver function. Furthermore, it is essential to engage in multi-omics research, investigate iron death, and explore the gut microbiota as potential observational indicators for the diagnosis and inclusion criteria. Conducting more high-quality clinical experiments is necessary to further validate these findings.

### Author contributions

- Conceptualization:** Xiang Zhang, QiuJun Zhou.
- Data curation:** Xiaoliang Jin, QiuJun Zhou.
- Formal analysis:** Xiang Zhang, QiuJun Zhou.
- Funding acquisition:** Zhenghao Jiang.
- Methodology:** Xiaoliang Jin.
- Software:** Xiaoliang Jin.
- Writing – original draft:** Xiang Zhang, Xiaoliang Jin, QiuJun Zhou.
- Writing – review & editing:** Zhenghao Jiang, Xiang Zhang, Xiaoliang Jin, QiuJun Zhou.

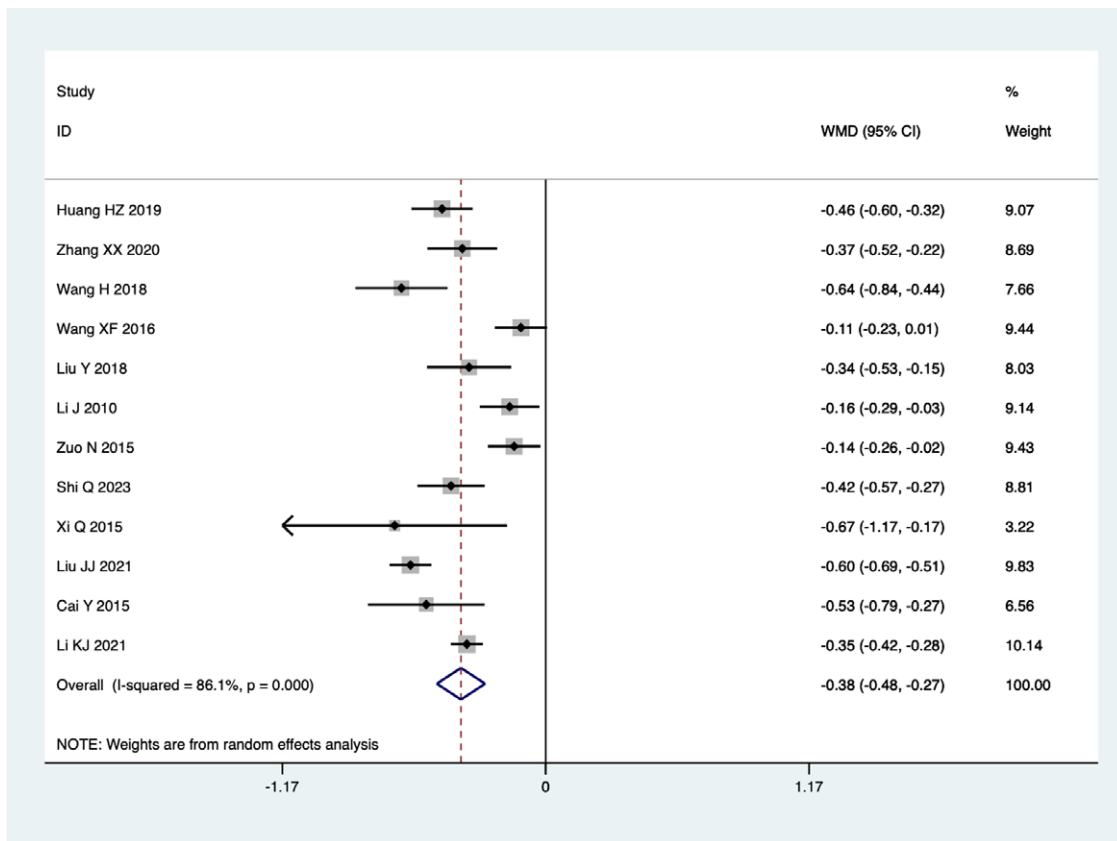


Figure 6. TG levels in the combined treatment group and the Silibinin group after treating NAFLD. NAFLD = non-alcoholic fatty liver disease.

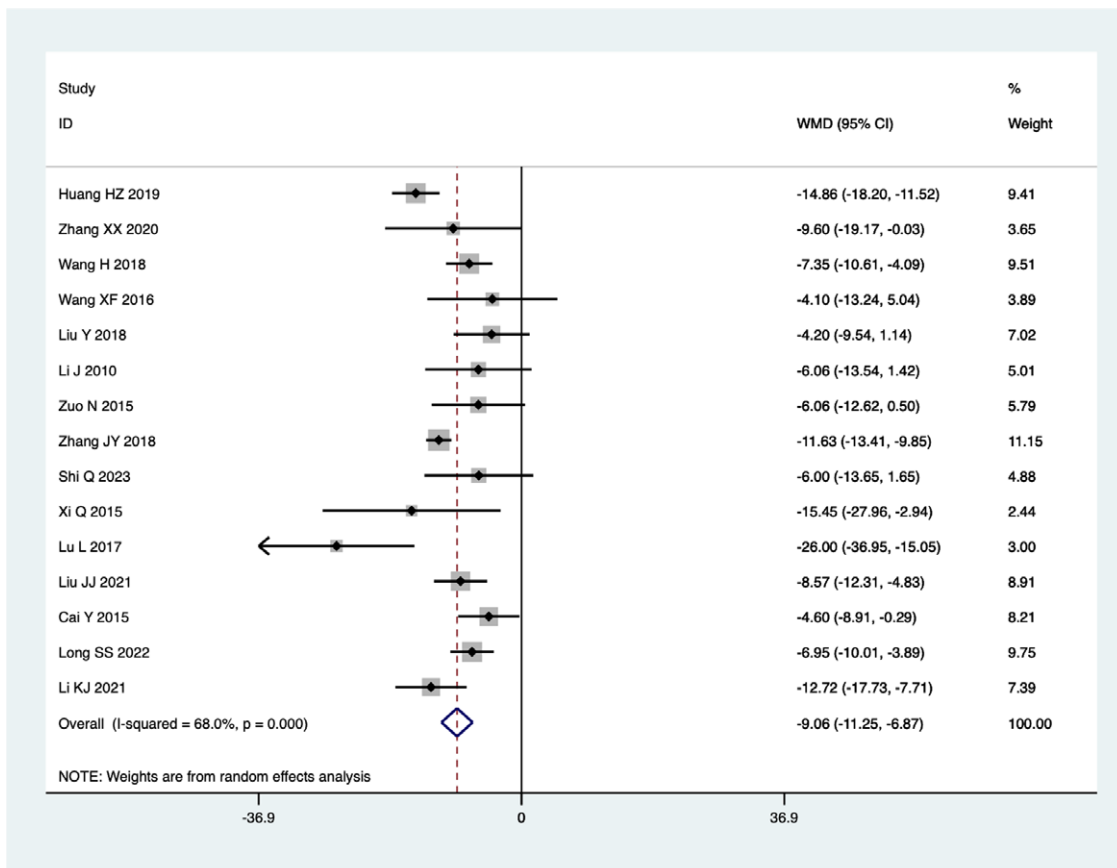
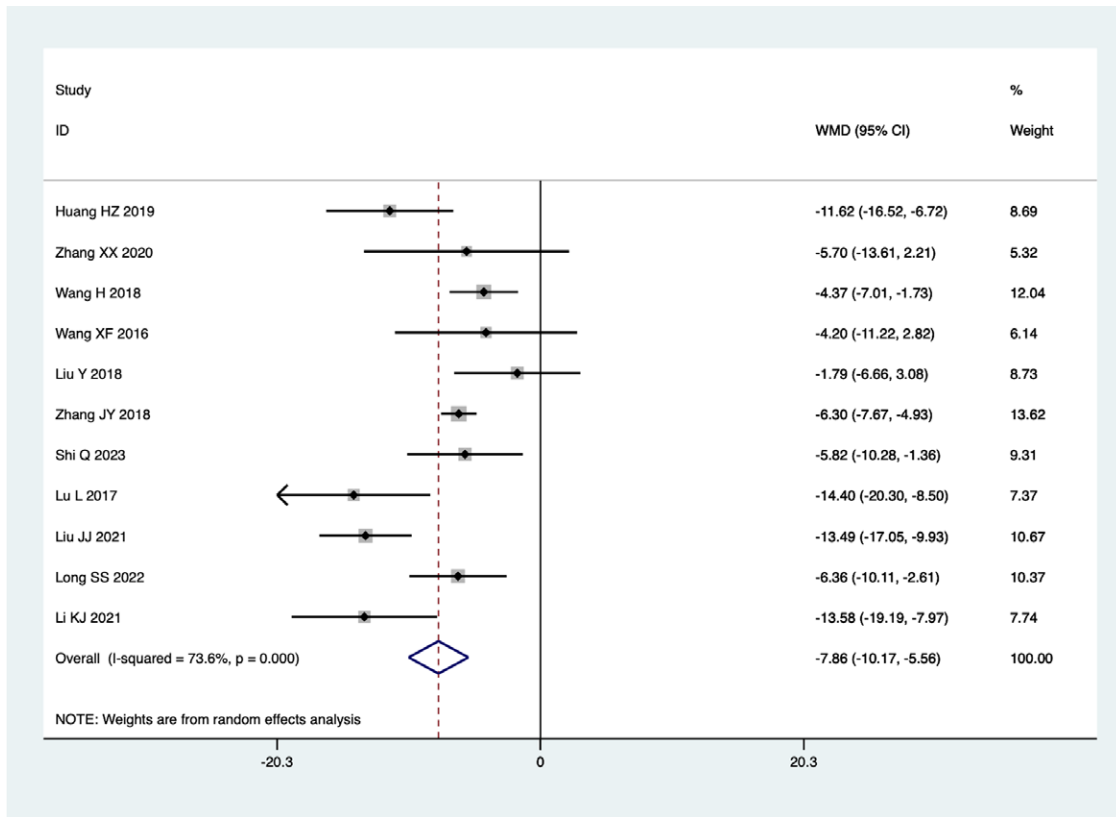
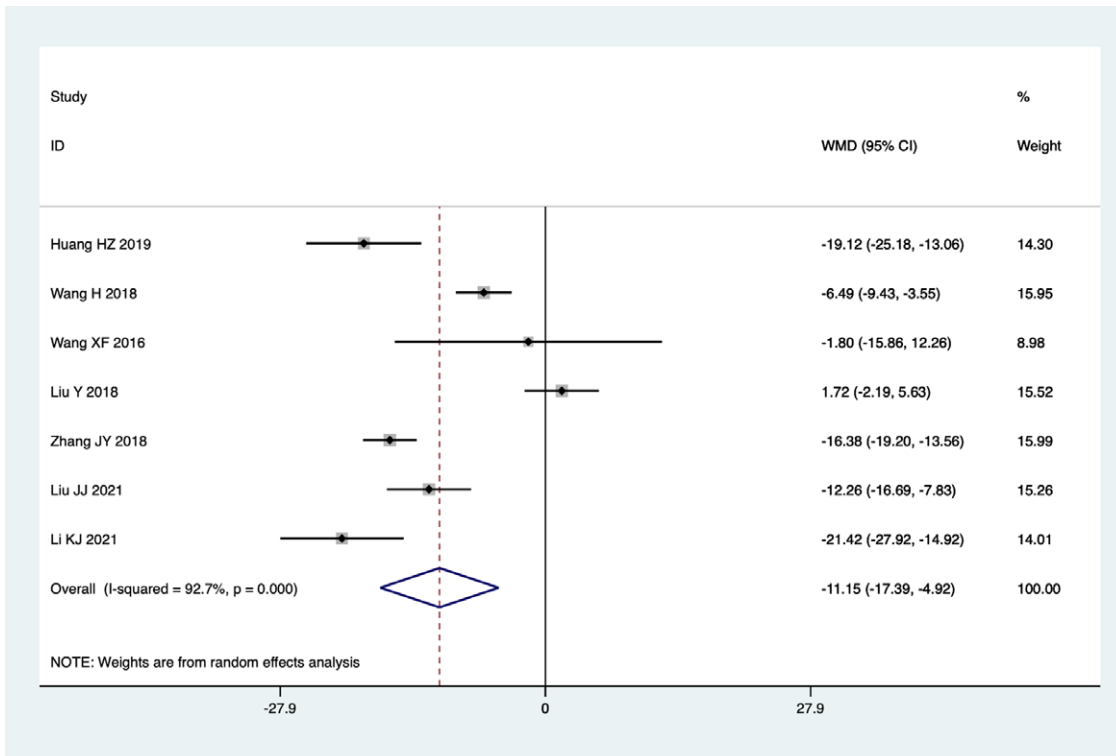


Figure 7. ALT levels in the combined treatment group and the Silibinin group after treating NAFLD. ALT = alanine aminotransferase, NAFLD = non-alcoholic fatty liver disease.

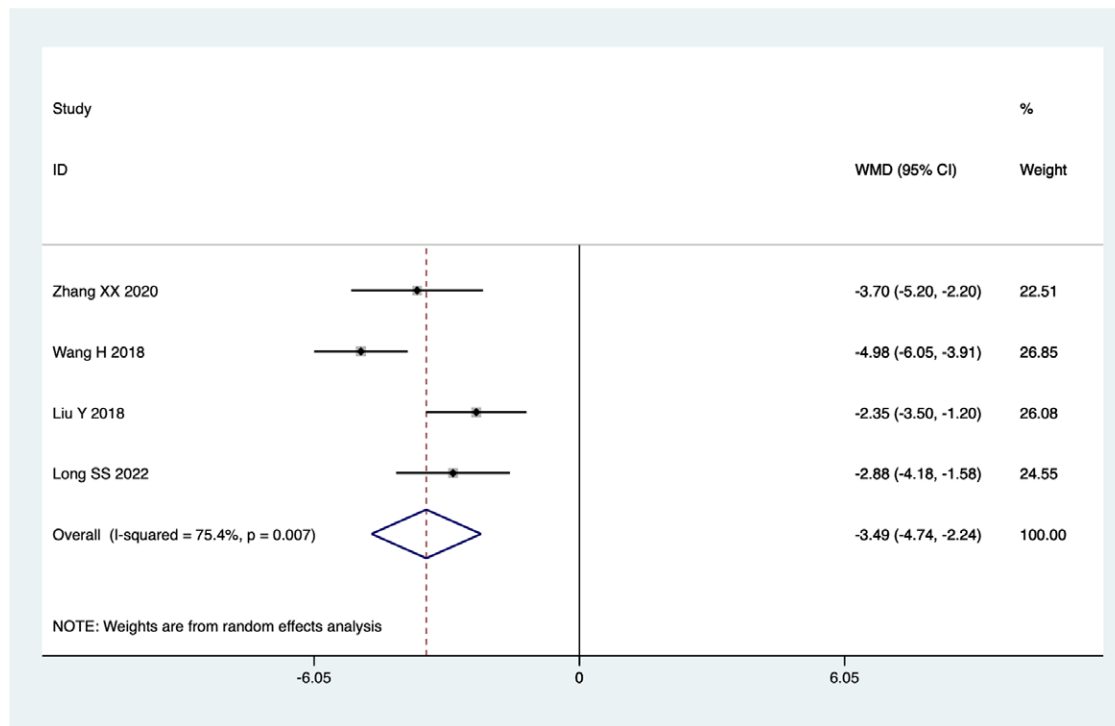




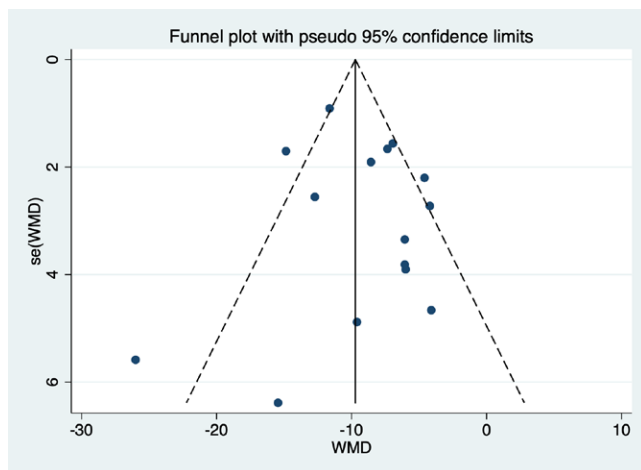
**Figure 8.** AST levels in the combined treatment group and the Silibinin group after treating NAFLD. AST = aspartate aminotransferase, NAFLD = non-alcoholic fatty liver disease.



**Figure 9.** GGT levels in the combined treatment group and the Silibinin group after treating NAFLD. GGT = gamma glutamyl transpeptidase, NAFLD = non-alcoholic fatty liver disease.



**Figure 10.** TCM syndrome score in the combined treatment group and the Silibinin group after treating NAFLD. NAFLD = non-alcoholic fatty liver disease, TCM = traditional Chinese medicine.



**Figure 11.** Funnel plot for evaluating the publication bias of this meta-analysis.

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