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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

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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

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JZ and YC both contributed equally to this work.

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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.[1,2] 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.[3] In China, NAFLD has also become a major public health problem, with a prevalence rate of 29.2%.[4]

Nonalcoholic steatohepatitis (NASH) is defined as a serious subtype of NAFLD with severe inflammation and liver cell damage. The adverse liver outcomes of NASH include cirrhosis, liver failure, and hepatocellular carcinoma. Nonliver adverse outcomes include cardiovascular disease and the occurrence of extrahepatic cancers.[5] NASH also increases the risk of liver-related death.[6] However, no drugs have been 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.[7,8]

Metabolic targeted drugs are aimed at either reducing the delivery of the metabolic substrate or facilitating its safe disposal in the NAFLD pathological process.[3] Of these agents, obeticholic acid, elafibranor, 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.[9–13] Silymarin could also significantly reduce transaminase levels in NAFLD patients.[14] However, resveratrol was not effective in relieving the degree of liver fibrosis and significantly reducing liver function parameters.[15]

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 14, 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 elafibranor 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, elafibranor, cenicriviroc, selonsertib, curcumin, silymarin, and resveratrol; and 5, outcomes included at least one improvement in liver pathology, hepatic biochemical indicators (AST, ALT, γ-glutamyltranspeptidase (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)). Exclusion indicators included 1, studies researching NAFLD in children; 2, studies not using placebo as control; 3, studies not researching the abovementioned drugs as the intervention; or 4, studies not reporting any of the above outcomes. Any discrepancy in study selection was resolved by a third author, and a final consensus was reached through discussion.

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.[16] 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

Table 1

Characteristics of included studies.

Author	Sample size	Age of intervention group[#]	Age of control group[#]	Registration number	Interventions	Follow-up[##]
B.M. Kelardeh 2020[17]	22	66.72±3.03	64.36±2.97	IRCT20190103042219N1	Curcumin	12W
M. Hariri 2020[18]	54	40.95±12.24	40.06±13.69	IRCT2015052322381N1	Curcumin	8W
M. Saberi-Karimian 2020[19]	55	NA	NA	IRCT201702209662N12	Curcumin	8W
M.S Siddiqui 2020[20]	196	52±11	50±12	NCT01265498	Obeticholic Acid	96W
S.A. Harrison 2020[21]	1679	59 (51–66)	61 (51–67)	NCT03053050, NCT03053063	Selonsertib	48W
V. Ratziu 2020[22]	289	54.9 (?)	52 (?)	NCT02217475	Cenicriviroc	2Y
A. Anushiravani 2019[23]	60	47±9.1	47±9.1	IRCT201705016312N4.	Silymarin	3M
A. Ghaffari 2019[24]	69	41.5±7.68	40.3±9.26	IRCT201406183664N12	Curcumin	12W
A.F.G. Cicero 2019[25]	80	54±3	53±5	NA	Curcumin	8W
P.J. Pockros 2019[26]	84	58.1±11.07	59.8±9.88	NCT02633956	Obeticholic Acid	16W
S. Chashmnian 2019[27]	45	46.56±2.25	37.75±3.22	IRCT2015052322381N1	Curcumin	8W
S. Saadati 2019[28]	50	46.19±11.5	45.13±10.9	NCT02908152, IRCT20100524004010N24	Curcumin	12W
S.A. Jazayeri-Tehrani 2019[29]	84	41.8±5.6	42.5±6.2	IRCT20160719155536N3	Curcumin	3M
S.R. Mirhafez 2019[30]	44	41.2±14.1	40.7±11.0	IRCT2015052322381N1	Curcumin	8W
S.R. Mirhafez 2019[31]	61	44.8±11.14	40.7±11.83	IRCT2015052322381N1	Curcumin	8W
V.J. Navarro 2019[32]	78	48.3±10.9	49.5±10.9	NCT00680407	Silymarin	50W
Y. Panahi 2019[33]	70	46.63±2.21	47.51±2.45	UMIN000033774	Curcumin	12W
Z.M. Younossi 2019[34]	931	55±11	55±12	NCT02548351, EudraCT:20150–025601–6	Obeticholic Acid	18M
L. Farzin 2018[35]	50	38.71±5.76	39.78±8.09	IRCT2015111233664N16	Resveratrol	12W
S. Asghari 2018[36]	60	40 (22–58)	38.5 (30–48)	NA	Resveratrol	12W
S. Asghari 2018[37]	60	39.8±7.74	39.27±5.51	IRCT2015111233664N16	Resveratrol	12W
R. Navekar 2017[38]	46	42.09±7.23	40.38±9.26	IRCT201406183664N12	Curcumin	12W
W.K. Chan 2017[39]	99	49.6±12.7	50.1±10.2	NCT02006498.	Silymarin	48W
Y. Panahi 2017[40]	87	44.98±12.59	47.21±10.29	IRCT2015122525641N2	Curcumin	8W
S. Heeboll 2016[41]	28	NA	NA	NCT01464801	Resveratrol	6M
S. Rahmani 2016[42]	80	46.37±11.57	48.95±9.78	IRCT2014110511763N18	Curcumin	8W
V. Ratziu 2016[43]	276	52.7±11.0	52.4±11.9	NCT01694849	Elafibranor	3M
Y. Panahi 2016[44]	87	44.98±12.59	47.21±10.29	IRCT2015122525641N2	Curcumin	8W
F. Faghihzadeh 2015[45]	50	44.04±10.10	46.28±9.52	IRCT201202014010N7	Resveratrol	12W
I.A. Memon 2015[46]	64	49.0±9.70	48±8.9	NA	Silymarin	3M
S. Chen 2015[47]	60	45.2±10.0	43.5±11.0	ChiCTR-TRC-12002378	Resveratrol	3M
H. Solhi 2014[48]	64	43.6±8.3	39.36±10.5	IRCT201202159018N1	Silymarin	8W
V.S. Chachay 2014[49]	20	48.8±12.2	47.5±11.2	ACTRN12612001135808	Resveratrol	8W
S. Mudaliar 2013[50]	64	50.5±10.8	53.1±12.1	NCT00501592	Obeticholic Acid	6W
S.J. Hashemi 2009[51]	100	39.28±11.117	39.0±10.70	NA	Silymarin	18M

NA = not available.

[#] Mean±Standard deviation or Median (Minimum-Maximum).

[##] Follow-up period: W = weeks, M = months, Y = years.

performed using STATA 14.0 (Stata Corp, College Station, TX). A P value $\leq .05$ 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,

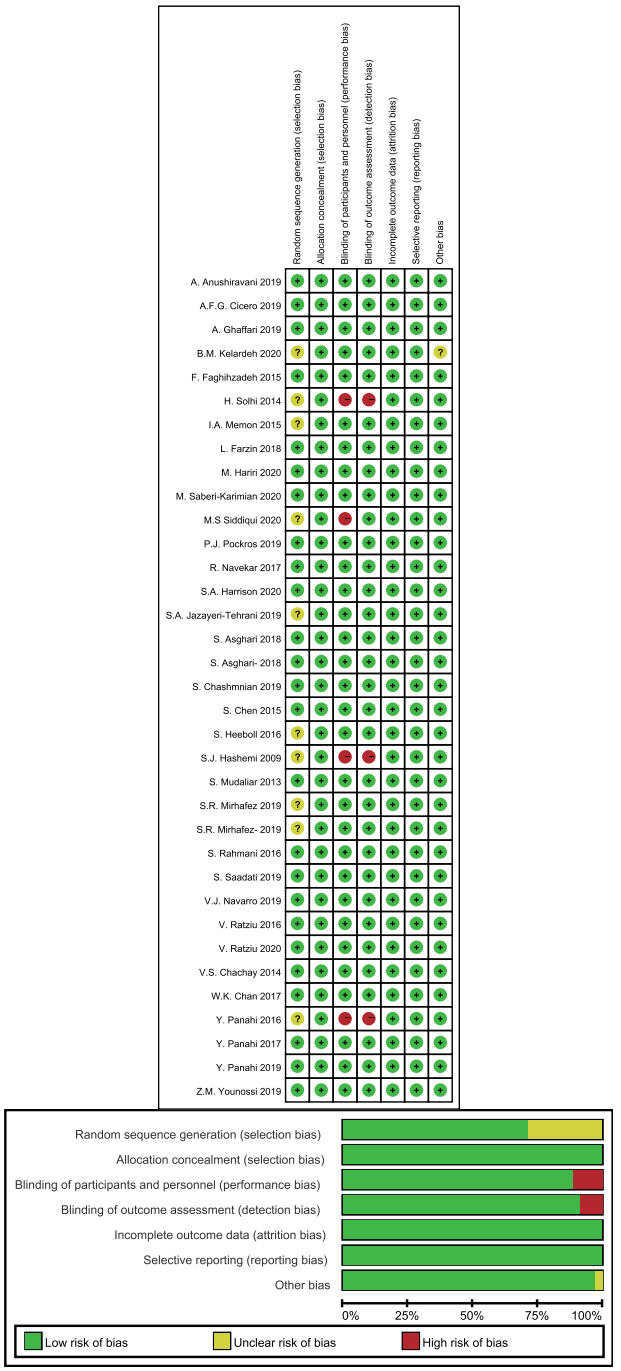

Figure 1. Risk of bias graph for each included study.

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 elafibranor (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 elafibranor (86.3%) had a relative advantage in reducing ALT levels. For AST, the elafibranor 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, elafibranor showed a clear advantage (100%), followed by obeticholic acid (78%) (Table 5). For ALP (Fig. 2, E), elafibranor 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 elafibranor 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 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%) could significantly reduce TG levels compared with placebo (Table 8). For LDL-C, all interventions were included (Fig. 2, H). Elafibranor 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: 2.59, 15.40; SUCRA: 1.6%)(Table 9). All interventions were also included for HDL-C (Fig. 2, I). Elafibranor 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 elafibranor 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 as seen with obeticholic acid. Previous meta-analyses have shown that curcumin and silymarin can improve liver biochemical indicators in patients with NAFLD.[9–14] The reason for the difference between our results and previous meta-analyses may

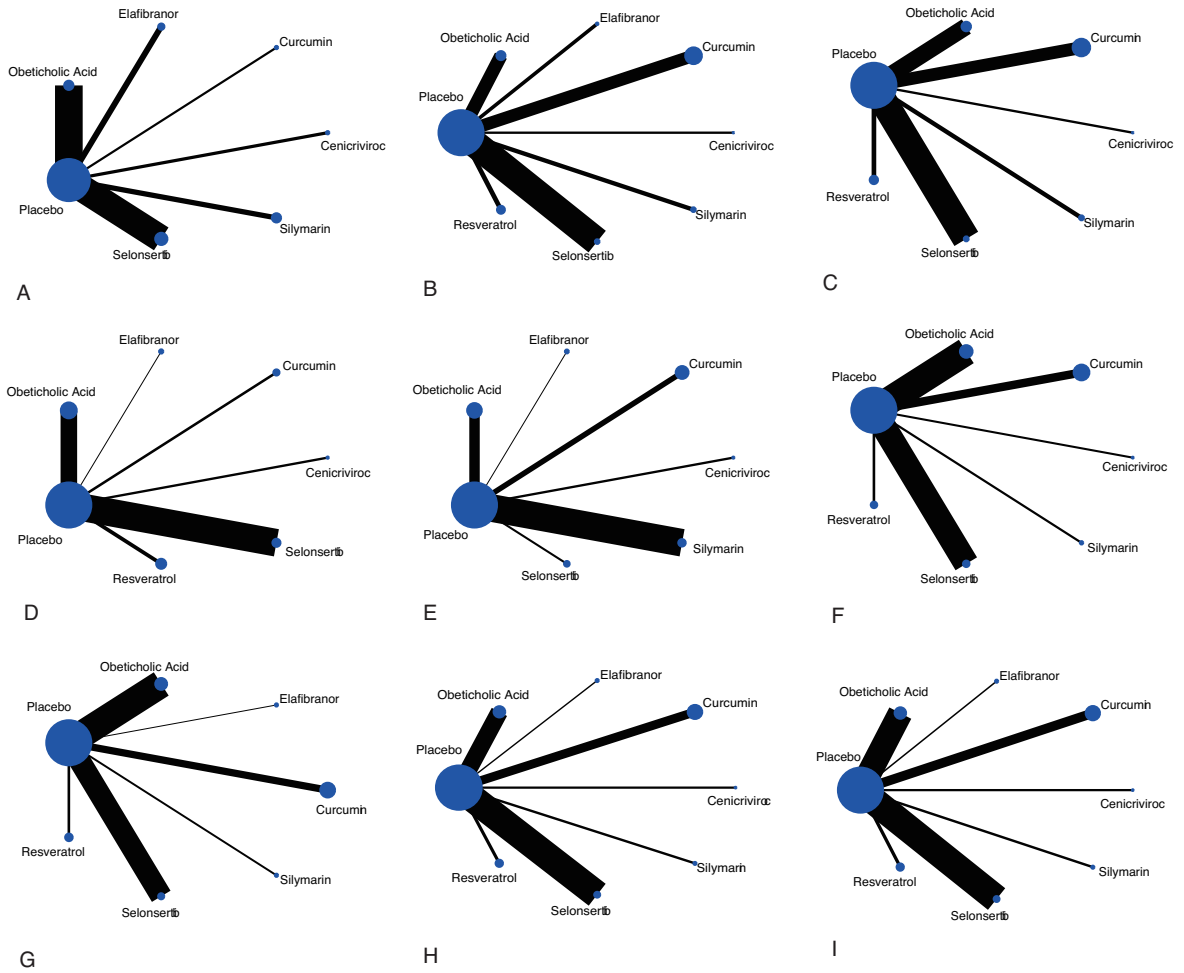

Figure 2. Network plots of outcomes among comparisons between agents and placebo in network meta-analysis. A: Liver pathology improvement; B: ALT; C: AST; D: GGT; E: ALP; F: TC; G: TG; H: LDL-C; I: HDL-C.

Table 2

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

Cenicriviroc						
0.86 (0.24,3.06)	Curcumin					
1.42 (0.52,3.90)	1.65 (0.53,5.19)	Elafibranor				
0.95 (0.40,2.23)	1.1 (0.40,3.02)	0.66 (0.34,1.28)	Obeticholic Acid			
1.99 (0.88,4.47)	2.31 (0.87,6.12)	1.4 (0.77,2.54)	**2.1 (1.60,2.77)**[#]	Placebo		
2.12 (0.90,5.00)	2.47 (0.90,6.79)	1.49 (0.77,2.89)	**2.25 (1.52,3.33)**	1.07 (0.81,1.41)	Selonsertib	
1.5 (0.53,4.19)	1.74 (0.54,5.56)	1.05 (0.44,2.51)	1.58 (0.79,3.16)	0.75 (0.40,1.42)	0.7 (0.35,1.41)	Silymarin

[#] Bold font represents statistical difference.

Table 3

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

Cenicriviroc							
1.89 (0.22,16.50)	Curcumin						
6.94 (0.53,90.74)	3.68 (0.75,18.01)	Elafibranor					
9.95 (1.07,92.65)[#]	**5.28 (2.06,13.55)**	1.43 (0.27,7.64)	Obeticholic Acid				
1.31 (0.16,10.69)	0.7 (0.40,1.21)	**0.19 (0.04,0.84)**	0.13 (0.06,0.28)	Placebo			
1.45 (0.15,13.78)	0.77 (0.29,2.07)	0.21 (0.04,1.14)	**0.15 (0.05,0.45)**	1.11 (0.49,2.51)	Resveratrol		
1.18 (0.11,12.23)	0.62 (0.19,2.03)	0.17 (0.03,1.04)	**0.12 (0.03,0.43)**	0.9 (0.32,2.54)	0.81 (0.22,3.05)	Selonsertib	
2.03 (0.19,21.33)	1.08 (0.32,3.58)	0.29 (0.05,1.83)	**0.2 (0.06,0.76)**	1.55 (0.53,4.48)	1.4 (0.37,5.37)	1.73 (0.39,7.64)	Silymarin

[#] 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						
1.79 (0.27,11.93)	Curcumin					
4.07 (0.58,28.62)	**2.28 (1.00,5.18)**[#]	Obeticholic Acid				
1.4 (0.22,8.77)	0.78 (0.48,1.28)	**0.34 (0.18,0.67)**	Placebo			
2.14 (0.30,15.40)	1.2 (0.50,2.87)	0.53 (0.20,1.41)	1.53 (0.74,3.16)	Resveratrol		
1.04 (0.13,8.03)	0.58 (0.21,1.63)	**0.25 (0.08,0.78)**	0.74 (0.30,1.84)	0.48 (0.15,1.55)	Selonsertib	
1.8 (0.23,14.10)	1.01 (0.35,2.89)	0.44 (0.14,1.39)	1.29 (0.51,3.27)	0.84 (0.26,2.74)	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						
1.36 (0.06,29.59)	Curcumin					
286.8 (10.70,7689.65)[#]	**211.62 (17.67,2534.83)**	Elafibranor				
4.7 (0.28,79.26)	3.46 (0.56,21.52)	**0.02 (0.00,0.14)**	Obeticholic Acid			
1.08 (0.08,15.48)	0.8 (0.17,3.79)	**0 (0.00,0.03)**	**0.23 (0.09,0.60)**	Placebo		
1.34 (0.07,24.89)	0.99 (0.14,7.11)	**0 (0.00,0.05)**	0.28 (0.06,1.33)	1.24 (0.37,4.15)	Resveratrol	
1.14 (0.06,22.24)	0.84 (0.11,6.49)	**0 (0.00,0.04)**	0.24 (0.05,1.24)	1.05 (0.28,3.95)	0.85 (0.14,5.12)	Selonsertib

[#] 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						
1 (0.02,49.29)	Curcumin					
1100000 (11437.28,1.1e+08)[#]	**1100000 (49352.52,2.6e+07)**	Elafibranor				
0.05 (0.00,2.18)	**0.05 (0.01,0.31)**	**0 (0.00,0.00)**	Obeticholic Acid			
0.75 (0.02,28.54)	0.75 (0.19,3.01)	**0 (0.00,0.00)**	**16.46 (4.46,60.78)**	Placebo		
0.51 (0.01,34.44)	0.51 (0.04,6.44)	**0 (0.00,0.00)**	11.18 (0.92,135.46)	0.68 (0.08,5.69)	Resveratrol	
0.79 (0.01,45.93)	0.79 (0.08,7.73)	**0 (0.00,0.00)**	**17.26 (1.84,161.76)**	1.05 (0.17,6.45)	1.54 (0.09,25.29)	Selonsertib

[#] 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						
1.15 (0.21,6.30)	Curcumin					
0.31 (0.05,1.71)	**0.27 (0.12,0.59)**[#]	Obeticholic Acid				
0.79 (0.16,4.01)	0.69 (0.41,1.17)	**2.6 (1.45,4.69)**	Placebo			
0.73 (0.12,4.58)	0.64 (0.23,1.74)	2.41 (0.85,6.79)	0.92 (0.39,2.17)	Resveratrol		
1.05 (0.17,6.38)	0.91 (0.35,2.38)	**3.44 (1.28,9.27)**	1.32 (0.59,2.93)	1.43 (0.44,4.60)	Selonsertib	
0.88 (0.12,6.44)	0.76 (0.21,2.74)	2.87 (0.78,10.59)	1.1 (0.34,3.54)	1.19 (0.28,5.06)	0.83 (0.20,3.43)	Silymarin

[#] 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						
114.43 (32.56,402.13)[#]	Elafibranor					
1.47 (0.70,3.10)	**0.01 (0.00,0.05)**	Obeticholic Acid				
0.71 (0.43,1.16)	**0.01 (0.00,0.02)**	**0.48 (0.28,0.84)**	Placebo			
0.66 (0.27,1.61)	**0.01 (0.00,0.02)**	0.45 (0.18,1.13)	0.94 (0.45,1.95)	Resveratrol		
0.87 (0.35,2.14)	**0.01 (0.00,0.03)**	0.59 (0.23,1.51)	1.23 (0.58,2.61)	1.31 (0.46,3.72)	Selonsertib	
0.69 (0.21,2.33)	**0.01 (0.00,0.03)**	0.47 (0.14,1.62)	0.98 (0.33,2.96)	1.05 (0.28,3.92)	0.8 (0.21,3.03)	Silymarin

[#] 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).

Cenicriviroc							
0.99 (0.07,13.45)	Curcumin						
66.56 (3.11,1425.03)[#]	**67.35 (9.48,478.55)**	Elafibranor					
0.13 (0.01,1.86)	**0.13 (0.04,0.44)**	**0 (0.00,0.01)**	Obeticholic Acid				
0.84 (0.07,10.09)	0.85 (0.38,1.89)	**0.01 (0.00,0.08)**	**6.32 (2.59,15.40)**	Placebo			
0.63 (0.04,9.78)	0.64 (0.16,2.59)	**0.01 (0.00,0.08)**	**4.77 (1.12,20.31)**	0.75 (0.24,2.37)	Resveratrol		
1.03 (0.06,16.59)	1.05 (0.24,4.55)	**0.02 (0.00,0.14)**	**7.77 (1.69,35.66)**	1.23 (0.36,4.23)	1.63 (0.30,8.78)	Selonsertib	
0.97 (0.05,20.60)	0.98 (0.14,6.88)	**0.01 (0.00,0.18)**	**7.31 (1.01,53.20)**	1.16 (0.20,6.82)	1.53 (0.19,12.66)	0.94 (0.11,8.17)	Silymarin

[#] 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).

Cenicriviroc							
0.77 (0.08,7.09)	Curcumin						
0.01 (0.00,0.19)[#]	**0.02 (0.00,0.10)**	Elafibranor					
3.42 (0.36,32.14)	**4.42 (1.60,12.23)**	**245.46 (44.69,1348.15)**	Obeticholic Acid				
0.86 (0.10,7.09)	1.11 (0.56,2.20)	**61.82 (13.45,284.11)**	**0.25 (0.12,0.54)**	Placebo			
0.73 (0.07,7.49)	0.95 (0.29,3.12)	**52.64 (8.60,322.34)**	**0.21 (0.06,0.74)**	0.85 (0.32,2.27)	Resveratrol		
0.69 (0.07,7.29)	0.9 (0.26,3.12)	**49.77 (7.83,316.28)**	**0.2 (0.06,0.74)**	0.81 (0.28,2.29)	0.95 (0.23,3.96)	Selonsertib	
0.97 (0.07,12.95)	1.25 (0.24,6.55)	**69.56 (8.14,594.14)**	0.28 (0.05,1.53)	1.13 (0.25,5.08)	1.32 (0.22,7.98)	1.4 (0.22,8.76)	Silymarin

[#] Bold font represents statistical difference.

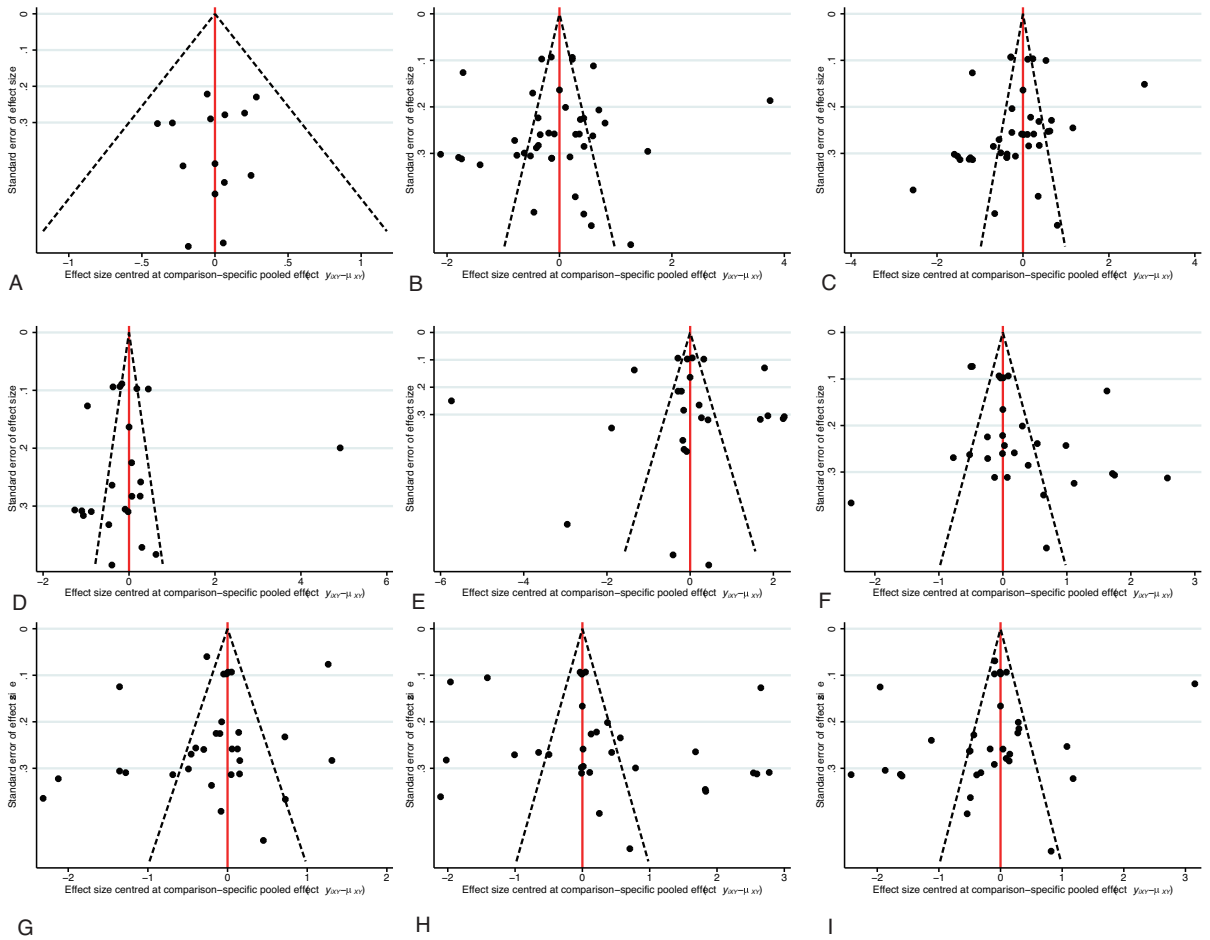

Figure 3. Comparison-adjusted funnel plots of outcomes in the network meta-analysis. A: Liver pathology improvement; B: ALT; C: AST; D: GGT; E: ALP; F: TC; G: TG; H: LDL-C; I: HDL-C.

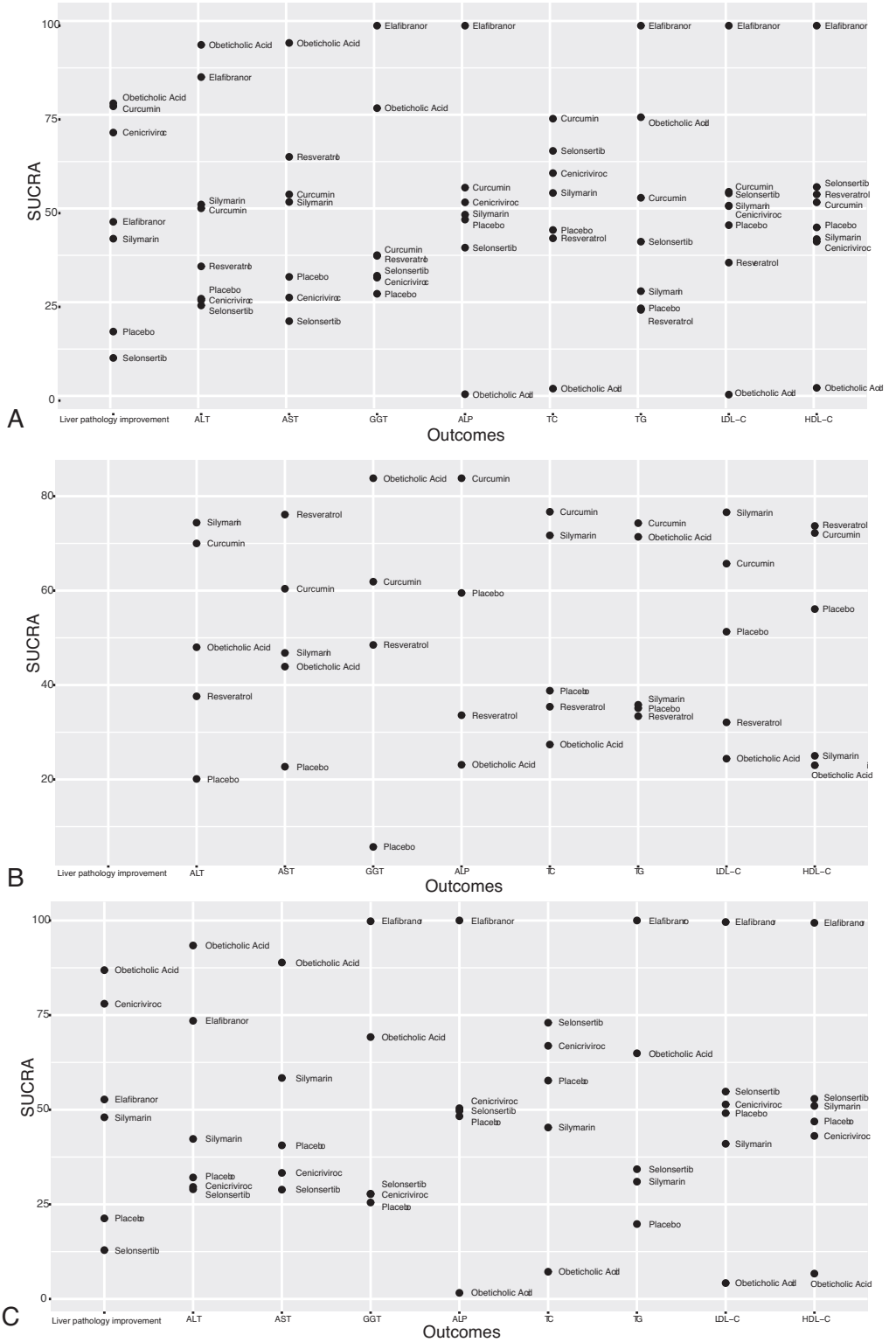

Figure 4. Subgroup analysis of outcomes by network meta-analysis. A: Overall NAFLD population; B: NAFLD population after excluding NASH patient studies; C: NASH population.

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.[52] 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.[53] 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.[54] 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 piperine 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.

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