The efficacy of novel metabolic targeted agents and natural plant drugs for nonalcoholic fatty liver disease treatment

A PRISMA-compliant network meta-analysis of randomized controlled trials

Jingwen Zhou, PhD^a, Yidi Chen, MS^b, Jun Yu, PhD^c, Tianci Li, MS^c, Ziyu Lu, BS^b, Yan Chen, MS^d, Xiaolong Zhang, PhD^a, Fang Ye, PhD^c,*

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease characterized by excess accumulation of fat in hepatocytes. Because no drug has been approved for NAFLD treatment, this work analyzed the effects of agents resulting from 2 research hotspots, metabolic target agents, and natural plant drugs, on NAFLD with network meta-analysis.

Methods: Public databases were searched through August 14, 2020. Randomized controlled trials that compared obeticholic acid, elafibranor, cenicriviroc, selonsertib, curcumin, silymarin, and resveratrol to placebo were included. Liver pathology improvement, hepatic biochemical indicators, and lipid metabolism indicators were analyzed.

Results: Thirty-five studies were included in the meta-analysis. Obeticholic acid was found to significantly increase the frequency of liver biopsy improvement compared to placebo (OR: 2.10; 95% CI: 1.60, 2.77). The ranking results among the hepatic biochemical indicators showed that obeticholic acid (94.9%) and elafibranor (86.3%) have a relative advantage in reducing alanine aminotransferase (ALT) levels, and obeticholic acid also had an advantage (95.4%) in reducing aspartate aminotransferase (AST) levels. Considering lipid metabolic indicators, elafibranor (expSMD: 0.01; 95% CI: 0.00, 0.05; SUCRA: 100%), and obeticholic acid (expSMD: 0.48; 95% CI: 0.28, 0.84; SUCRA: 75.6%) significantly reduced triglyceride (TG) levels compared with placebo; moreover, obeticholic acid, but not elafibranor, caused a serious increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and a decrease in high-density lipoprotein cholesterol (HDL-C) levels.

Conclusions: Novel metabolic targeted agents generally have better effects than natural plant drugs, especially obeticholic acid, and elafibranor. However, obeticholic acid showed serious adverse effects such as increasing LDL-C levels and decreasing HDL-C levels. Curcumin showed potential advantages for NAFLD but lacked statistical significance.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CIs = confidence intervals, GGT = γ-glutamyltranspeptidase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, ORs = odds ratios, SMD = standard mean difference, SUCRA = surface under the cumulative ranking curve, TC = total cholesterol, TG = triglyceride.

Keywords: meta-analysis, natural plant drugs, nonalcoholic fatty liver disease, targeted agents
1. Introduction
Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent fatty liver disease caused by genetic susceptibility and overnutrition after excluding alcohol abuse and other causes of hepatic diseases. Globally, the prevalence rate of NAFLD is approximately 25%, with a high incidence in the Middle East and South America and a low incidence in Africa. In the United States, the number of NAFLD patients was expected to increase from 83.1 million (25% of the population) in 2015 to 100.9 million in 2030. In China, NAFLD has also become a major public health problem, with a prevalence rate of 29.2%. Without drugs approved by the Food and Drug Administration and recommended for the treatment of NAFLD and NASH at this stage; only lifestyle interventions are recommended. Unfortunately, the current scientific research is far from fully clarifying the origin and underlying mechanisms of NAFLD/NASH, so few appropriate therapeutic approaches for greatly reducing or eliminating NAFLD/NASH have been proposed. However, although there is still a long way to go, research in this field is very active, and significant progress has been made in reducing the burdens of such diseases.

Metabolic targeted drugs are aimed at either reducing the delivery of the metabolic substrate or facilitating its safe disposal in the NAFLD pathological process. Of these agents, obeticholic acid, elafibraror, cenicriviroc, and selonsertib have entered the Phase III clinical trial stage. In addition to novel metabolic target agents, natural plant drugs based on local traditional medicine for NAFLD treatment is also a research hotspot. Several widely researched drugs, including curcumin, resveratrol, and silymarin, were selected for this analysis. In a previous meta-analysis, curcumin significantly reduced NAFLD-related visceral adiposity and abdominal obesity and had acceptable effects on reducing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Silymarin could also significantly reduce transaminase levels in NAFLD patients. However, resveratrol was not effective in relieving the degree of liver fibrosis and significantly reducing liver function parameters.

The above 2 types of drugs represent 2 hotspots for NAFLD treatment research, and which drugs may have potential effects on NAFLD is an important question. Therefore, in this work, we analyzed the effects of metabolic targeted agents and natural plant drugs on NAFLD with network meta-analysis.

2. Methods
The guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses – extension for network meta-analysis statement was followed in writing this report. Ethical approval was not necessary because this study was a meta-analysis; our data were based on published studies only.

2.1. Databases and search strategy
Public databases PubMed, Embase, and Cochrane Library were used for systematic retrieval from database inception to August 2020. The keywords and search terms used were (curcumin OR curcuminoid OR turmeric OR silymarin OR “milk thistle” OR resveratrol) OR (“obeticholic acid” OR ocaliva OR elafibraror OR cenicriviroc OR selonsertib) AND (nonalcoholic fatty liver disease OR NAFLD OR nonalcoholic steatohepatitis OR NASH) AND (random*) AND (blind OR blindness OR mask OR placebo). References of relevant reviews were also checked to avoid omission.

2.2. Study selection
Two authors selected potentially relevant literature by viewing the title and abstract. The full texts of articles with further potential were reviewed for final inclusion. The inclusion criteria included the following: 1, articles published in English; 2, well-designed randomized controlled trials (RCTs) that used placebo as a control; 3, studies that researched NAFLD or NASH patients; 4, interventions were one of the following: obeticholic acid, elafibraror, cenicriviroc, selonsertib, curcumin, silymarin, and resveratrol; and 5, outcomes included at least one improvement in liver pathology, hepatic biochemical indicators (AST, ALT, γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP)), and lipid metabolism indicators (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG)).

2.3. Data extraction and risk of bias assessment
The following contents were extracted from the included studies: the first author’s name, publication year, registration number, sample size, average age, intervention agents, and follow-up period. Any disagreement was discussed with a third author to reach consensus. The primary outcome was liver pathology improvement, defined as improvements in NASH or fibrosis without worsening of either; the secondary outcome included hepatic biochemical indicators and lipid metabolism indicators. Risk of biases were assessed using the Cochrane Risk of Bias Tool, which included items of random sequence generation, allocation concealment, and blinding as well as detection of incomplete outcome data, selective outcome reporting, and other potential sources of bias.

2.4. Statistical analysis
Pairwise meta-analysis with a random-effects model was used to estimate the treatment effect, odds ratios (ORs), and standard mean difference (SMD) with 95% confidence intervals (CIs) for dichotomous and continuous outcomes, respectively. The most frequent framework random-effects model was used for mixed multiple treatment comparisons. Inconsistency was assessed by closed loops in the network comparisons. The surface under the cumulative ranking curve (SUCRA) probabilities were used to rank the treatments for each outcome. Comparison-adjusted funnel plots were also used to assess the potential small-study effects. We also performed subgroup analyses according to NAFLD and NASH patient characteristics. All analyses were...
performed using STATA 14.0 (Stata Corp, College Station, TX). A P value ≤ .05 was considered statistically significant.

3. Results

Through database searching, 65 articles were obtained from PubMed, 217 from Embase, and 192 from the Cochrane Library. After removing duplications, 271 articles were acquired. A total of 194 articles were excluded after screening titles and abstracts. Following full-text screening, 41 articles were excluded because they did not include NAFLD or NASH patients (2); did not use placebo as a control (1); repeated research (13); were review articles (11); did not report the desired outcomes (8); were not published in English (3); researched NAFLD in children (2); or were protocols (1). Finally, 35 studies were included in the meta-analysis, including 1 study each for cenicriviroc, elafibranor, and selonsertib, 4 for obeticholic acid, 6 for silymarin, 7 for resveratrol, and 15 for curcumin (Table 1). [17–51]

A total of 5246 patients were included. Although 15 curcumin-related studies were included, the total sample size was 934. The sample sizes analyzed in obeticholic acid- and selonsertib-related studies were 1275 and 1679, respectively. Most of the included studies were published in 2020 and 2019. The longest follow-up period was 2 years, and the shortest was 6 weeks. Considering the quality of the included studies, only 3 of the included studies used placebo-only as a control without the set blinding method, and the others were double-blind RCTs. Overall, the quality of the included studies was satisfactory (Fig. 1).

For liver pathology results, cenicriviroc, curcumin, elafibranor, obeticholic acid, selonsertib, and silymarin were included in the analysis (Fig. 2, A). Since all comparisons were head-to-head between interventions and placebo and no loop was formed, a consistency model was used in the analysis. In the pairwise comparisons, only obeticholic acid significantly increased the frequency of liver biopsy improvement compared to placebo (OR: 2.10; 95% CI: 1.60, 2.77) and selonsertib (OR: 2.25; 95% CI: 1.52, 3.33) (Table 2). In the SUCRA ranking results,
Obeticholic acid (79.3%), curcumin (78.5%), and cenicriviroc (71.5%) had the relative advantage of improving liver biopsy.

Among the hepatic biochemical indicators, the ALT analysis included all intervention agents (Fig. 2, B). The pairwise comparison results showed that elaflibranor (exponentiated standard mean difference, expSMD: 0.19; 95% CI: 0.04, 0.84) and obeticholic acid (expSMD: 0.13; 95% CI: 0.06, 0.28) could significantly reduce ALT levels (Table 3). The ranking results showed that obeticholic acid (94.9%) and elaflibranor (86.3%) had a relative advantage in reducing ALT levels. For AST, the elaflibranor was missing in the analysis (Fig. 2, C). In the pairwise comparisons, obeticholic acid significantly reduced AST levels compared with placebo (expSMD: 0.34; 95% CI: 0.18, 0.67) and selonsertib (expSMD: 0.25; 95% CI: 0.08, 0.78) (Table 4). Moreover, ranking results showed that obeticholic acid had an advantage (95.4%). For GGT, silymarin was missing in the analysis (Fig. 2, D). In the pairwise comparison and the ranking result, elaflibranor showed a clear advantage (100%), followed by obeticholic acid (78%) (Table 5). For ALP (Fig. 2, E), elaflibranor showed a significant advantage (100%), but obeticholic acid (1.7%) significantly increased the ALP level compared with placebo (expSMD: 16.46; 95% CI: 4.46, 60.78) (Table 6).

Considering lipid metabolic indicators, the total cholesterol analysis lacked elaflibranor as an intervention (Fig. 2, F). Pairwise comparisons found that obeticholic acid (SUCRA: 3.2%) was significantly inferior to curcumin (expSMD: 0.27; 95% CI: 0.12, 0.59), placebo (expSMD: 2.6; 95% CI: 1.45, 4.69), and selonsertib (expSMD: 3.44; 95% CI: 1.28, 9.27) in reducing TC levels (Table 7). There was no other significant difference in comparisons. For the TG results, cenicriviroc was missing in the analysis (Fig. 2, G). Pairwise comparisons found that elaflibranor (expSMD: 0.01; 95% CI: 0.00, 0.05; SUCRA: 100%) and obeticholic acid (expSMD: 0.48; 95% CI: 0.28, 0.84; SUCRA: 75.6%) could significantly reduce TG levels compared with placebo (Table 8). For LDL-C, all interventions were included (Fig. 2, H). Elaflibranor showed a significant advantage over placebo (expSMD: 0.01; 95% CI: 0.00, 0.08; SUCRA: 100%) in reducing TG levels, but obeticholic acid significantly increased the level of LDL-C compared to placebo (expSMD: 6.32; 95% CI: 2.39, 15.40; SUCRA: 1.6%) (Table 9). All interventions were also included for HDL-C (Fig. 2, I). Elaflibranor showed a significant increase in HDL-C levels compared to placebo (expSMD: 61.82; 95% CI: 13.45, 284.11; SUCRA: 100%), but obeticholic acid significantly reduced the level of HDL-C compared to placebo (expSMD: 0.25; 95% CI: 0.12, 0.54; SUCRA: 3.4%) (Table 10). The comparison-adjusted funnel plots showed no obvious publication bias among the above analyses (Fig. 3). Furthermore, we analyzed the NASH patients separately and performed subgroup analysis (Fig. 4).

4. Discussion

This study analyzed the effects of agents resulting from 2 research hotspots on NAFLD treatment by network meta-analysis, including novel metabolic targeted agents, and natural plant drugs. The results showed that obeticholic acid has advantages in relieving and reversing the NAFLD pathological process, but it causes serious increases in TC and LDL-C levels and decreases in HDL-C levels. Although elaflibranor did not show a significant effect in relieving NAFLD pathological processes, it has obvious advantages in reducing liver biochemical and lipid metabolism indicators.

Among natural plant drugs, curcumin had a relatively high ranking in improving the NAFLD pathological process, but the effect was not significant. Other comparisons also did not find a significant difference between natural medicine and placebo. Generally, natural plant drugs are inferior to novel metabolic targeted drugs for NAFLD intervention; moreover, they do not cause a serious increase in LDL-C levels or a reduction in HDL-C levels. Although elaflibranor did not show a significant effect in relieving NAFLD pathological processes, it has obvious advantages in reducing liver biochemical and lipid metabolism indicators.
Figure 2. Network plots of outcomes among comparisons between agents and placebo in network meta-analysis. A: Liver pathology improvement; B: ALT; C: AST; D: GGT; E: ALP; F: TC; G: TG; H: LDL-C; I: HDL-C.

Table 2
The league table for liver pathology improvement in network comparisons (odds ratio and its 95% confidence intervals).

| Treatment         | OR (95% CI)          | Curcumin | Elafibranor | Obeticholic Acid | Placebo | Resveratrol | Selonsertib | Silymarin |
|-------------------|----------------------|----------|-------------|------------------|---------|-------------|-------------|-----------|
| Cenicriviroc      | 0.86 (0.24,3.06)     | 1.65 (0.53,5.19) | 0.66 (0.34,1.28) | 2.1 (1.60,2.77)  | 2.12 (0.90,5.00) | 1.49 (0.77,2.69) | 1.07 (0.81,1.41) | 2.25 (1.52,3.33) |
| Curcumin          | 1.42 (0.52,3.90)     | 1.1 (0.40,3.02)  | 1.99 (0.14, 92.65) | 2.31 (0.87,6.12) | 2.47 (0.90,6.79) | 1.58 (0.79,3.16) | 0.75 (0.40,1.42) | 1.07 (0.81,1.41) |
| Elafibranor       | 0.95 (0.40,2.23)     | 1.05 (0.44,2.51) | 0.95 (0.40,2.23) | 2.12 (0.90,5.00) | 2.12 (0.90,5.00) | 2.25 (1.52,3.33) | 1.07 (0.81,1.41) | 1.07 (0.81,1.41) |
| Obeticholic Acid  | 0.95 (0.40,2.23)     | 1.05 (0.44,2.51) | 2.12 (0.90,5.00) | 2.12 (0.90,5.00) | 2.12 (0.90,5.00) | 2.25 (1.52,3.33) | 1.07 (0.81,1.41) | 1.07 (0.81,1.41) |
| Placebo           | 2.12 (0.90,5.00)     | 1.49 (0.77,2.69) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) |
| Resveratrol       | 2.47 (0.90,6.79)     | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) |
| Selonsertib       | 1.49 (0.77,2.69)     | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 1.58 (0.79,3.16) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) |
| Silymarin         | 1.07 (0.81,1.41)     | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) | 0.75 (0.40,1.42) |

*Bold font represents statistical difference.

Table 3
The league table for ALT in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

| Treatment         | E(SMD) (95% CI)          | Curcumin | Elafibranor | Obeticholic Acid | Placebo | Resveratrol | Selonsertib | Silymarin |
|-------------------|--------------------------|----------|-------------|------------------|---------|-------------|-------------|-----------|
| Cenicriviroc      | 1.89 (0.22,16.50)        | 3.68 (0.75,18.01) | 1.43 (0.27,7.64) | 0.19 (0.04,0.84) | 0.13 (0.06,0.28) | 0.1 (0.06,0.76) | 0.2 (0.06,0.76) |
| Curcumin          | 6.94 (0.53,90.74)        | 5.28 (2.06,13.55) | 1.43 (0.27,7.64) | 0.19 (0.04,0.84) | 0.13 (0.06,0.28) | 0.1 (0.06,0.76) | 0.2 (0.06,0.76) |
| Elafibranor       | 9.95 (1.07,92.65)*       | 1.43 (0.27,7.64) | 0.13 (0.06,0.28) | 1.45 (0.15,13.78) | 0.77 (0.29,2.07) | 0.21 (0.04,1.14) | 0.15 (0.05,0.45) |
| Obeticholic Acid  | 1.31 (0.16,10.69)        | 0.7 (0.40,1.21)  | 0.13 (0.06,0.28) | 0.15 (0.05,0.45) | 0.21 (0.04,1.14) | 0.15 (0.05,0.45) | 0.12 (0.03,0.43) |
| Placebo           | 1.60 (0.14,10.65)        | 0.21 (0.04,1.14) | 0.15 (0.05,0.45) | 0.12 (0.03,0.43) | 0.17 (0.03,1.04) | 0.12 (0.03,0.43) | 0.17 (0.03,1.04) |
| Resveratrol       | 0.43 (0.06,3.48)         | 0.17 (0.03,1.04) | 0.12 (0.03,0.43) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) |
| Selonsertib       | 0.17 (0.03,1.04)         | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) | 0.17 (0.03,1.04) |
| Silymarin         | 1.73 (0.39,7.64)         | 1.73 (0.39,7.64) | 1.73 (0.39,7.64) | 1.73 (0.39,7.64) | 1.73 (0.39,7.64) | 1.73 (0.39,7.64) | 1.73 (0.39,7.64) |

*Bold font represents statistical difference.
### Table 4

The league table for AST in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

|                | Cenicriviroc | Curcumin | Obeticholic Acid | Placebo | Resveratrol | Selonsertib |
|----------------|--------------|----------|------------------|---------|-------------|-------------|
| 1.79 (0.27,11.93) | 4.07 (0.58,28.62) | 1.4 (0.22,8.77) | 2.14 (0.30,15.40) | 1.04 (0.13,8.03) | 1.8 (0.23,14.10) |
| 2.28 (1.00,5.18) | 0.78 (0.48,1.28) | 0.34 (0.18,0.67) | 1.53 (0.74,3.16) | 0.74 (0.30,1.84) | 1.29 (0.51,3.27) |
| 4.07 (0.58,28.62) | 0.53 (0.20,1.41) | 0.25 (0.08,0.78) | 0.94 (0.45,1.95) | 0.48 (0.15,1.55) | 0.84 (0.26,2.74) |
| 1.04 (0.13,8.03) | 0.74 (0.30,1.84) | 1.29 (0.51,3.27) | 0.48 (0.15,1.55) | 1.29 (0.51,3.27) | 1.73 (0.47,6.38) |
| 1.8 (0.23,14.10) | 1.29 (0.51,3.27) | 0.84 (0.26,2.74) | 1.73 (0.47,6.38) | 1.73 (0.47,6.38) | Silymarin |

*Bold font represents statistical difference.*

### Table 5

The league table for GGT in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

|                | Cenicriviroc | Curcumin | Etaflonar | Obeticholic Acid | Placebo | Resveratrol | Selonsertib |
|----------------|--------------|----------|-----------|------------------|---------|-------------|-------------|
| 1.36 (0.06,29.59) | 286.8 (10.70,7689.65) | 4.7 (0.28,79.26) | 1.08 (0.08,15.48) | 1.34 (0.07,24.89) | 1.14 (0.06,22.24) |
| 211.62 (17.67,2534.83) | 3.46 (0.56,21.52) | 0.8 (0.17,3.79) | 0.99 (0.14,7.11) | 0.84 (0.11,6.49) | 0.05 (0.01,0.31) |
| 1.47 (0.70,3.10) | 0.05 (0.00,0.00) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.75 (0.19,3.01) | 0 (0.00,0.00) |
| 0.69 (0.13,2.54) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.51 (0.04,6.44) | 0 (0.00,0.00) |
| 0.79 (0.01,45.93) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.79 (0.08,7.73) | 0 (0.00,0.00) |

*Bold font represents statistical difference.*

### Table 6

The league table for ALP in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

|                | Cenicriviroc | Curcumin | Elaflonar | Obeticholic Acid | Placebo | Resveratrol | Selonsertib |
|----------------|--------------|----------|-----------|------------------|---------|-------------|-------------|
| 1 (0.02,49.29) | 114.43 (32.56,402.13) | 4.7 (0.28,79.26) | 1.08 (0.08,15.48) | 1.34 (0.07,24.89) | 1.14 (0.06,22.24) |
| 1100000 (49352.52,2.6e+07) | 3.46 (0.56,21.52) | 0.8 (0.17,3.79) | 0.99 (0.14,7.11) | 0.84 (0.11,6.49) | 0 (0.00,0.00) |
| 0.05 (0.00,2.18) | 0.05 (0.01,0.31) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.75 (0.19,3.01) | 0 (0.00,0.00) |
| 0.75 (0.02,28.54) | 0.75 (0.19,3.01) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.51 (0.04,6.44) | 0 (0.00,0.00) |
| 0.79 (0.01,45.93) | 0.79 (0.08,7.73) | 0 (0.00,0.00) | 0 (0.00,0.00) | 0.79 (0.08,7.73) | 0 (0.00,0.00) |

*Bold font represents statistical difference.*

### Table 7

The league table for TC in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

|                | Cenicriviroc | Curcumin | Obeticholic Acid | Placebo | Resveratrol | Selonsertib |
|----------------|--------------|----------|------------------|---------|-------------|-------------|
| 1.15 (0.21,6.30) | 0.31 (0.05,1.71) | 0.27 (0.12,0.59) | 0.79 (0.16,0.01) | 0.73 (0.12,4.58) | 1.05 (0.17,6.38) |
| 0.69 (0.13,2.54) | 0.69 (0.41,1.17) | 2.6 (1.45,4.69) | 2.41 (0.85,6.79) | 0.92 (0.39,2.17) | 1.32 (0.59,2.93) |
| 0.31 (0.05,1.71) | 0.45 (0.18,1.13) | 2.87 (0.78,10.59) | 1.1 (0.34,3.54) | 1.19 (0.28,5.06) | 0.98 (0.03,3.96) |
| 0.88 (0.12,6.44) | 0.88 (0.12,6.44) | 1.54 (0.28,3.95) | 1.05 (0.17,6.45) | 1.54 (0.28,3.95) | 1.05 (0.28,3.95) |

*Bold font represents statistical difference.*

### Table 8

The league table for TG in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

|                | Curcumin | Etaflonar | Obeticholic Acid | Placebo | Resveratrol | Selonsertib |
|----------------|----------|-----------|------------------|---------|-------------|-------------|
| 114.43 (32.56,402.13) | 1.47 (0.70,3.10) | 0.01 (0.00,0.05) | 0.48 (0.28,0.84) | 0.94 (0.45,1.95) | 0.59 (0.23,1.51) |
| 0.71 (0.42,1.16) | 0.01 (0.00,0.02) | 0.45 (0.18,1.13) | 1.23 (0.58,2.61) | 1.31 (0.46,3.72) | 1.05 (0.28,3.92) |
| 0.69 (0.21,2.33) | 0.01 (0.00,0.03) | 0.47 (0.14,1.62) | 0.98 (0.33,2.96) | 0.8 (0.21,3.03) | 0.83 (0.20,3.43) |

*Bold font represents statistical difference.*
Table 9
The league table for LDL-C in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

| Treatment                | Exp(SMD) (95% CI) |
|--------------------------|-------------------|
| Cenicriviroc             | 0.99 (0.07,13.45) |
| Curcumin                 | 66.56 (9.48,478.55) |
| Elafibran                | 0.13 (0.01,1.86)  |
| Obeticholic Acid         | 0.84 (0.07,10.09) |
| Placebo                  | 0.63 (0.04,9.78)  |
| Resveratrol              | 1.03 (0.00,16.59) |
| Selonsertib              | 0.97 (0.05,20.60) |
| Silymarin                | 1.03 (0.06,16.59) |

*Bold font represents statistical difference.

Table 10
The league table for HDL-C in network comparisons (exponentiated standardised mean difference and its 95% confidence intervals).

| Treatment                | Exp(SMD) (95% CI) |
|--------------------------|-------------------|
| Cenicriviroc             | 0.77 (0.08,7.09)  |
| Curcumin                 | 0.01 (0.00,0.19)  |
| Elafibran                | 3.42 (0.36,32.14) |
| Obeticholic Acid         | 0.86 (0.10,7.09)  |
| Placebo                  | 0.73 (0.07,7.49)  |
| Resveratrol              | 0.69 (0.07,7.29)  |
| Selonsertib              | 0.97 (0.07,12.95) |
| Silymarin                | 0.69 (0.07,7.29)  |

*Bold font represents statistical difference.

Figure 3. Comparison-adjusted funnel plots of outcomes in the network meta-analysis. A: Liver pathology improvement; B: ALT; C: AST; D: GGT; E: ALP; F: TC; G: TG; H: LDL-C; I: HDL-C.
be that our study collected only well-designed RCTs with placebo as a control. In the subgroup analysis for the NASH population, obeticholic acid also had advantages in improving pathological results and reducing ALT and AST levels. Elafibranor had advantages in reducing GGT, ALP, TG, and LDL-C levels and increasing HDL-C levels. For the NASH population subgroup analysis, there were relatively few studies on natural plant drugs, and silymarin did...
not show therapeutic advantages. After excluding studies on the NASH group, the relative ranking of natural plant drugs increased. For example, resveratrol showed a relative advantage in reducing AST levels and silymarin in reducing TC and LDL-C levels and improving HDL-C levels.

Obeticholic acid, a farnesoid X-receptor agonist, has obvious advantages in improving the pathological process of NAFLD. Farnesoid X-receptor is a bile acid binding transcription factor that plays an important role in inflammation, glucose control, and lipid metabolism.[12] The Food and Drug Administration did not support the accelerated approval of obeticholic acid for NASH treatment of patients because its expected benefits based on histopathological endpoints are still uncertain, and the benefits of treatment have not exceeded the potential adverse effect risks.[13] Its histopathological result was still superior among the novel metabolic agents and natural plant drugs in this analysis. However, obeticholic acid showed serious adverse effects of increasing LDL-C levels and decreasing HDL-C levels, which will increase the risk of cardiovascular disease and all-cause mortality. These effects will ultimately affect the clinical application, at least the long-term application.

In addition to obeticholic acid, the PPARα/δ dual agonist elafibranor was another potential agent. Although it did not show obvious advantages in improving the NAFLD pathological process, it showed clear advantages in reducing ALT, GGT, ALP, TG, and LDL-C levels and increasing HDL-C levels. With PPARs as the target of action, a variety of drugs can be used to reduce lipids, such as fibrates. Mechanistically, it activates PPARs to form heterodimers with the retinoid X receptor and regulate gene transcription to further reduce the content of fatty acids in the liver and improve insulin sensitivity, glucose homeostasis, lipid metabolism, and inflammation relief.[14] In addition, elafibranor had also turned to treatment for primary biliary cholangitis patients with insufficient response to ursodeoxycholic acid and showed good tolerance and therapeutic effects.

Curcumin is a natural plant medicine extracted from the rhizomes of the ginger family. Curcumin had potential advantages in improving the NAFLD pathological process, but the effect was not statistically significant. Although it was believed in many basic and clinical studies that curcumin has the effect of reducing AST and ALT levels and reversing the NAFLD pathological process, well-designed RCTs still lack obvious advantages. Even so, in the ranking results, curcumin was superior to metabolic targeted agents except obeticholic acid. In further research, it is still possible to improve the bioavailability through the development of curcuminoids to produce more obvious therapeutic effects.

Liver biopsy is a key result that directly reflects the improvement of the NAFLD pathological process. Unfortunately, there was no unified assessment definition. The main definitions were improvement in the NAFLD activity score (≥1 or 2) without worsening of fibrosis and improvement in fibrosis with no worsening of NASH (≥1 point increase in hepatocellular ballooning or lobular inflammation). This difference in definition will affect the heterogeneity among studies. The problem also exists in the evaluation of biochemical indicators and lipid indicators. Some studies reported the actual measurement results of indicators at the end of follow-up. However, others reported the change in results from the baseline. Based on the potential source of heterogeneity, we selected the random-effects model in the network analysis. Therefore, in further research, especially for natural plant drug-related research, it was necessary to standardize the reporting of liver biopsy results.

There were still several limitations in this work. First, this analysis was based at the study level instead of at the individual level. Second, this work analyzed only widely researched medicines in the fields of metabolic targeted agents and natural plant drugs and did not analyze all NAFLD therapeutic medicines, such as pioglitazone and vitamin E. Third, we did not subdivide curcumin medicines into curcumin, curcuminoids, and mixed drugs containing pipeline in the analysis. Fourth, the influence of intervention time and detection time point on the results were not considered. Fifth, this study analyzed only the liver biopsy, hepatic biochemical, and lipid metabolism results but not ultrasonographic liver fatty content, physical parameters, noninvasive fibrosis biomarkers, and adverse effect results.

Author contributions
Conceptualization: Jingwen Zhou, Yidi Chen.
Data curation: Jun Yu, Tianci Li.
Formal analysis: Tianci Li.
Resources: Tianci Li.
Software: Jun Yu, Ziyu Lu, Yan Chen.
Validation: Xiaolong Zhang, Fang Ye.
Visualization: Ziyu Lu, Yan Chen.
Writing – original draft: Jingwen Zhou, Yidi Chen, Xiaolong Zhang, Fang Ye.
Writing – review & editing: Xiaolong Zhang, Fang Ye.

References
[1] Karamfilova V, Gateva A, Assyov Y, et al. PNPLA3 I148M polymorphism in patients with nonalcoholic fatty liver disease, obesity and prediabetes. J Gastrointestin Liver Dis 2019;28:433–8.
[2] Zou C, Mantovani A, Oliveri F, et al. Contribution of a genetic risk score to clinical prediction of hepatic steatosis in obese children and adolescents. Dig Liver Dis 2019;51:1586–92.
[3] Friedman SL, Neuschwander-Tetri BA, Rinella M, et al. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908–22.
[4] Zhou F, Zhou J, Wang W, et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. Hepatology 2019;70:1119–33.
[5] Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672–82.
[6] Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65:1857–65.
[7] Atta SL, Softic S, Mounzaki M. Evolving role for pharmacotherapy in NAFLD/NASH. Clin Transl Sci 2020;14:11–9. In press.
[8] Tarantino G, Citro V, Capone D. Nonalcoholic fatty liver disease: a challenge from mechanisms to therapy. J Clin Med 2019;9:15.
[9] Bazar N, Parohan M. The effects of curcumin supplementation on body mass index, body weight, and waist circumference in patients with nonalcoholic fatty liver disease: a systematic review and dose-response meta-analysis of randomized controlled trials. Phytother Res 2020;34:646–74.
[10] Goodarzi R, Sabzian K, Shishhebor F, et al. Does turmeric/curcumin supplementation improve serum alanine aminotransferase and aspartate aminotransferase levels in patients with nonalcoholic fatty liver disease? A systematic review and meta-analysis of randomized controlled trials. Phytother Res 2019;33:561–70.
[11] Jalili M, Mahmodi M, Mosallanezhad Z, et al. The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 2020;48:102283.
[12] Wei Z, Liu N, Tantai X, et al. The effects of curcumin on the metabolic parameters of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Hepatol Int 2019;13:302–13.

[13] Mansour-Ghanaei F, Pourmasoumi M, Hadi A, et al. Efficacy of curcumin/turmeric on liver enzymes in patients with non-alcoholic fatty liver disease: a systematic review of randomized controlled trials. Integr Med Res 2019;8:57–61.

[14] Zhong S, Fan Y, Yan Q, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty liver disease: a meta-analysis (PRISMA) of randomized control trials. Medicine (Baltimore) 2017;96:e9061.

[15] Elgebaly A, Radwan IA, AboElnas MM, et al. Resveratrol supplementation in patients with non-alcoholic fatty liver disease: systematic review and meta-analysis. J Gastrointestin Liver Dis 2017;26:59–67.

[16] Lee DW, Shin IS. Critical quality evaluation of network meta-analyses in dental care. J Dent 2018;57:7–11.

[17] Moradi B, Rahmati-Ahmadabad S, Farzaneh P, et al. Effects of nonlinear resistance training and curcumin supplementation on the liver biochemical markers level and structure in older women with non-alcoholic fatty liver disease. J Bodiy Mov Ther 2020;24:134–60.

[18] Hariri M, Gholami A, Mirhafez SR, et al. A pilot study of the effect of curcumin on epigenetic changes and DNA damage among patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. Complement Ther Med 2020;31:102447.

[19] Saberi-Karimian M, Keshvar M, Ghayour-Mobarhan M, et al. Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Complement Ther Med 2020;49:102322.

[20] Siddiqui MS, Van Natta ML, Connelly MA, et al. Impact of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic fatty liver disease: a randomized phase III STELLAR trial. Hepatology 2020;72:25–33.

[21] Harrison SA, Wong WVS, Okanoue T, et al. A randomized, double-blind, placebo-controlled trial. J Gastrointestin Liver Dis 2019;28:183–9.

[22] Ratziu V, Sanyal A, Harrison SA, et al. Cenicriviroc treatment for adults with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled trial. Adv Pharm Bull 2018;8:307–17.

[23] Farzin L, Pourmasoumi M, Hadi A, et al. Efficacy of curcumin/turmeric on liver enzymes in patients with non-alcoholic fatty liver disease: a meta-analysis of randomized control trials. Medicine (Baltimore) 2017;96:e9061.

[24] Elgebaly A, Radwan IA, AboElnas MM, et al. Resveratrol supplementation in patients with non-alcoholic fatty liver disease: systematic review and meta-analysis. J Gastrointestin Liver Dis 2017;26:59–67.

[25] Lee DW, Shin IS. Critical quality evaluation of network meta-analyses in dental care. J Dent 2018;57:7–11.

[26] Moradi B, Rahmati-Ahmadabad S, Farzaneh P, et al. Effects of nonlinear resistance training and curcumin supplementation on the liver biochemical markers level and structure in older women with non-alcoholic fatty liver disease. J Bodiy Mov Ther 2020;24:134–60.

[27] Hariri M, Gholami A, Mirhafez SR, et al. A pilot study of the effect of curcumin on epigenetic changes and DNA damage among patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. Complement Ther Med 2020;31:102447.

[28] Saberi-Karimian M, Keshvar M, Ghayour-Mobarhan M, et al. Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Complement Ther Med 2020;49:102322.

[29] Siddiqui MS, Van Natta ML, Connelly MA, et al. Impact of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic fatty liver disease: a randomized phase III STELLAR trial. Hepatology 2020;72:25–33.

[30] Harrison SA, Wong WVS, Okanoue T, et al. A randomized, double-blind, placebo-controlled trial. J Gastrointestin Liver Dis 2019;28:183–9.

[31] Mirhafez SR, Farimani AR, Dehhabe M, et al. Effect of phytosomal curcumin on serum metabolomic profile in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Eur J Clin Nutr 2019;73:1224–30.

[32] Panahi Y, Kianpour P, Mohstahami R, et al. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. Drug Res (Stuttg) 2017;67:244–51.

[33] Heeboll S, Kreuzfeld M, Hamilton-Dutoit S, et al. Placebo-controlled, randomised clinical trial: high-dose resveratrol treatment for non-alcoholic fatty liver disease. Scand J Gastroenterol 2016;51:456–64. 

[34] Rahman S, Asgary S, Askari G, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. Phytother Res 2016;30:1540–8.

[35] Ratziu V, Harrison SA, Francus C, et al. Elsparibran, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147–59.

[36] Panahi Y, Kianpour P, Mohstahami R, et al. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial. J Cardiovasc Pharmacol 2016;68:223–9.

[37] Fahlulizadeh F, Addbi P, Hekmatdoost A. The effects of resveratrol supplementation on cardiovascular risk factors in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled study. Br J Nutr 2015;114:796–803.

[38] Memon IA, Akbar M, Bhurgri AN. Effect of silymarin therapy on liver aminotransferase in non-alcoholic fatty liver disease. Med Forum Monthly 2015;26:46–9.

[39] Chen S, Zhao X, Ran L, et al. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Dig Liver Dis 2015;47:226–32.

[40] Solhi H, Ghahtremani R, Kazemifar AM, et al. Silymarin in treatment of non-alcoholic steatohepatitis: a randomized clinical trial. Caspian J Intern Med 2014;5:9–12.

[41] Chachay VS, Macdonald GA, Martin JH, et al. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2014;12:2092–103, e1–6.

[42] Mudaliar S, Henry RR, Sanyal AJ, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574–82, e1.

[43] Hashemi SJ, Hajiani E, Sardabi EH. A placebo-controlled trial of silymarin in patients with nonalcoholic fatty liver disease. Hepatol Int 2009;3:218–9.

[44] Sanyal AJ, Henry RR, Sanyal S, et al. Resveratrol improves liver inflammation, and Nesfatin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. J Gastroenterol Hepatol 2012;27:313–20.

[45] Sanyal AJ, Henry RR, Sanyal S, et al. Resveratrol improves liver inflammation, and Nesfatin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. J Gastroenterol Hepatol 2012;27:313–20.

[46] Sanyal AJ, Henry RR, Sanyal S, et al. Resveratrol improves liver inflammation, and Nesfatin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. J Gastroenterol Hepatol 2012;27:313–20.

[47] Sanyal AJ, Henry RR, Sanyal S, et al. Resveratrol improves liver inflammation, and Nesfatin in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled clinical trial. J Gastroenterol Hepatol 2012;27:313–20.