


# Treatment of primary biliary cirrhosis with ursodeoxycholic acid combined with traditional Chinese medicine

## A protocol for systematic review and meta analysis

Xing Chen, PhD<sup>a,b</sup> , Xiao Ma, PhD<sup>b</sup>, Ruilin Wang, MD<sup>c</sup>, Lifu Wang, MD<sup>c</sup>, Jianyu Li, MD<sup>c</sup>, Honghong Liu, MD<sup>c</sup>, Tingting He, MD<sup>c</sup>, Shizhang Wei, PhD<sup>a</sup>, Haotian Li, PhD<sup>a</sup>, Min Wang, PhD<sup>a</sup>, Yanling Zhao, PhD<sup>a,\*</sup>

### Abstract

**Objective:** Ursodeoxycholic acid is the priority drug of primary biliary cirrhosis (PBC) and is usually combined with traditional Chinese medicine. This study aimed to systematically evaluate the benefits of integrated Chinese and western interventions for PBC.

**Methods:** Searched the randomized controlled trials in PubMed, Web of Science, CNKI, CBM, Wanfang, VIP databases. The Cochrane risk of bias tool was used for methodological quality assessment and all data analysis was performed using Revman5.3 and Stata14.2 software.

**Result:** 30 randomized controlled trials involving 10 interventions with a total of 1948 participants were included. Identified the direct and indirect evidence of trials, and used network meta analyses ranked the benefits of different interventions based on pairwise meta analysis. The primary outcome was clinical efficacy rate. Secondary outcome was liver function, including alkaline phosphatase and total bilirubin.

**Conclusion:** The conclusion of this systematic review provide credible evidence - based for the relative advantages of integrated Chinese and western interventions for PBC.

**Abbreviations:** ALHX = Anluo Huaxian Pill, ALP = alkaline phosphatase, ALT = alanine transaminase, BJRG = compound Biejia Ruangan Tablet, CER = clinical efficacy rate, CI = confidence interval, FZHY = Fuzheng Huayu Capsule, GSHX = Guishao Huoxue Decoction, HZJD = Huazhuo Jiedu Tiaogan Decoction, OCA = obeholic acid, PBC = primary biliary cirrhosis, QYHX = Qingying Huoxue Decoction, RCTs = randomized controlled trials, SGLD = Shugan Lidan Huoxue Huayu Decoction, SMD = The standardized mean difference, SUCRA = surface under the cumulative ranking, TBil = total bilirubin, TCM = traditional Chinese medicine, UDCA = ursodeoxycholic acid, YGF = Yugan Fang.

**Keywords:** Meta-analysis, Primary biliary cirrhosis, Systematic review, Traditional Chinese medicine

## 1. Introduction

Primary Biliary Cirrhosis (PBC), also known as primary biliary cholangitis, is a rare chronic cholestatic autoimmune liver disease. The disease is characterized by progressive idiopathic

stricturing of the biliary system, typically leading to cirrhosis, end-stage liver disease, and colonic or hepatobiliary malignancy.<sup>[1]</sup> PBC affects predominantly middle-aged women, the age of onset is 30 to 65 years old, 30% to 50% of asymptomatic patients are usually found in routine examinations.<sup>[2]</sup> In the past few decades,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.

<sup>a</sup> Department of Pharmacy, Chinese PLA General Hospital, Beijing, <sup>b</sup> College of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, <sup>c</sup> Integrative Medical Center, Chinese PLA General Hospital, Beijing, China.

\* Correspondence: Yanling Zhao, Department of Pharmacy, Chinese PLA General Hospital, Beijing, China (e-mail: zhaoyl2855@126.com).

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the morbidity and prevalence of PBC varied widely and have been rising around the world.<sup>[1]</sup> Liver transplantation is the preferred treatment for patients with end-stage PBC which yields excellent outcomes in advanced cases. Patients should consider liver transplantation to achieve long-term survival before the condition deteriorates. The 1 year and 5 years survival rate after liver transplantation are approximately 90% and 80%, however, the recurrence rate is as high as 10.9% to 42.3%, which poses a significant challenge for the treatment of PBC.<sup>[3]</sup>

PBC patients have received multiple medications. Ursodeoxycholic acid (UDCA) is the only therapy approved by the Food and Drug Administration for PBC. It is also the primary recommended drug for PBC by both the European Association for the Study of Liver Diseases and the American Association for the Study of Liver Diseases.<sup>[4]</sup> A number of clinical randomized controlled trials (RCTs) supported that UDCA can delay histological progression of liver transplantation, and the prognosis is significantly better than untreated patients. However, some patients respond poorly or even no respond.<sup>[5,6]</sup> In this regard, although obexcholic acid (OCA) was approved in 2016 as an alternative treatment option for PBC in UDCA refractory patients, the efficacy of OCA is disappointing, and OCA data on disease endpoints (such as death or liver transplantation) have been not reported.<sup>[7]</sup> Over the years, a number of other drugs have been tried for the treatment of PBC, including budesonide,<sup>[8]</sup> corticosteroids,<sup>[9]</sup> and fibrates,<sup>[10]</sup> and immunomodulatory drugs, such as methotrexate,<sup>[11]</sup> colchicine,<sup>[12]</sup> prednisolone,<sup>[13]</sup> azathioprine,<sup>[14]</sup> D-penicillamine<sup>[15]</sup> or cyclosporine.<sup>[16]</sup> However, these drugs have not been widely accepted by patients associated with a number of adverse events.

Currently, traditional Chinese medicine (TCM) has an extraordinary effect in improving symptoms, biochemical indicators and response rate with PBC.<sup>[17,18]</sup> Integrated of Chinese and western medicine is more recognized for the treatment of PBC and hepatic fibrosis.<sup>[49–52]</sup> However, all of these are direct comparisons between paired therapies, and there is no direct or indirect systematic comparison study between multiple interventions. Moreover, the diversity of TCM treatment determines the different therapeutic advantages when combined with western medicine, which causes great confusion to the choice of clinical operators. Therefore, in order to solve the above problems, this study analyzed the overall benefits of integrated Chinese and western medicine in the treatment of PBC, and then used network meta-analysis to obtain the comparative advantages between different integrated therapies, paving the way for future solutions for PBC.

## 2. Methods

### 2.1. Search strategy

Two investigators independently searched PubMed, Web of Science, CNKI, CBM, Wanfang, VIP databases prior to June 2019 for RCTs with the terms: “traditional Chinese medicine,” “ursodeoxycholic acid,” “primary biliary cirrhosis” or “primary biliary cholangitis,” without any limitations on language or publication status. Eligible trials must compare the drug classes listed in the search strategy.

### 2.2. Inclusion and exclusion criteria

**2.2.1. Inclusion criteria.** Studies were included in the analysis if they met the following criteria:

- (1) Studies designed as clinical RCTs.
- (2) Populations have a clear diagnosis basis, specifically refer to the PBC diagnostic criteria established by the American College of Liver Diseases<sup>[19]</sup>

(I. No evidence of biliary obstruction confirmed by ultrasonography or other related tests; II. Alkaline phosphatase (ALP) and / or Glutamyl transpeptidase higher than normal; III. Serum anti-mitochondrial antibody, anti-mitochondrial antibody-M2 positive at a titer of 1:40) or with strict medical diagnosis conclusion. 3. Patients receiving therapeutic interventions including TCM combined with UDCA and/or UDCA monotherapy, and drug was only administered within the therapeutic dose range. 4. Outcome indicators were clinical efficacy rate (CER) and / or liver function [ALP and Total bilirubin (TBil)].

**2.2.2. Exclusion criteria.** Studies were excluded if they met the following criteria:

- (1) Non-randomized design or comparison of other interventions.
- (2) The interventions reported less than 2 studies.
- (3) RCTs recruitment treatment time was less than 4 weeks or total sample size was less than 10 participants.

### 2.3. Data extraction

**2.3.1. Extraction strategy.** Two authors independently extracted the data. Discrepancies about the extraction of data were resolved by other investigators. A pre-designed spreadsheet was used to extract data from each study. Baseline characteristics including trial background (research topic, author, publication time and trial scale); interventions (dose, duration of treatment); patient characteristics (age, gender); outcome indicators and key elements of bias risk.

**2.3.2. Primary outcomes.** The primary outcome was CER, with specific reference to the relevant criteria for the “Basic and clinical aspects of autoimmune liver disease”<sup>[21]</sup>.

Effective: including complete or partial response, complete response referred to significant improvement in clinical symptoms, liver function was improved by 50% at 4 weeks of administration and the Alanine transaminase, ALP, and glutamyl transpeptidase levels continued to fall within 2 times of the upper limit of normal at 24 weeks.

Remission: partial improvement of clinical symptoms and biochemical indicators.

Invalid: clinical symptoms and serum liver biochemical indicators had not ameliorated or even worsened.

**2.3.3. Secondary outcome.** Secondary outcome was liver function, including ALP and TBil. Selected the end of treatment as the final data source for subsequent analysis uniformly.

### 2.4. Quality assessment

Two investigators independently performed a methodological quality and risk of bias assessment. Any disagreement arising between the investigators were resolved by arbitration with third author. The Cochrane collaborations tool assessed the risk of bias in following items<sup>[20]</sup>:

- (1) randomly generated allocation sequence;
- (2) allocation concealment;
- (3) blinding of participants and investigators;

- (4) incomplete research data;
- (5) selective outcome reporting;
- (6) other sources of bias.

Trials were regarded as high risk of bias if they met 3 items above with high or unclear risk for bias. Otherwise, they were considered as trials with low risk of bias.

### 2.5. Statistical analysis

Pairwise meta and network meta - analyses were conducted with the random - effect models by using Revman5.3 and Stata (version 14.2) respectively. Statistical heterogeneity in each pairwise comparison was assessed with the  $I^2$  statistic and  $P$  value,  $P$  value less than .1 and  $I^2$  more than 50% indicated substantial statistical heterogeneity. The direct and indirect data of interventions were compared based on the transferability of network meta - analysis. The odds ratio and 95% confidence interval (CI) were described the primary outcome - CER, the standardized mean difference (SMD) and 95% CI were summarized secondary outcomes - liver function (ALP and TBil).

Interventions were ranked using the surface under the cumulative ranking (SUCRA) probabilities of each intervention relative to the percentage of efficacy or safety to the hypothetical intervention, large SUCRA scores indicated a more effective or safer. The cluster ranking plot compared the comprehensive ranking of secondary outcomes. In addition, funnel plot and Egger test could be used to detect publication bias if more than 10 studies were available.

### 2.6. Ethics and dissemination

The research was a systematic review, and the data used comes from relevant data in published academic papers, no ethical approval was therefore required.

## 3. Results

### 3.1. Study selection

According to the search strategy, RCTs of TCM combined with UDCA and/or UDCA monotherapy for PBC were searched. Reviewed the title and abstract, the repetitive literature, animal experiments, and literature reviews were excluded. Downloaded the full text further and removed literatures that not met the inclusion criteria. 30 RCTs involving 10 relevant interventions were ultimately identified, including Anluo Huaxian (ALHX) Pill, compound Biejia Ruangan (BJRG) Tablet, Fuzheng Huayu (FZHY) Capsule, Guishao Huoxue (GSHX) Decoction, Huazhuo Jiedu (HZJD) Tiaogan Decoction, Qingying Huoxue (QYHX) Decoction, Shugan Lidan (SGLD) Huoxue Huayu Decoction, Tongdan Decoction and Yugan Fang (YGF) combined with UDCA and UDCA monotherapy. The literature screening process and results were shown in Fig. 1.

### 3.2. Study characteristics

Table 1 summarised the baseline characteristics and methodological quality. The 30 trials enrolled 1948 participants, of which 976 were randomly assigned to the combination group and 972 were assigned to the monotherapy group. The inclusion criteria for the 27 studies were the American College of Hepatology PBC

criteria and 3 were medical diagnoses. Only 23 RCTs reported full clinical and demographic characteristics (Table 1), some studies were not stated the gender ratio and patient age. In the reported data, the mean age of patients ranged from 31 to 63, the median duration of the treatment was 24 weeks and the percentage of woman ranged from 50% to 97%. The interventions were divided into two categories: TCM combined with UDCA and UDCA monotherapy, different doses of administered existed in different studies, 13 - 15 mg/kg/d was the most common dose of UDCA, the main prescription of the TCM were listed in Supplement Content (Table S1, <http://links.lww.com/MD/F159>).

### 3.3. Quality assessment

The risk of bias assessment of RCTs based on the Cochrane Collaboration tool. Only 4 RCTs (13%) with wrong random methods (treatment regimen or admission sequence) were judged to have a high risk of bias. 26 RCTs (87%) reported random assignments, 6 of them were accomplished by method of random number table, others were not explicitly explain the specific randomization. In addition, only 1 RCT showed double - blind in patients and therapists and 2 RCTs reported concealment of allocation (sequential coding, sealed, opaque envelopes). The risk of bias from other sources was not recorded if not indicated in studies (Fig. 2).

### 3.4. Results of pairwise meta analysis

**3.4.1. CER.** 24 RCTs were performed pairwise meta analysis to obtain the overall benefits of integrated Chinese and western medicine treatment of PBC on the primary outcome - CER. 1598 participants were randomly assigned to combination group and monotherapy group averagely. Heterogeneity test showed no evidence of statistical heterogeneity ( $P=1.00$ ,  $I^2=0\%$ ) that the fix - effect model could be carried out to meta-analysis. The results showed that the CER of combination group was significantly better than the monotherapy group (odds ratio = 4.26, 95% CI [3.07, 5.91]  $P<.001$ ) (Fig. 3).

**3.4.2. Liver function.** 18 RCTs were performed Pairwise meta analysis to obtain the overall benefits of integrated Chinese and Western medicine treatment of PBC on the secondary outcome - liver function. 18 studies reported the ALP, 539 participants were randomly assigned to combination group and 536 to monotherapy group.  $I^2$  value showed that there was significant heterogeneity among those studies ( $P<.001$ ,  $I^2=63\%$ ), and the random - effect model was used for meta-analysis. The results showed that combination group had a significant advantage in improving ALP compared with monotherapy group ( $SMD=-0.77$ , 95% CI [-0.97, -0.56]  $P<.001$ ) (Fig. 4). Heterogeneous source was found in one study<sup>[33]</sup> which had a longer treatment period (48 weeks) in the same intervention, the heterogeneity could significantly reduce after excluding the study ( $P=0.02$ ,  $I^2=46\%$ ). 22 studies reported the TBil, 718 participants were randomly assigned to combination group and 714 to monotherapy group. Heterogeneity test suggested to execute random - effect model for meta - analysis ( $P<.001$ ,  $I^2=76\%$ ). The results showed that combination group could better improve the TBil in patients ( $SMD=-0.86$ , 95% CI [-1.09, -0.63]  $P<.001$ ) (Fig. 5). One trial<sup>[36]</sup> included patients with a wide range of disease (3 months to 7 years), and another trial<sup>[29]</sup> with unclear randomization methods were the main source of heterogeneity,

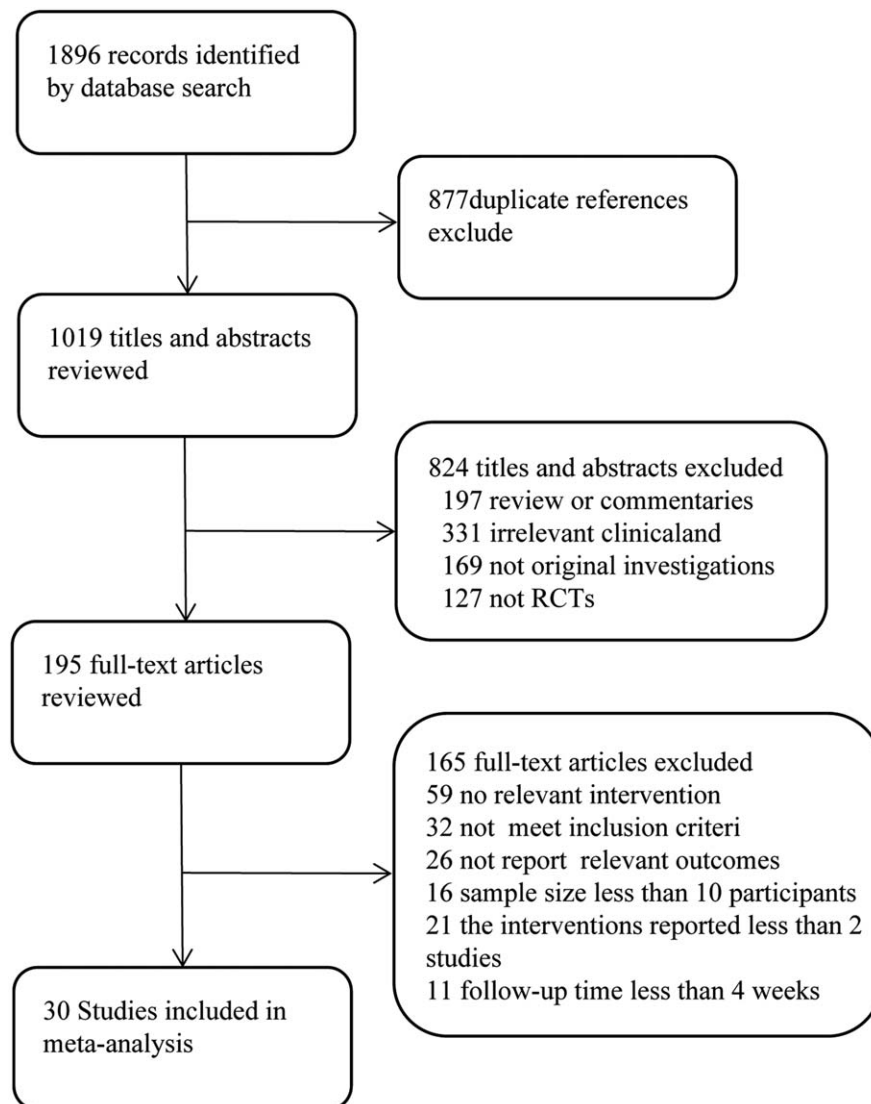


Figure 1. Study selection process.

excluding the two tests, the heterogeneity was reduced to an acceptable range ( $P=0.008$ ,  $I^2=50\%$ ). The above data showed that TCM combined with UDCA was more beneficial to liver function.

### 3.5. Results of network meta analyses

Fig. 6 showed the evidence network for the primary and secondary outcome. Each node concerned different interventions with specific daily dose of administration, larger diameter represented a larger sample size. The inter - point connection indicated a direct comparison between the two interventions, and the thicker the line indicated the more the number of studies, lack of a line indicated no direct comparison between interventions and a network analysis could be used for indirect comparison. Fig. 6 showed that each intervention in the 30 trials was directly compared to UDCA monotherapy, 24 studies (80%) involving 10 interventions had direct evidence for primary outcomes - CER; a total of 9 interventions analyzed secondary

outcome - liver function, of which 18 studies (60%) reported ALP and 22 studies (73%) reported TBil. The closed loop was not formed, so the inspection of the consistency model did not need to be performed.

**3.5.1. CER.** In order to make the data closer to real and objective conditions, the random - effect model was used for subsequent network meta-analysis. The forest map showed that ALHX (Coef. = 1.61, 95% Conf. [0.50, 2.71]  $P<.001$ ), BJRG (Coef. = 1.51, 95% Conf. [0.05, 2.98]  $P=0.04$ ), GSHX (Coef. = 2.05, 95% Conf. [0.95, 3.15]  $P<.001$ ), QYHX (Coef. = 1.60, 95% Conf. [0.56, 2.63]  $P=0.003$ ), SGLD (Coef. = 1.49, 95% Conf. [0.58, 2.39]  $P=0.001$ ), YGF (Coef. = 1.43, 95% Conf. [0.84, 2.02]  $P<.001$ ) combined with UDCA could significantly improve CER (Fig. 7 and Supplement Digital Content (Fig.S1, <http://links.lww.com/MD/F160>)). SUCRA probabilities was performed to rank the interventions for CER and presented in Fig. 8, the top three interventions were GSHX + UDCA (82.2%), QYHX + UDCA (64.8%), ALHX + UDCA (64.4%).



**Table 1**  
**Baseline characteristics and assessment of bias risk of included trials.**

Study (Year)	Diagnostic criteria	Treatments (dose range)	Mean age (years)	Number of patients/ proportion of women (%)	Follow-up (weeks)	Random methods	Outcome indicator
Wang W (2015) <sup>[22]</sup>	AASLD	T:ALHX+UDCA (18g/d+15mg/kg/d) C:UDCA(15mg/kg/d)	T:47.5 C:48.2	64/82%	12	Unclear	①②
Li ZQ (2013) <sup>[23]</sup>	AASLD	T:ALHX+UDCA(12g/d+15mg/kg/d) C:UDCA(15mg/kg/d)	T:45.6 C:42.2	60/91%	24	Unclear	①③
Qiu HQ (2015) <sup>[24]</sup>	AASLD	T:ALHX+UDCA(12g/d+8~10mg/kg/d) C:UDCA(8~10mg/kg/d)	T:31.6 C:31.2	84/67%	24	Unclear	①③
Pang YM (2017) <sup>[25]</sup>	AASLD	T:BJRG+UDCA(6g/d+30~45mg/kg/d) C:UDCA(30~45mg/kg/d)	T:52.1 C:52.3	50/62%	96	Unclear	①②③
Huang LY (2015) <sup>[26]</sup>	AASLD	T:BJRG+UDCA(6g/d+10~15mg/kg/d) C:UDCA(10~15mg/kg/d)	T:57.97 C:57.59	56/—	48	DB	②③
Wang DT (2015) <sup>[27]</sup>	AASLD	T:BJRG+UDCA(6g/d+30~45mg/kg/d) C:UDCA(30~45mg/kg/d)	T:53.7 C:52.1	78/82%	48	Unclear	②③
Zhang SS (2015) <sup>[28]</sup>	AASLD	T:BJRG+UDCA(6g/d+15mg/kg/d) C:UDCA(15mg/kg/d)	T:51.9 C:53.4	64/93%	48	CA	①②③
Gao F (2015) <sup>[29]</sup>	AASLD	T:FZHY+UDCA(4.5g/d+15mg/kg/d) C:UDCA(15mg/kg/d)	T:43.6 C:45.2	61/93%	24	Unclear	①③
Zhang JY (2014) <sup>[30]</sup>	AASLD	T:FZHY+UDCA(4.5g/d+10mg/kg/d) C:UDCA(10mg/kg/d)	T:56.52 C:58.04	60/90%	24	Unclear	②③
Ying HJ (2017) <sup>[31]</sup>	AASLD	T:FZHY+UDCA(4.5g/d+750mg/d) C:UDCA(750mg/d)	—	130/—	24	RNT	①③
Xie XR (2012) <sup>[32]</sup>	AASLD	T:FZHY+UDCA(4.5g/d+750mg/d) C:UDCA(750mg/d)	—	30/—	24	Unclear	②③
Wu Y (2012) <sup>[33]</sup>	AASLD	T:FZHY+UDCA(4.5g/d+13~15mg/kg/d) C:UDCA(13~15mg/kg/d)	T:43.7 C:45.0	80/88%	48	RNT	①②③
Han HM (2012) <sup>[34]</sup>	AASLD	T:GSHX+UDCA(1dose/d+500mg/d) C:UDCA(500mg/d)	T:56.52 C:58.04	50/88%	24	Unclear	①②③
Xu Y (2014) <sup>[35]</sup>	AASLD	T:GSHX+UDCA(1dose/d+500mg/d) C:UDCA(500mg/d)	—	44/—	24	Unclear	①②
Zhong R (2012) <sup>[36]</sup>	AASLD	T:HZJD+UDCA(1dose/d+15mg/kg/d) C:UDCA(15mg/kg/d)	—	60/88%	8	Unclear	①②③
Su CZ (2011) <sup>[37]</sup>	AASLD	T:HZJD+UDCA(1dose/d+13~15mg/kg/d) C:UDCA(13~15mg/kg/d)	T:52.3 C:51.2	60/96%	24	Unclear	②③
Gan X (2016) <sup>[38]</sup>	AASLD	T:QYHX+UDCA(1dose/d+13~15mg/kg/d) C:UDCA(13~15mg/kg/d)	T:48.97 C:49.25	98/85%	24	RNT	①
Liu YH (2018) <sup>[39]</sup>	AASLD	T:QYHX+UDCA(1dose+15mg/kg/d) C:UDCA(15mg/kg/d)	T:47.80 C:47.52	70/77%	24	Unclear	①
Chen YF (2013) <sup>[40]</sup>	AASLD	T:SGLD+UDCA(1dose+15mg/kg/d) C:UDCA(15mg/kg/d)	T:53.20 C:56.04	50/88%	24	RNT	①②③
Xu H (2015) <sup>[41]</sup>	AASLD	T:SGLD+UDCA(1dose/d+750mg/d) C:UDCA(750mg/d)	T:42.5 C:44.5	70/87%	24	Unclear	①③
Sheng HZ (2016) <sup>[42]</sup>	MD	T:SGLD+UDCA(1dose/d+750mg/d) C:UDCA(750mg/d)	T:54.93 C:53.44	70/50%	—	Unclear	①
Tang HH (2008) <sup>[43]</sup>	AASLD	T:TDD+UDCA(1dose/d+15~20mg/kg/d) C:UDCA(15~20mg/kg/d)	T:51.20 C:53.20	60/90%	24	RNT+CA	①②③
Xia YX (2012) <sup>[44]</sup>	MD	T:TDD+UDCA(1dose/d+20mg/kg/d) C:UDCA(20mg/kg/d)	T:55.30 C:-	60/—	12	Error	①
Liao YH (2014) <sup>[45]</sup>	AASLD	T:TDD+UDCA(1dose/d+15~20mg/kg/d) C:UDCA(15~20mg/kg/d)	T:51.8 C:52.8	60/88%	26	Unclear	①③
Zhang XY (2016) <sup>[46]</sup>	AASLD	T:TDD+UDCA(1dose/d+10mg/kg/d) C:UDCA(10mg/kg/d)	T:63.1 C:62.9	50/82%	24	Unclear	①
Wei CS (2014) <sup>[47]</sup>	AASLD	T:TDD+UDCA(1dose/d+750mg/d) C:UDCA(750mg/d)	T:49.94 C:48.12	66/89%	48	RNT	②③
Zhang N (2011) <sup>[48]</sup>	AASLD	T:YGF+UDCA(1dose/d+13~15mg/kg/d) C:UDCA(13~15mg/d)	—	66/—	4	Error	①②③
Sun YQ (2014) <sup>[49]</sup>	AASLD	T:YGF+UDCA(1dose/d+750mg/d) C:UDCA(750mg/d)	55.21	60/91%	12	Unclear	①②
Giang GC (2014) <sup>[50]</sup>	MD	T:YGF+UDCA(1dose/d+15mg/kg/d) C:UDCA(15mg/kg/d)	—	74/—	12	Error	①②③
Gong M (2012) <sup>[51]</sup>	AASLD	T:YGF+UDCA(1dose/d+13~15mg/d) C:UDCA(13~15mg/d)	50.21	63/88%	12	Error	①②③

Diagnostic criteria: AASLD = the guidelines set by AASLD; MD = Medical diagnosis. 2. Random methods: RNT = Random number table; DB = Double blinding (blinding of participants and investigators); CA = Concealed allocation; 4. Outcome indicator:

① = CER; ① = ALP; ② = TBil.

AASLD = The American Association for the Study of Liver Diseases, FZHY = Fuzheng Huayu Capsule, TDD = Tongdan decoction, YGF = Yugan Fang.

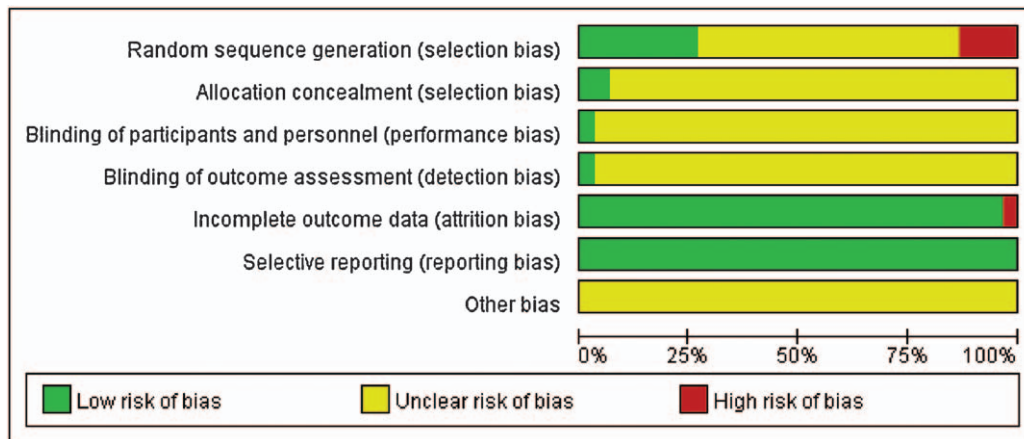


Figure 2. Methodological quality assessment of the risk of bias for each included study.

**3.5.2. Liver function.** The results of the secondary outcome were presented as a league table in Fig. 9. In terms of ALP, only SGLD + UDCA had no obvious advantage over UDCA monotherapy ( $SMD = -0.14, 95\% CI [-1.03, 0.76]$ ), and GSHX + UDCA was more effective than SGLD + UDCA ( $SMD = -1.23, 95\% CI [-2.35, 0.11]$ ). In terms of TBil, GSHX ( $SMD = -1.26, 95\% CI [-2.28, -0.25]$ ), ALHX ( $SMD = -1.68, 95\% CI [-2.38, -0.99]$ ), HZJD ( $SMD = -1.27, 95\% CI [-1.97, -0.56]$ ),

Tongdan Decoction ( $SMD = -0.93, 95\% CI [-1.49, -0.37]$ ) and FZHY ( $SMD = -1.05, 95\% CI [-1.50, -0.61]$ ) combination with UDCA could significantly better than UDCA monotherapy; ALHX + UDCA was more efficacious than BJRG + UDCA ( $SMD = -1.30, 95\% CI [-2.14, -0.45]$ ), YGF + UDCA ( $SMD = -1.24, 95\% CI [-2.12, -0.35]$ ), and SGLD + UDCA ( $SMD = -1.18, 95\% CI [-2.16, 0.21]$ ); in addition HZJD + UDCA was better than BJRG + UDCA ( $SMD = -0.88, 95\% CI$

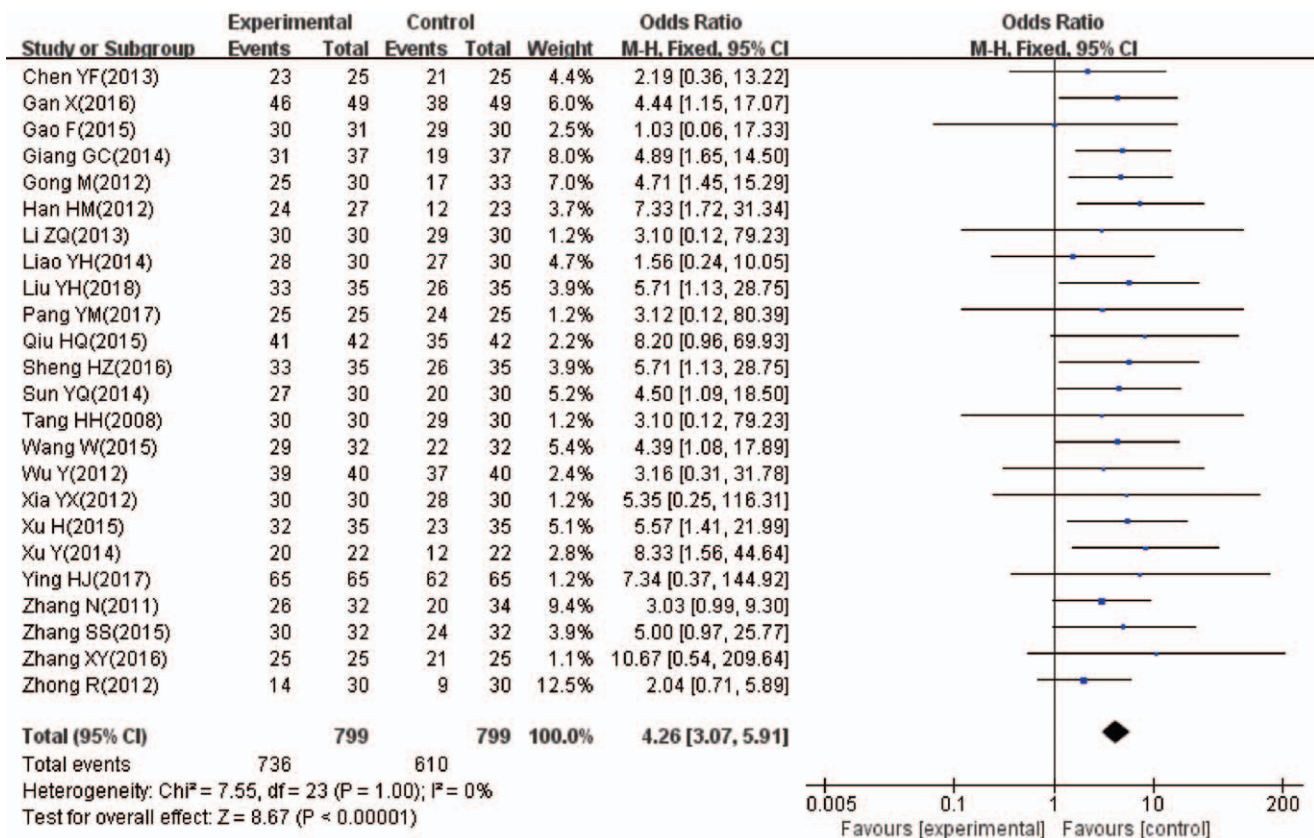


Figure 3. The CER of combination group vs monotherapy group.  $I^2$  and  $P$  are the criterion for the heterogeneity test, pooled odds ratio, —■— odds ratio and 95% CI.

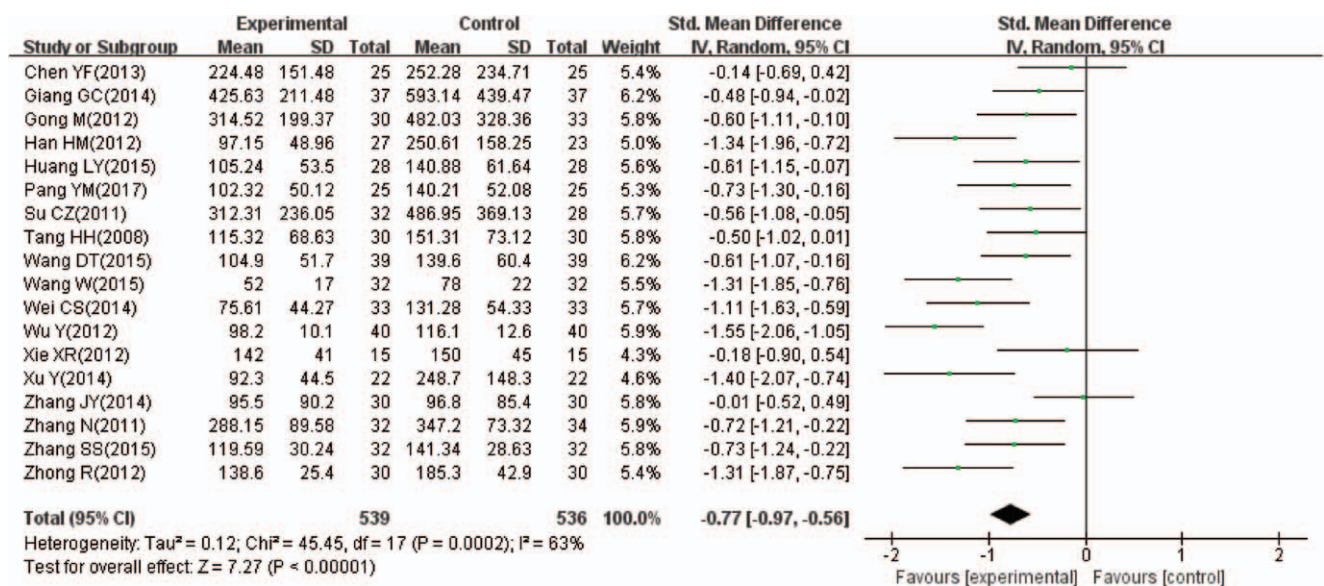


Figure 4. Improvement of ALP in combination group vs monotherapy group. I<sup>2</sup> and P are the criterion for the heterogeneity test, pooled odds ratio, —■— odds ratio and 95% CI.

[-1.74, -0.03] ); and BJRG + UDCA was more effective than FZHY + UDCA (SMD = -0.67, 95% CI [-1.32, -0.02] ).

The cluster ranking map was used to provide a comprehensive ranking of interventions for liver function, and the upper right corner indicated the better overall efficacy. The results showed that the most effective interventions for liver function were ALHX + UDCA, GSHX +UDCA, HZJD + UDCA (Fig. 10).

### 3.6. Publication bias

Funnel plot and Egger test were used to assess the publication bias of inclusion studies. Funnel plots is basically symmetrical (Fig. 11), and the Egger test did not imply any publication bias (P = .783 > 0.05, 95% Conf. [-0.84, 0.64] ) (See Fig. S2, Supplement Digital Content, <http://links.lww.com/MD/F161>).

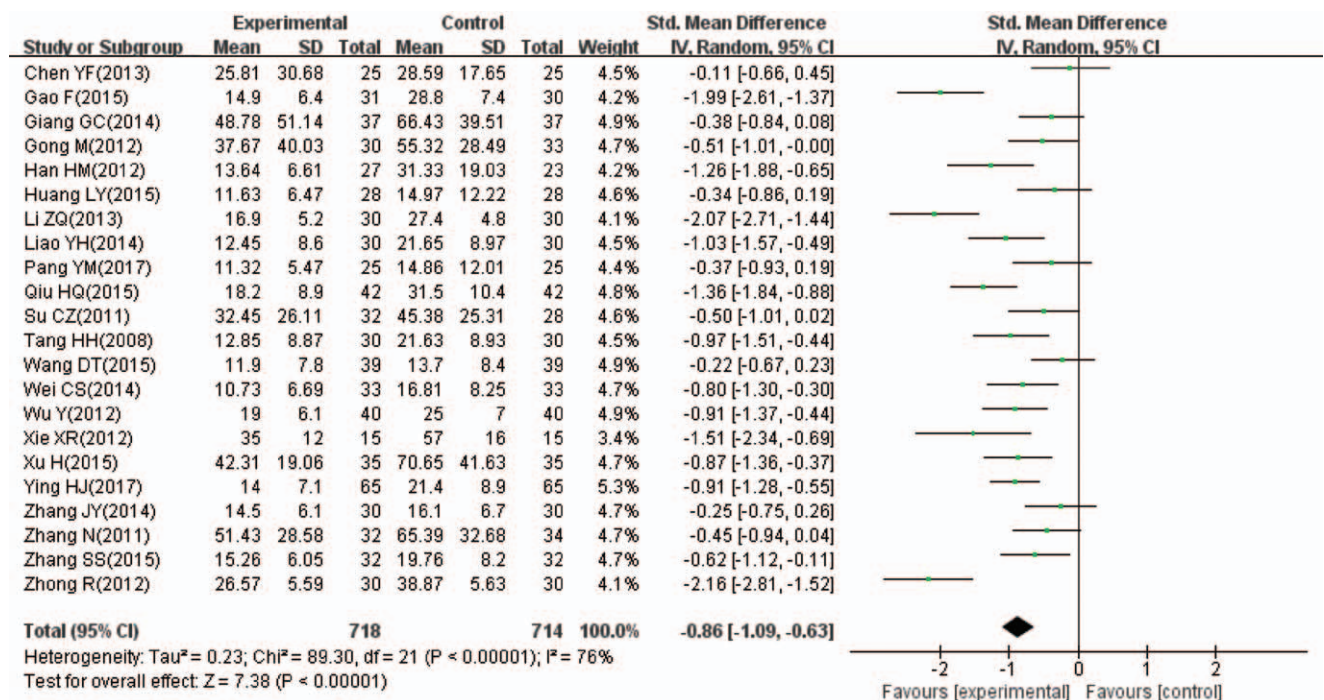
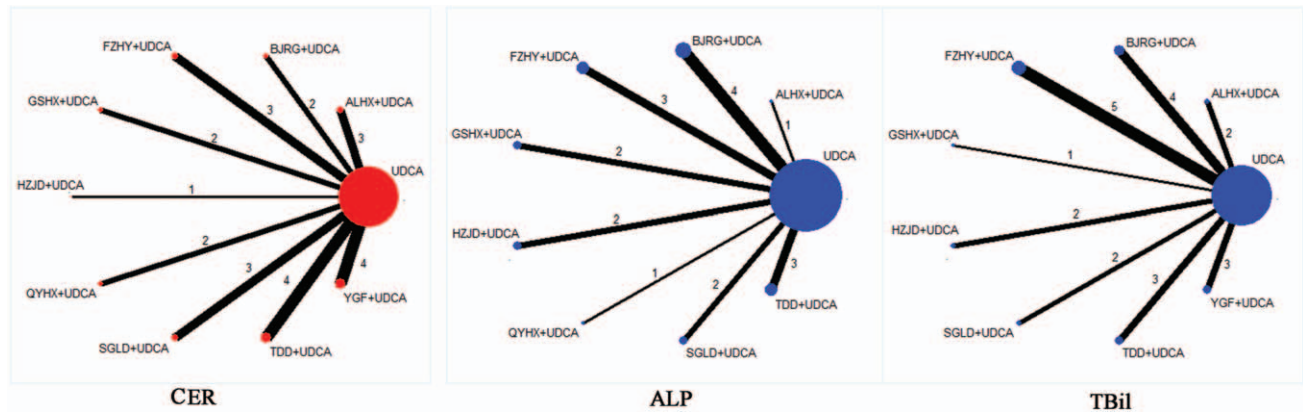


Figure 5. Improvement of TBil in combination group vs monotherapy group. I<sup>2</sup> and P are the criterion for the heterogeneity test, pooled odds ratio, —■— odds ratio and 95% CI.



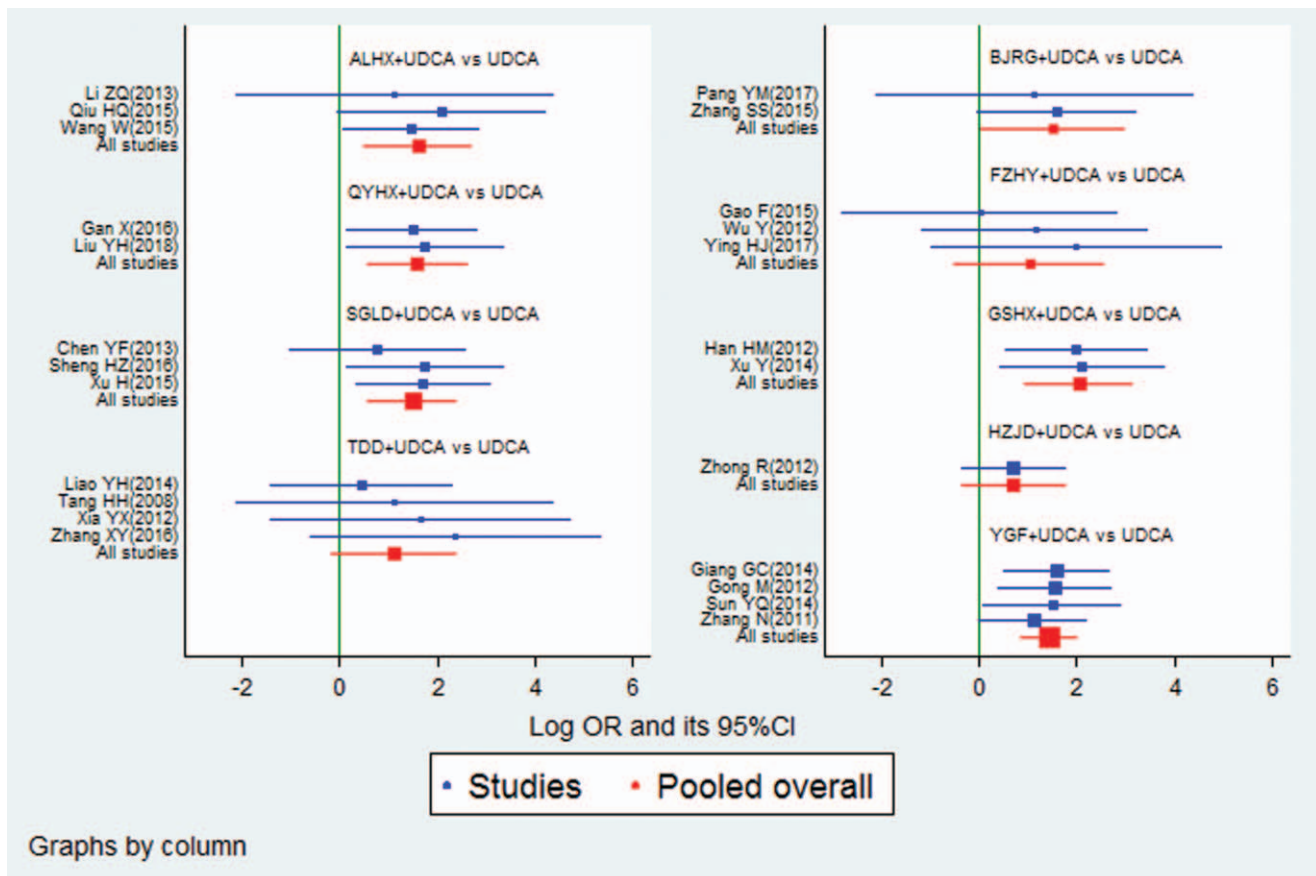


**Figure 6.** Network of eligible comparisons for efficacy (A: CER; B: ALP; C: TBil). The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size).

**4. Discussion**

In the absence of treatment, PBC is a progressive disease, most patients advanced 1 histologic stage every 2 years, and the development of hepatic decompensation was estimated to be 15% to 25% within 5 years, manifested as ascites, hemorrhage, hyperbilirubinemia or hepatic encephalopathy.<sup>[52,53]</sup> Majority of asymptomatic patients develop symptoms over the course of 4.5 to

17.8 years, however, the median survival of symptomatic and asymptomatic patients is 7.5 years and 16 years, indicating that the survival rate of asymptomatic PBC patients is still worse.<sup>[54]</sup> At present, the difficulty of drug development has posed huge challenges to the treatment of PBC. First, PBC as a rare disease makes it difficult to recruit enough patients to support clinical trials. Second, the progress of PBC requires long-term and large-



**Figure 7.** Forest map of the CER in different TCM combined with UDCA vs UDCA.



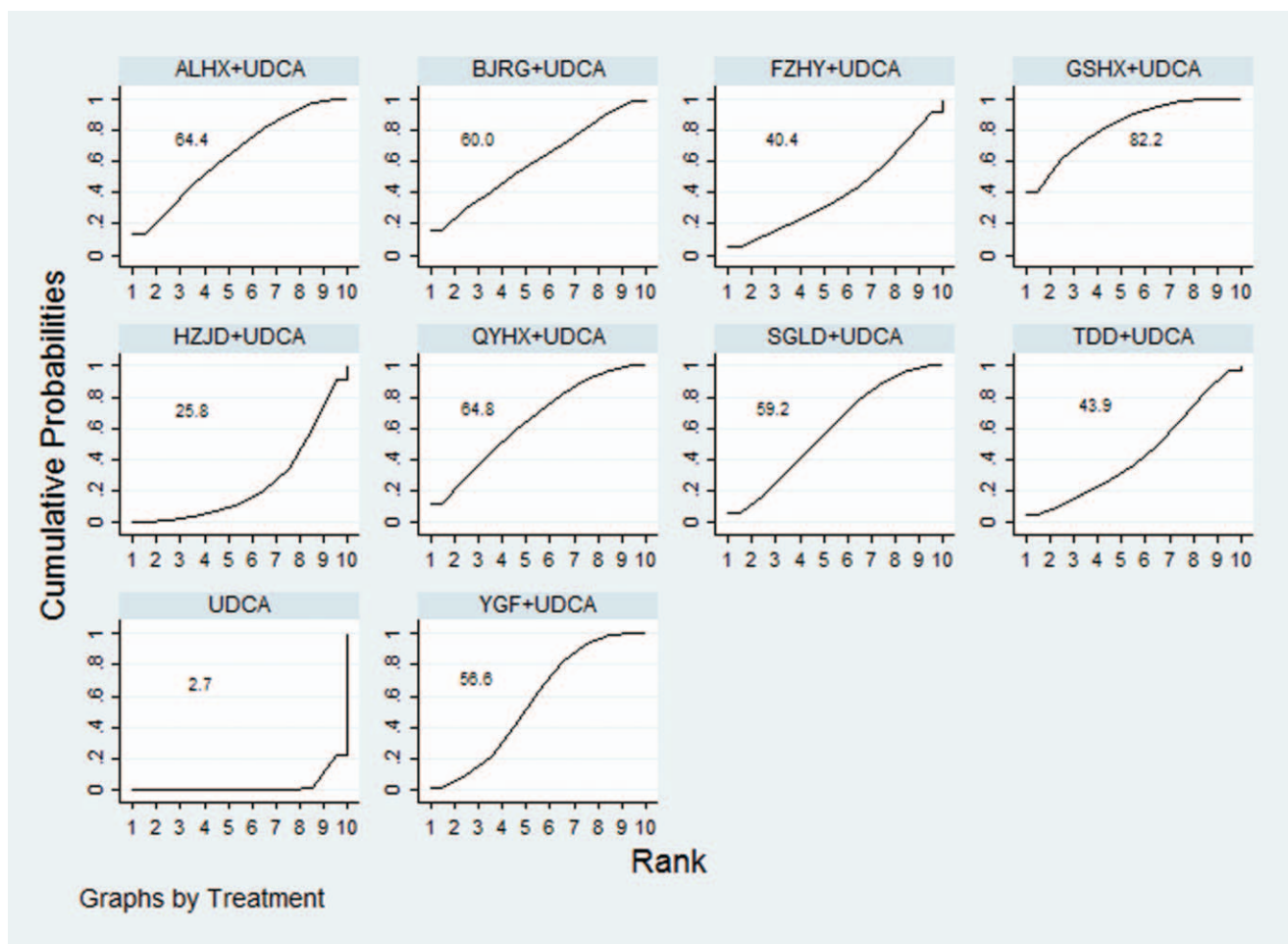


Figure 8. SUCRA diagram of CER in different TCM combined with UDCA vs UDCA.

scale clinical trials to prove the effect of drugs on clinical outcomes such as liver transplantation and survival. Third, with the progress of treatment, only the most refractory cases can be used to develop new and more effective treatments. Based on these limitations, drug development for PBC mainly focuses on surrogate clinical endpoints, the only exception being UDCA.<sup>[55]</sup>

UDCA is the most effective and approved therapy for PBC. It is a choleric and hydrophilic endogenous bile acid which has hepatoprotective and immunomodulatory properties with multiple sites and mechanisms of action. Firstly, it stimulates biliary bicarbonate secretion, increases the hydrophilicity index of the circulating bile pool, provides protection against the damage induced by hydrophobic bile acid and cytokine and subsequent inflammation and fibrosis. Secondly, UDCA treatment can enrich and expand the bile acid pool to induce less toxic bile composition by activating AE2 transporters.<sup>[56]</sup> Although the efficacy of UDCA varies with dose duration of treatment, stage of disease, and measurement results, the vast majority of research evidence suggested that sufficient duration and sufficient UDCA (13–15 mg/kg/d) eventually showed biochemical and histological benefits for PBC, and most probably to improve survival without transplantation.<sup>[57–59]</sup> UDCA is well tolerated and can partially prevent PBC progression, reduce liver transplantation rate and prolong survival.<sup>[60,61]</sup> Unfortunately, UDCA does not complete-

ly improve the overall condition of patients, most patients eventually progress cirrhosis.<sup>[44]</sup> In addition, approximately 40% of PBC patients do not have a sufficient biochemical response to UDCA and ineffective therapies lead to a faster progression of PBC and higher risk of death or liver transplantation.<sup>[62,63]</sup> These patients must be identified early and considered for adjuvant therapies.

The clinical features of PBC are vary from patient to patient, it is necessary to identifying more sensitive and specific biomarkers to predict clinical outcomes can make PBC treatment more individual.<sup>[7]</sup> ALP is the most prominent abnormal biochemical index of PBC, which usually increases to 2 to 10 times in 96% of patients. Next, TBil continues to rise during the disease progression, which is a typical feature of PBC progression.<sup>[64]</sup> The The American Association for the Study of Liver Diseases guidelines for PBC updated in 2019 indicated that ALP is a reliable predictor of PBC treatment response and TBil is the best predictor of survival or PBC patients.<sup>[65–67]</sup> Therefore, this study used ALP and TBil as a measure the benefit of therapy. In the paired meta-analysis, the integration of Chinese and western medicine could significantly improve CER and liver function than western medicine alone. In the network meta-analysis, for improving CER, the efficacy ranking showed GSHX+UDCA was superior to others, followed by QYHX + UDCA and ALHX

<b>GSHX+UDCA</b>	-0.42 (-1.65,0.81)	-0.00 (-1.24,1.24)	-0.33 (-1.49,0.83)	-0.88 (-2.01,0.25)	-0.21 (-1.32,0.90)	-0.82 (-1.98,0.34)	-0.76 (-1.99,0.46)	<b><u>-1.26</u></b> <b><u>(-2.28,-0.25)</u></b>
-0.06 (-1.18,1.05)	<b>ALHX+UDCA</b>	-0.42 (-1.41,0.57)	-0.75 (-1.64,0.14)	<b><u>-1.30</u></b> <b><u>(-2.14,-0.45)</u></b>	-0.63 (-1.45,0.19)	<b><u>-1.24</u></b> <b><u>(-2.12,-0.35)</u></b>	<b><u>-1.18</u></b> <b><u>(-2.16,-0.21)</u></b>	<b><u>-1.68</u></b> <b><u>(-2.38,-0.99)</u></b>
-0.44 (-1.36,0.48)	-0.38 (-1.47,0.70)	<b>HZJD+UDCA</b>	-0.33 (-1.24,0.57)	<b><u>-0.88</u></b> <b><u>(-1.74,-0.03)</u></b>	-0.21 (-1.04,0.62)	-0.82 (-1.72,0.07)	-0.77 (-1.75,0.22)	<b><u>-1.27</u></b> <b><u>(-1.97,-0.56)</u></b>
-0.56 (-1.48,0.35)	-0.50 (-1.58,0.58)	-0.12 (-1.00,0.76)	<b>TDD+UDCA</b>	-0.55 (-1.29,0.19)	-0.12 (-0.83,0.59)	-0.49 (-1.27,0.29)	-0.43 (-1.32,0.45)	<b><u>-0.93</u></b> <b><u>(-1.49,-0.37)</u></b>
-0.70 (-1.50,0.10)	-0.64 (-1.63,0.35)	-0.26 (-1.02,0.51)	-0.14 (-0.89,0.62)	<b>BJRG+UDCA</b>	<b><u>-0.67</u></b> <b><u>(-1.32,-0.02)</u></b>	-0.06 (-0.79,0.67)	-0.12 (-0.95,0.72)	-0.38 (-0.86,0.09)
-0.76 (-1.61,0.10)	-0.69 (-1.72,0.34)	-0.31 (-1.13,0.50)	-0.19 (-1.00,0.62)	-0.06 (-0.74,0.63)	<b>FZHY+UDCA</b>	-0.61 (-1.31,0.09)	-0.55 (-1.37,0.26)	<b><u>-1.05</u></b> <b><u>(-1.50,-0.61)</u></b>
-0.77 (-1.61,0.06)	-0.71 (-1.72,0.31)	-0.33 (-1.12,0.47)	-0.21 (-1.00,0.58)	-0.07 (-0.73,0.59)	-0.01 (-0.73,0.70)	<b>YGF+UDCA</b>	-0.06 (-0.93,0.82)	-0.44 (-0.99,0.10)
<b><u>-1.23</u></b> <b><u>(-2.35,-0.11)</u></b>	-1.17 (-2.43,0.09)	-0.79 (-1.88,0.31)	-0.67 (-1.75,0.42)	-0.53 (-1.53,0.47)	-0.47 (-1.51,0.56)	-0.46 (-1.48,0.56)	<b>SGLD+UDCA</b>	-0.50 (-1.19,0.18)
<b><u>-1.37</u></b> <b><u>(-2.04,-0.70)</u></b>	<b><u>-1.31</u></b> <b><u>(-2.19,-0.42)</u></b>	<b><u>-0.92</u></b> <b><u>(-1.55,-0.30)</u></b>	<b><u>-0.80</u></b> <b><u>(-1.42,-0.19)</u></b>	<b><u>-0.67</u></b> <b><u>(-1.10,-0.23)</u></b>	<b><u>-0.61</u></b> <b><u>(-1.14,-0.09)</u></b>	<b><u>-0.60</u></b> <b><u>(-1.09,-0.10)</u></b>	-0.14 (-1.03,0.76)	<b>UDCA</b>

Figure 9. Funnel plot of CER in different TCM combined with UDCA vs UDCA. A = UDCA, B = ALHX + UDC, C = BJRG + UDCA, D = FZHY + UDCA, E = GSHX + UDCA, F = HZJD + UDCA, G = QYHX + UDCA, H = SGLD + UDCA, I = TDD + UDCA, J = YGF + UDCA.

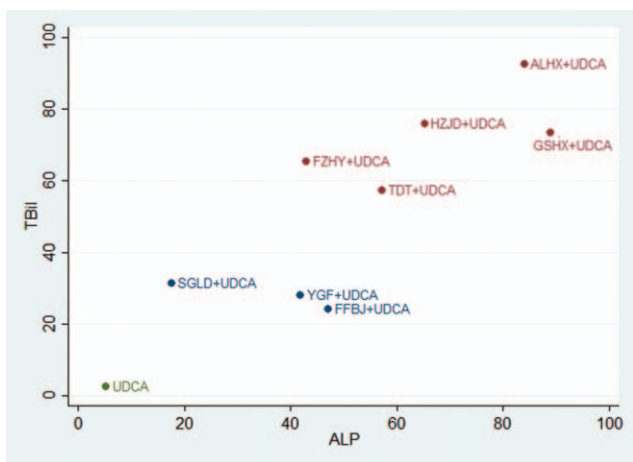


Figure 10. League table of ALP and TBil in different TCM combined with UDCA vs UDCA. Comparisons should be read from left to right. The ALP and TBil estimate is located at the intersection of the column - defining treatment and the row-defining treatment. SMD below 0 favours the column defining treatment in ALP and favours the row defining treatment in TBil. Significant results are in bold and underlined.

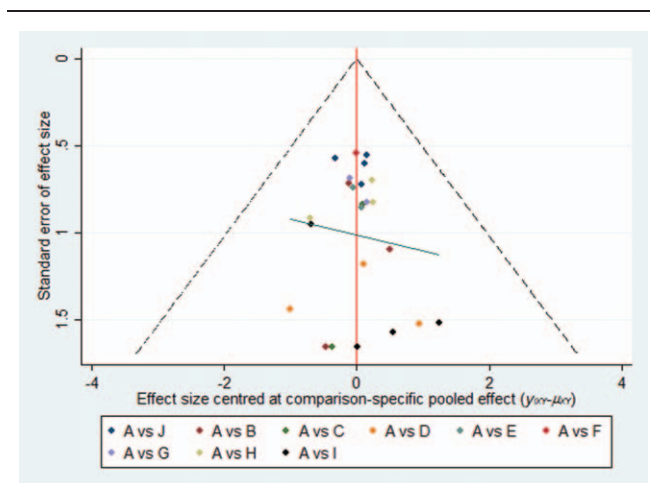


Figure 11. Ranking map of ALP and TBil in different TCM combined with UDCA vs UDCA on the ALP and TBil.

+ UDCA; for improving liver function, the cluster ranking chart suggested that ALHX + UDCA was more comprehensive, followed by GSHX + UDCA and HZJD + UDCA.

GSHX is one of the most common complementary therapies for PBC, more and more studies regarding the effects of single herb in GSHX on PBC is available. For instance, Modern pharmacological studies have shown that *Angelica sinensis* has a clear antioxidant and anti-inflammatory effect,<sup>[68]</sup> and its active ingredient *Angelica sinensis* polysaccharide can improve oxidation by inhibiting the expression of inflammatory cytokines, attenuating oxidative response and reduce apoptosis to achieving effective protection against liver damage,<sup>[69]</sup> Levistilide A can not only inhibit the proliferation of hepatic stellate cells, but also prevent the progression of liver fibrosis through anti-angiogenesis,<sup>[70]</sup> suggested that *Angelica sinensis* may be a great potential drug for treating hepatitis and liver fibrosis. Animal experiments have shown that Paeoniflorin which extracted from *Paeonia lactiflora* can attenuate liver damage and cholestasis by ANIT in rats, increase the biliary excretion in addition to achieve anti-inflammatory effects.<sup>[71]</sup> ALHX has a more comprehensive role in improving liver function (ALP and TBil), which can reduce serum indicators, resist collagen regeneration, suppress the activation of hepatic stellate cells, and even promote the softening and decomposition of fibrous connective tissue to reverse fibrosis.<sup>[72,73]</sup> Combined TCM with UDCA, the diversity of active ingredients and the potential synergy can make a wide range of targets and multiple mechanisms for PBC.

In summary, TCM combined with UDCA was better than UDCA monotherapy in the treatment of PBC. It is worth noting that GSHX + UDCA was the best choice to improve CER, while ALHX + UDCA had a satisfactory effect in improving liver function. However, some limitations that affect the results need to be considered, the quality of the research literature included in this study was relatively low, many problems in randomization methods, allocation concealment and blind method in studies, and some researches were few in number, which made the lack of systematic and comprehensive comparison in this study; In addition, the limitation of this study was that the treatment process included in trials were not uniform. These factors all affected the reliability of the results of the systematic analysis.

## 5. Conclusion

This study performed a systematic review and meta-analysis of RCTs of TCM combined with UDCA in the treatment of PBC. Systematic analysis confirmed that TCM-assisted UDCA had obvious advantages over UDCA monotherapy for PBC, GSHX + UDCA was mainly beneficial to CER while ALHX + UDCA had a more comprehensive effect on liver function. Most importantly, the effective components compatibility theory of GSHX and ALHX is worth exploring and learning, and the effectiveness and safety of these therapies for PBC need to be further validated by large-scale and high quality RCTs in future.

## Author contributions

CRedit authorship contribution statement

All authors were major contributors in the writing of the manuscript. All authors approved the final manuscript.

**Conceptualization:** Xing Chen

**Funding acquisition:** Yanling Zhao

**Investigation:** Ruilin Wang, Lifu Wang, Jianyu Li, Honghong Liu, Tingting He

**Methodology:** Xiao Ma

**Writing – original draft:** Xing Chen

**Writing – review & editing:** Shizhang Wei, Haotian Li, Min Wang

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