Comparative Evidence for Intrahepatic Cholestasis of Pregnancy Treatment With Traditional Chinese Medicine Therapy: A Network Meta-Analysis

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Background: Intrahepatic cholestasis of pregnancy (ICP) seriously threatens the health of pregnant women and newborns. A various number of Chinese prescriptions and patent medicines combined with ursodeoxycholic acid (UDCA) are used for treating ICP in China. However, there are still many doubts in choosing the suitable therapeutic drugs for the treatment of ICP in clinical practice.

Methods: Several electronic databases, including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Wanfang, and VIP, were comprehensively searched from the database inception to February 22, 2021. Randomized controlled trials (RCTs) reporting the use of UDCA only, Chinese prescriptions plus UDCA, and patent medicine plus UDCA for the treatment of ICP were collected according to their inclusion and exclusion criteria. Cochrane Reviewers’ Handbook version 5.2 was applied for the risk assessment of the included trials. STATA 16.0 software was used for network meta-analysis (NMA). The pruritus score and the serum levels of total bile acid (TBA), alanine aminotransferase (ALT), and aspartate transaminase (AST) in ICP patients served as the primary outcomes. Moreover, this study had been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#joinuppage), and the registration number is CRD42020188831.

Results: Thirty-eight RCTs comprising 3,841 patients meeting the inclusion criteria were included in the network meta-analysis. The NMA results showed that compared with UDCA used alone, Yinchenhao decoction (seven different Chinese prescriptions or patent medicines) plus UDCA dramatically alleviated the primary outcomes of ICP, including the

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CBM, China Biology Medicine; CNKI, Chinese databases including China National Knowledge Infrastructure; HSCs, hepatic stellate cells; ICP, intrahepatic cholestasis of pregnancy; IP-a, intervention plan a; IP-b, intervention plan b; NMA, network meta-analysis; TBA, total bile acid; RCT, randomized controlled trial; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking curve; UDCA, ursodeoxycholic acid; α-SMA, α-smooth muscle actin.
pruritus score, as well as the serum levels of TBA, ALT, and AST. The NMA results showed that the optimal drug ratio for the treatment of ICP was different from the dosage ratio of traditional Yinchenhao decoction. Significantly, the intervention plan f (IP-f) group [the similar prescription of Yinchenhao decoction 2 (Artemisia capillaris Thunb > 15 g, Gardenia > 9 g, and Rhubarb < 5 g) + UDCA] was the best therapeutics among the eight therapies.

**Conclusion:** Overall, the combined use of Chinese prescriptions or patent medicine with UDCA was generally better than UDCA used alone. The dose of IP-f might be a beneficial therapeutic method for the clinical medication of ICP.

**Clinical Trail Registration:** https://www.crd.york.ac.uk/, identifier CRD42020188831.

**Keywords:** intrahepatic cholestasis of pregnancy, ursodeoxycholic acid, Yinchenhao decoction, traditional Chinese medicine, network meta-analysis

**INTRODUCTION**

Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disease in pregnant women, with high cases in different regions all over the world (Piechota and Jelski, 2020). In general, ICP often occurs in the middle and later stages of pregnancy and rarely occurs in early pregnancy (Wongjarupong et al., 2020). The primary clinical symptoms of ICP include maternal pruritus and the serum level of total bile acid (TBA) more than 10 μmol/l (Walker et al., 2002; Glantz et al., 2004). Simultaneously, a study found that the alcohol dehydrogenase activity was increased in women with ICP compared with healthy pregnant and non-pregnant women. Alcohol dehydrogenase activity could become a new outcome that diagnoses ICP in the future (Jelski et al., 2020). In addition, in-depth research on ICP found that genetic defects in canalicular transporters were related to bleeding (Hou, 1988; Arthuis et al., 2020). Simultaneously, a long-term investigation found that women with a history of ICP had a higher risk of suffering the following diseases: cholelithiasis, cholecystitis, hypothyroidism, and diseases of the pancreas and the digestive system (Hämäläinen et al., 2019). For newborns, the threats caused by ICP are mainly as follows: premature birth, lesser weight, amniotic fluid contamination, cardiac arrhythmias, infant respiratory distress syndrome, and the most serious is sudden fetal death (Arthuis et al., 2020; Brouwers et al., 2015; Lin et al., 2019).

Currently, ursodeoxycholic acid (UDCA) is the only first-line drug approved by the U.S. Food and Drug Administration for the treatment of cholestasis. According to clinical trials, the therapeutic effectiveness and safety of UDCA have been fully proven for relieving symptoms in patients with ICP in the past several decades (Wood et al., 2018). However, UDCA is not effective in treating part diseases related to cholestasis and is also limited to a certain extent (Shah and Kowdley, 2020). As one of the most significant challenges in drug discovery, more effective and reasonable ICP intervention drugs still need to be further developed. At present, the combination use of UDCA with other drugs is often applied for treating ICP in clinical practice with good curative effect and few adverse reactions. In China, traditional Chinese medicine prescriptions and Chinese patent medicines combined with UDCA are widely applied for the treatment of ICP. However, these therapies are different from each other and lack systematic research. Furthermore, compatible dosage of traditional Chinese medicine is particularly important in clinical practice, and the effective dose is difficult to determine. As different prescriptions have different medicinal properties with complex systems, it is difficult to systematically study prescriptions for the treatment of ICP. Simultaneously, among these prescriptions, we found that the famous Yinchenhao decoction is the most commonly used prescription.

Traditional Chinese medicine Yinchenhao decoction consist of Artemisia capillaris Thunb, Gardenia, and Rhubarb. Among these medicinal materials, A. capillaris Thunb is the most important medicinal material. A. capillaris Thunb is also named Yinchenhao in China. Its medicinal part is the dry above-ground part. It has multiple chemical components such as coumarin compounds (e.g., 6,7-dimethylesculetin and sabandin A), flavonoids (e.g., luteolin and aracapillin), and organic acids (e.g., rhein and ferulic acid, 2-ethyl furan, and irisone) (Huang et al., 2021). Therefore, it has multiple pharmacological activities including anti-inflammatory, anti-liver injury, anti-liver fibrosis, and anti-tumor (Liu and Zhao, 2017; Gao et al., 2016; Kim et al., 2018; Nam et al., 2018; Tsui et al., 2018; Yan et al., 2018; Jung et al., 2018). For example, a study found that the essential oil of A. capillaris Thunb could improve the level of alanine aminotransferase (ALT) and aspartate transaminase (AST) on CCl4-induced liver injury in mice. In addition, scoparone is an active ingredient of A. capillaris Thunb (Gao et al., 2016).

Based on the previous clinical studies, a network meta-analysis of Chinese prescriptions or patent medicines combined with UDCA in patients with ICP was comprehensively performed. This study was aimed to assess the effectiveness of different treatment methods and the effective dose of these prescriptions based on Yinchenhao decoction so that the clinical efficacy of Yinchenhao decoction can be approved by the international community and possibly enter the international market.

**MATERIALS AND METHODS**

The methodology of this study was in accordance with the network meta-analysis criteria of PRISMA (Moher et al., 2009)
and the PRISMA Extension Statement (Hutton et al., 2015). This study has been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#joinuppage), and the registration number is CRD42020188831.

Ethical Approval and Consent to Participate
As this study does not involve animal and patient experiments, the ethical approval and consent to participate are not applicable.

Search Strategy
PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Wanfang database, and VIP database were comprehensively searched from database inception to February 22, 2021. Intrahepatic cholestasis of pregnancy, UDCA, Artemisia capillaris Thunb, Yinzhuhuang, salvia or Chinese medicine were searched as keywords. All databases were retrieved twice. For the first time, the keyword composition including intrahepatic cholestasis of pregnancy, ursodeoxycholic acid, and interventions (Artemisia capillaris Thunb or Yinzhuhuang or salvia or Chinese medicine) were used to retrieve key information from the databases. For the second time, we used the keyword composition including intrahepatic cholestasis of pregnancy and ursodeoxycholic acid to check if we missed part of the studies. The search strategy in PubMed is listed in Table 1. The search strategy in other databases is similar to the search strategy in PubMed.

Selection Criteria
Two investigators independently examined the titles and abstracts of all searched databases to access the trials for inclusion. The inclusion criteria were as follows: randomized controlled trial (RCT); the patient has itchy skin as the main symptom during pregnancy; and the level of related indicators including TBA, ALT, and AST increase. Exclusion criteria were as follows: other liver and gallbladder diseases such as viral hepatitis. Document criteria were as follows: treatment interventions including UDCA, UDCA plus Yinzhuhuang oral liquid, UDCA plus salvia injection, and UDCA plus traditional Chinese medicine prescription were included.

Basis for Grouping
In this study, we found that most of the traditional Chinese medicine prescriptions used to treat ICP are associated with Yinchenhao decoction. Traditionally, Yinchenhao decoction consists of A. capillaris Thunb, Gardenia, and Rhubarb. Therefore, the included traditional Chinese medicine...

| TABLE 1 | Search strategy in PubMed. |
| Search number | Query | Sort by | Filters | Results |
| --- | --- | --- | --- | --- |
| 1 | [(Intrahepatic cholestasis of pregnancy (MeSH Terms) AND ursodeoxycholic acid (MeSH Terms))] AND (Artemisia capillaris Thunb OR yinzhuhuang OR salvia OR Chinese medicine) | Most recent | Randomized controlled trial | 0 |
| 2 | [Intrahepatic cholestasis of pregnancy (MeSH Terms) AND ursodeoxycholic acid (MeSH Terms)] | Most recent | Randomized controlled trial | 16 |

| TABLE 2 | Basis for grouping. |
| Intervention plan | Acronym | Group standard/interventions |
| --- | --- | --- |
| a | IP-a or a | UDCA |
| b | IP-b or b | Yinzhuhuang oral liquid + UDCA |
| c | IP-c or c | Salvia injection + UDCA |
| d | IP-d or d | Yinchenhao decoction (Artemisia capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb >5 g) + UDCA |
| e | IP-e or e | The similar prescription of Yinchenhao decoction 1 (Artemisia capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb >5 g) + UDCA |
| f | IP-f or f | The similar prescription of Yinchenhao decoction 2 (Artemisia capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb <5 g) + UDCA |
| g | IP-g or g | The similar prescription of Yinchenhao decoction 3 (Artemisia capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb <5 g) + UDCA |
| h | IP-h or h | Other traditional Chinese medicine prescriptions (Artemisia capillaris Thunb <15 g, Gardenia <9 g, and Rhubarb <5 g) + UDCA |
| No | Study | Intervention | Number of patients | Ages (\(x \pm s\)) | Pregnancy time/week (\(x \pm s\)) | Period of treatment (days) | Outcomes |
|----|--------|--------------|-------------------|-------------------|-------------------|-------------------|----------|
| 1  | Jiang (2014) | a  b | 30 | 26.7 ± 2.8 | 33.19 ± 0.97 | 20 | 1234 |
| 2  | Yuan and Lan (2014) | a  b | 30 | 27.0 ± 2.6 | 33.16 ± 0.77 | 20 | 1234 |
| 3  | Deng (2015) | a  b | 30 | 26.7 ± 2.7 | 33.23 ± 0.93 | 20 | 1234 |
| 4  | Dai (2016) | a  b | 160 | 26.8 ± 2.3 | 33.1 ± 0.96 | 20 | 1234 |
| 5  | Wu and Yang (2016) | a  b | 43 | 26.81 ± 4.69 | 33.52 ± 1.03 | 20 | 1234 |
| 6  | Bo (2017) | a  b | 43 | 24.2 ± 4.8 | 30.2 ± 3.4 | 10 | 1234 |
| 7  | Zhang (2017) | a  b | 62 | 29.7 ± 3.8 | 30.8 ± 3.1 | 10 | 1234 |
| 8  | Liang (2018) | a  b | 62 | 28.6 ± 4.5 | – | 14 | 1234 |
| 9  | Yu and Chen (2018) | a  b | 33 | 22.4 ± 4.3 | 24.4 ± 2.1 | 10 | 1234 |
| 10 | Fang et al. (2009) | a  c | 72 | 27.3 ± 2.6 | 33.8 ± 2.1 | 10 | 1234 |
| 11 | Pan et al. (2013) | a  c | 45 | – | – | 7 | 1234 |
| 12 | Peng (2015) | a  c | 45 | 26.1 ± 1.4 | 35.8 ± 0.9 | 7 | 1234 |
| 13 | Hua (2010) | a  d | 40 | 25.6 ± 1.2 | 35.6 ± 0.7 | 7 | 1234 |
| 14 | Wu (2010) | a  d | 30 | – | – | 10 | 1234 |
| 15 | Liu and Yang (2014) | a  d | 71 | 28.31 ± 5.28 | 26.93 ± 5.14 | 10 | 1234 |
| 16 | Fu (2017) | a  d | 40 | 28.6 ± 2.5 | 29.1 ± 2.2 | 10 | 1234 |
| 17 | Luo et al. (2019) | a  d | 44 | 34.88 ± 6.37 | 29.51 ± 3.09 | 10 | 1234 |
| 18 | Zhu and Huang (2008) | a  e | 35 | 25.1 ± 2.8 | 34.5 ± 1.9 | 10 | 1234 |
| 19 | Wang and Lai (2011) | a  e | 25 | 23.9 ± 2.3 | 35.1 ± 2.2 | 10 | 1234 |
| 20 | Wang et al. (2016) | a  e | 55 | 25.1 ± 4.2 | >32 | 10 | 1234 |
| 21 | Wang and Hu (2007) | af  f | 36 | – | >32 | 10 | 1234 |
| 22 | Xie et al. (2015) | af  f | 36 | 27.06 ± 4.93 | 34.4 ± 2.6 | 10 | 1234 |
| 23 | Qiu et al. (2017) | af  f | 46 | 28.7 ± 3.22 | 31.78 ± 3.67 | 10 | 1234 |
| 24 | Fang et al. (2018) | af  f | 40 | 28.7 ± 3.9 | 32.4 ± 9.2 | 10 | 1234 |
| 25 | Guo and Pei (2018) | af  f | 19 | 38 ± 2.12 | 30.10 ± 2.42 | 10 | 1234 |
| 26 | Wang (2009) | af  g | 72 | – | >32 | 10 | 1234 |
| 27 | Wang and Du (2011) | af  g | 62 | – | >32 | 10 | 1234 |
| 28 | Lv (2013) | af  g | 35 | 26.3 ± 2.4 | 35.7 ± 1.8 | 10 | 1234 |
| 29 | Han et al. (2013b) | af  g | 124 | – | – | 10 | 1234 |
| 30 | Chen et al. (2014) | af  g | 62 | 27.4 ± 3.1 | >32 | 10 | 1234 |
| 31 | He et al. (2014) | af  g | 29 | 27.8 ± 3.4 | – | 10 | 1234 |
prescriptions in this study were divided into five groups based on the different doses of Yinchen, Zhizi, and Dahuang. Finally, all studies were divided into seven groups based on the treatment intervention plans as follows: intervention plan a (IP-a): UDCA; intervention plan b (IP-b): Yinzhihuang oral liquid + UDCA; intervention plan c (IP-c): salvia injection + UDCA; intervention plan d (IP-d): Yinchenhao decoction (A. capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb >5 g) + UDCA; intervention plan e (IP-e): the similar prescription of Yinchenhao decoction 1 (A. capillaris Thunb >15 g, Gardenia <9 g, and Rhubarb >5 g) + UDCA; intervention plan f (IP-f): the similar prescription of Yinchenhao decoction 2 (A. capillaris Thunb >15 g, Gardenia >9 g, and Rhubarb <5 g) + UDCA; intervention plan g (IP-g): the similar prescription of Yinchenhao decoction 3 (A. capillaris Thunb <15 g, Gardenia <9 g, and Rhubarb <5 g) + UDCA; and intervention plan h (IP-h): other traditional Chinese medicine prescriptions + UDCA. Among these groups, IP-a was the control group (Table 2). The details of the botanical drugs are listed in Supplementary Table S1.

Outcomes
As the therapeutic effects of Yinchenhao decoction on ICP is the main question, the pruritus score and the levels of ALT, AST, and TBA were set as the primary outcomes. Among these indices, pruritus score complied with the standards that Ribalta et al. (1991) set (0 marks: no pruritus; one point: occasional pruritus; two points: intermittent pruritus and symptoms are not fluctuating; three points: intermittent pruritus and symptoms are fluctuating; and four points: continuous pruritus at day and night).

Data Extraction and Quality Assessment
Excel 2010 was used to collect the basic characteristics of patients or participants such as intervention, comparisons, and outcomes by two investigators. The basic characteristics of patients, including intervention plan, number of patients, age, pregnancy time, and period of treatment, were collected (Table 3). Primary outcomes included pruritus score and the level of ALT, AST, and TBA. Simultaneously, the missing or repeated data were excluded. Quality assessment was performed using Review Manager 5.3 according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.2. Disagreements on the assessment of data were resolved by discussion, and consensus was reached in all cases.

Statistical Analysis
The random-effects model with STATA (version 16.0) was selected to perform the network meta-analysis. All outcomes were continuous outcomes. Therefore, a standardized mean difference (SMD) was selected to calculate the effect size with 95% CI. The intervention plan a (IP-a) is the public control group. The study that does not have IP-a was filled with IP-a data according to the following method. The “mean” of this study is the average of all means of IP-a. The “SD” is more than double the maximum SD of IP-a. The “n” is zero. Global inconsistency between direct and indirect sources of evidence was assessed by fitting the inconsistency model. When inconsistency is not significant ($p > 0.05$), it was assessed further to fit the consistency model. We further estimated the ranking probabilities of all treatments that were at different possible ranks for all intervention. At the same time, the result of treatment sequence was summarized and showed with the help of surface under the cumulative ranking curve (SUCRA). Finally, according to the result of SUCRA value, we selected two main outcomes to synthetically analyze the treatment effect of each intervention.

### Table 3 | (Continued) Basic characteristics of randomized controlled trials included in network meta-analysis.

| No | Study | Intervention | Number of patients | Ages ($\bar{x} \pm s$) | Pregnancy time/week ($\bar{x} \pm s$) | Period of treatment (days) | Outcomes |
|---|---|---|---|---|---|---|---|
| 32 | Yin and Zhou (2015) | a | 32 | 27.8 ± 3.4 | – | 20 | – |
| 32 | | g | 30 | – | 30–34 | 14 | 1234 |
| 33 | Gao and Zhao (2017) | g | 75 | 27.42 ± 2.47 | 32.19 ± 3.37 | 14 | 12 |
| 33 | | a | 75 | 27.14 ± 2.42 | 32.24 ± 3.85 | 14 | 2 |
| 34 | Luo and Chen (2017) | g | 43 | 25.63 ± 4.43 | – | 14 | 2 |
| 34 | | a | 43 | 26.50 ± 2.41 | – | 14 | – |
| 35 | Hu and Yang (2013) | ah | h | 88 | 27.5 ± 4.6 | 31.2 ± 5.7 | 20 | 234 |
| 35 | | a | 80 | 27.9 ± 4.3 | 31.3 ± 5.5 | 20 | – |
| 36 | Wei (2016) | h | 30 | 28.5 ± 6.1 | 32.3 ± 3.6 | 14 | 234 |
| 36 | | a | 30 | 30.5 ± 5.2 | 31.5 ± 4.3 | 14 | – |
| 37 | Nie and Lu (2019) | h | 40 | 26.78 ± 2.45 | 32.24 ± 3.85 | 14 | 1234 |
| 37 | | a | 40 | 25.68 ± 2.21 | 32.24 ± 3.85 | 14 | – |
| 38 | Gu et al. (2014) | adh | d | 36 | 27.8 ± 6.2 | 31.5 ± 2.8 | 20 | 234 |
| 38 | | a | 47 | 28.2 ± 5 | 31.1 ± 3.1 | 20 | – |
| 38 | | h | 54 | 29.2 ± 4.9 | 32.4 ± 2.4 | 20 | – |

Notes: a: UDCA, b: Yinzhihuang oral liquid + UDCA, c: salvia injection + UDCA, d: Yinchenhao decoction + UDCA, e: the similar prescription of Yinchenhao decoction 1 + UDCA, f: the similar prescription of Yinchenhao decoction 2 + UDCA, g: the similar prescription of Yinchenhao decoction 3 + UDCA, and h: other traditional Chinese medicine prescriptions + UDCA, 1: pruritus score, 2: TBA, 3: ALT, and 4: AST.
RESULTS

Basic Characteristics of Included Randomized Controlled Trials

A total of 1,620 studies were retrieved from database searches as potentially eligible records. Among them, 1,540 studies were excluded based on reviewed titles and abstracts. Eighty studies were reviewed for further assessment. For the preserved records, 42 studies were excluded due to missing data, same data, or use of other medicine. Finally, 38 RCTs with 3,841 patients with ICP who met the criteria were included in the network meta-analysis. The flow chart of study selection is shown in Figure 1. The basic characteristics of randomized controlled trials included in network meta-analysis is shown in Table 3. The number of patients in each study trial ranged from 32 to 242. Among the included trials, 1,783 patients were included in IP-a; 494 patients were included in IP-b; 160 patients were included in IP-c; 253 patients were included in IP-d; 125 patients were included in IP-e; 177 patients were included in IP-f; 560 patients were included in IP-g; and 212 patients were included in IP-h. The age of the participants ranged from 20.86 to 38 years. The mean pregnancy time of patients ranged from 22.4 to 38 weeks. The period of treatment ranged from 7 to 21 days. Furthermore, among the 38 studies, the outcome of pruritus score was researched in 18 studies. The outcome of TBA was researched in 31 studies. The outcome of ALT was researched in 34 studies. The outcome of AST was researched in 27 studies (Table 3). According to the Cochrane Reviewers’ Handbook, six studies (Wu and Yang, 2016; Liang, 2018; Liu and Yang, 2014; Luo et al., 2019; Zhu and Huang, 2008; Qiu et al., 2017) used a random
number table method to group included studies. A double-blind method was used only in one study (Hu and Yang, 2013). However, other risks of quality of the included studies were not mentioned (Figure 2). Figure 3 shows the network of comparisons for efficacy. IP-a was the public control group, and other intervention plans were directly compared with IP-a (Figure 3).

The Therapeutic Effect Ranking
According to the tests of global inconsistency, the inconsistency model showed that all outcomes had no significant inconsistency ($p > 0.05$) (Table 4). Figure 4 shows the different probabilities when every intervention plan was at different possible rankings. For pruritus score, the probability that IP-f was the best treatment plan was the highest. The probability that IP-a was the worst treatment plan was the highest (Figure 4A). For TBA, the probability that IP-f was the best treatment plan was the highest; the probability that IP-a was the worst treatment plan was the highest (Figure 4B). For ALT, the probability that IP-e was the best treatment plan was the highest; the probability that IP-d was the worst treatment plan was the highest (Figure 4C). For AST, the probability that IP-b was the best treatment plan was the highest; the probability that IP-a was the worst treatment plan was the highest (Figure 4D). Figure 5 shows SUCRA. It shows the different cumulative probabilities when every intervention plan was at different possible rankings. Simultaneously, it also shows the trend of cumulative probability as the ranking changes. Furthermore, we got the ranking of therapeutic effect from the best to worst combining all the corresponding results. For pruritus, the therapeutic effect from the best to worst combining all the corresponding results. For pruritus, the therapeutic effect from the best to worst combining all the corresponding results. For pruritus, the therapeutic effect from the best to worst combining all the corresponding results. For pruritus, the therapeutic effect from the best to worst combining all the corresponding results. For pruritus, the therapeutic effect from the best to worst combining all the corresponding results.

Risk of Bias of Included Trials
The risk of bias for each included trial was evaluated according to the Cochrane risk of bias estimation. According to the Cochrane Reviewers’ Handbook, six studies (Wu and Yang, 2016; Liang, 2018; Liu and Yang, 2014; Luo et al., 2019; Zhu and Huang, 2008; Qiu et al., 2017) used a random number table method to group included studies. A double-blind method was used only in one study (Hu and Yang, 2013). However, other risks of quality of the included studies were not mentioned (Figure 2). Figure 3 shows the network of comparisons for efficacy. IP-a was the public control group, and other intervention plans were directly compared with IP-a (Figure 3).

We chose TBA and ALT to analyze the comprehensive effect of each intervention plan on these two outcomes. According to the network meta-analysis, the comprehensive therapeutic effect of intervention plans could be divided into six levels. The six
levels from the best to worst are as follows: the first level included IP-f; the second level included IP-g, IP-b, and IP-e; the third level included IP-h; the fourth level included IP-c; the fifth level included IP-d; and the sixth level included IP-a (Figure 6).

**Result Clarification of Network Meta-Analysis**

Figure 7 shows the results of the network meta-analyses for the primary outcomes. In the outcome of pruritus score, the therapeutic effect of IP-a was significantly lower than that of IP-f [SMD −2.36, 95% credible interval (CrI) −4.33, −0.39] and IP-g (SMD −2.03, 95% CrI −3.41, −0.64) (Figure 5A). In the outcome of TBA, the therapeutic effect of IP-a was substantially lower than that of IP-f (SMD −1.84, 95% CrI −2.73, −0.94), IP-g (SMD −1.49, 95% CrI −2.24, −0.75), IP-b (SMD −1.49, 95% CrI −2.24, −0.75), IP-h (SMD −1.02, 95% CrI −1.97, −0.08), and IP-d (SMD −0.91, 95% CrI −1.70, −0.13) (Figure 5B). In the outcome of ALT, the therapeutic effect of IP-a was dramatically lower than that of IP-e (SMD −3.31, 95% CrI −6.48, −0.15), IP-f (SMD −2.74, 95% CrI −5.18, −0.30), and IP-b (SMD −2.23, 95% CrI −4.16, −0.31) (Figure 8A). In the outcome of AST, the therapeutic effect
of IP-a was lower than that of IP-b (SMD −2.38, 95% CrI −3.77, −0.99) and IP-f (SMD −2.29, 95% CrI −3.93, −0.65) (Figure 8B).

**DISCUSSION**

The activation of hepatic stellate cells (HSCs) is the key factor in the liver fibrosis process. Scoparone could inhibit Smad3 phosphorylation level; ROS production; and the expression of α-smooth muscle actin (α-SMA), collagen I, and NADPH oxidase (NOX) isoforms in HSC-T6 cells. The above content showed that scoparone had potential therapeutic effects on improving liver fibrosis (Liu and Zhao, 2017). *Gardenia* is also named zhizi in China. Geniposide, quercetin, and crocin are the main active constituents of *Gardenia* (Lai et al., 2020). Among these active constituents, quercetin and crocin could increase the levels of autophagy-related protein (LC3, beclin-1, Atg5, and p-ANPK) in the liver, further reducing fat accumulation in the liver (Lai et al., 2020). For the other active constituent, geniposide had multiple pharmacological activities that were related to liver protection.

**FIGURE 5** | Surface under the cumulative ranking curve (SUCRA) of pruritus score and TBA. Notes: (i): UDCA, (ii): Yinzhihuang oral liquid + UDCA, (iii): salvia injection + UDCA, (iv): Yinchhenhao decoction + UDCA, (v): the similar prescription of Yinchhenhao decoction 1 + UDCA, (vi): the similar prescription of Yinchhenhao decoction 2 + UDCA, (vii): the similar prescription of Yinchhenhao decoction 3 + UDCA, and (viii): other traditional Chinese medicine prescriptions + UDCA. (A) Pruritus score, (B) TBA.
A research found that geniposide could inhibit STAT3/Sp1-dependent VEGF overexpression in HCC angiogenesis. The mechanism was related to the direct suppression effect of geniposide on TLR4/MyD88 activation (Zhang C. et al., 2020). Rheubarb is also named dahuang in China. Rheubarb also contains many active constituents with pharmacological activities such as rhein, emodin, and danthron (Xian et al., 2020; Zhang N. et al., 2020; Ma et al., 2021). Rhein is the main active constituent of Rheubarb with pharmacological activity. A research found that rhein helped maintain bile acid homeostasis in rats. The mechanism was associated with upregulating the expression of Mrp3 mRNA and FXR mRNA (Xian et al., 2020). ICP is frequently accompanied by the damage to the liver. Simultaneously, abnormal liver function indicators are the main manifestation. Therefore, the pharmacological activities of Yinchenhao, Zhizi, and Dahuang explain well why Yinchenhao decoction could improve cholestasis.

According to the result of our research, the probability that IP-f [the change of Yinchenhao decoction 2 (A. capillaris Thunb >15 g, Gardenia >9 g, and Rheubarb <5 g) + UDCA] was the best therapeutics was the highest in eight therapies. We found the dose of Rheubarb was reduced in IP-f. Combined with the pharmacological activities of A. capillaris Thunb, Gardenia, and Rheubarb, the main pharmacological activities of A. capillaris Thunb and Gardenia included anti-inflammatory, anti-oxidation, and anti-fibrotic (Han JM. et al., 2013; Hui et al., 2020; Shen et al., 2020). All of these play an important role in protecting the liver. Relative to A. capillaris Thunb and Gardenia, Rheubarb can also reduce the level of bile acid (Xian et al., 2020).

### Table 1: Primus score comparison

| Outcome | Intervention plan | MD (95% CI) |
|---------|------------------|-------------|
| BKA     | UDCA             | -0.89 (0.22, 3.89) |
| ALB     | UDCA             | -0.90 (2.02, 3.89) |
| ALT     | UDCA             | -0.89 (2.02, 3.89) |
| AST     | UDCA             | -0.89 (2.02, 3.89) |
| TBA     | UDCA             | -0.89 (2.02, 3.89) |

### Table 2: League table of network meta-analysis of pruritus score, TBA, ALT, and AST

Intervention plans are in order of each outcome ranking basing on SUCRAs. The table should be read from the top left to the bottom right. Notes: a: UDCA; b: Yinzhuhuang oral liquid + UDCA; c: saliva injection + UDCA; d: Yinchenhao decoction + UDCA; e: the similar prescription of Yinchenhao decoction 1 + UDCA; f: the similar prescription of Yinchenhao decoction 2 + UDCA; g: the similar prescription of Yinchenhao decoction 3 + UDCA; h: other traditional Chinese medicine prescriptions + UDCA.

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**FIGURE 6** | Sequence analysis of comprehensive efficacy. From the top right to bottom left, the comprehensive effect gradually decreases. Notes: a: UDCA, b: Yinzhuhuang oral liquid + UDCA, c: saliva injection + UDCA, d: Yinchenhao decoction + UDCA, e: the similar prescription of Yinchenhao decoction 1 + UDCA, f: the similar prescription of Yinchenhao decoction 2 + UDCA, g: the similar prescription of Yinchenhao decoction 3 + UDCA, and h: other traditional Chinese medicine prescriptions + UDCA.

**FIGURE 7** | League table of network meta-analysis of pruritus score, TBA, ALT, and AST. Intervention plans are in order of each outcome ranking basing on SUCRAs. The table should be read from the top left to the bottom right. Notes: a: UDCA; b: Yinzhuhuang oral liquid + UDCA; c: saliva injection + UDCA; d: Yinchenhao decoction + UDCA; e: the similar prescription of Yinchenhao decoction 1 + UDCA; f: the similar prescription of Yinchenhao decoction 2 + UDCA; g: the similar prescription of Yinchenhao decoction 3 + UDCA; h: other traditional Chinese medicine prescriptions + UDCA.
et al., 2020). At the same time, we know the level of bile acid in the human body is dynamically balanced. Therefore, we guessed using too much *Rhubarb* could break the dynamic balance. Also, the level of bile acid is harmful whether it is too high or too low. This can be seen as an explanation why the dose of *Rhubarb* is reduced in IP-f. The probability that IP-a (UDCA only) was the worst therapeutics was the highest in eight therapies. At the same time, the result showed the intervention plans of combination medication are generally better than UDCA alone in terms of improving pruritus and the level of TBA, ALT, and AST. It was only an accident that IP-a was better than IP-d in terms of improving the level of ALT. The research process is as follows, at first, we calculated the probability of different intervention plans at different possible rankings. In terms of improving pruritus and the level of TBA and AST, the probability that IP-f is the best therapeutics is the highest. At the same time, in terms of improving the level of ALT, although the probability that IP-f was the best therapeutics was not the highest, we found the probability that IP-f was the second-ranked therapeutics was the highest. Not only that, IP-f still had the highest probability of being the best therapy compared with other therapies except IP-e. In addition, the result showed that the probability that IP-a was
the worst therapeutics was the highest in terms of improving pruritus and the level of TBA and AST. In terms of improving the level of ALT, the probability that only IP-d was the worst therapy was higher than that of IP-a. Furthermore, we chose the outcomes of ALT and TBA to conduct a comprehensive analysis. According to the result, the comprehensive therapeutic effect of intervention plans was divided into six levels by our group. The six levels from the best to worst are as follows: the first level included IP-f; the second level included IP-g, IP-b, and IP-e; the third level included IP-h; the fourth level included IP-c; the fifth level included IP-d; and the sixth level included IP-a. The result showed that IP-f still is the best therapeutic. Finally, the league table was used to show the comparison result between two intervention plans. The result showed that the quality of evidence was low in most comparisons. In the outcome of pruritus score, the therapeutic effect of IP-a was significantly lower than that of IP-f (SMD $-2.36$, 95% CrI $-4.33$, $-0.39$) and IP-g (SMD $-2.03$, 95% CrI $-3.41$, $-0.64$). In the outcome of TBA, the therapeutic effect of IP-a was significantly lower than that of IP-f (SMD $-1.84$, 95% CrI $-2.73$, $-0.94$), IP-g (SMD $-1.49$, 95% CrI $-2.24$, $-0.75$), IP-b (SMD $-1.49$, 95% CrI $-2.24$, $-0.75$), IP-h (SMD $-1.02$, 95% CrI $-1.97$, $-0.08$), and IP-d (SMD $-0.91$, 95% CrI $-1.70$, $-0.13$). In the outcome of ALT, the therapeutic effect of IP-a was significantly lower than that of IP-e (SMD $-3.31$, 95% CrI $-6.48$, $-0.15$), IP-f (SMD $-2.74$, 95% CrI $-5.18$, $-0.30$), and IP-b (SMD $-2.23$, 95% CrI $-4.16$, $-0.31$). In the outcome of AST, the therapeutic effect of IP-a was lower than that of IP-b (SMD $-2.38$, 95% CrI $-3.77$, $-0.99$) and IP-f (SMD $-2.29$, 95% CrI $-3.93$, $-0.65$).

This study used a novel method to divide Chinese prescriptions into different groups. The method contributes to systematic research for Chinese prescriptions. This study systematically researched and compared different Chinese prescriptions and patent medicine combine with UDCA in the treatment efficacy for intrahepatic cholestasis of pregnancy. In this study, the result showed the probability of every intervention plan at different possible rankings. Simultaneously, the result also showed the comparison between different intervention plans. More than that, an interesting result was found. We found the similar prescription of Yinchenhao decoction 2 (A. capillaris Thumb $>15$ g, Gardenia $>9$ g, and Rhubarb $<5$ g + UDCA] was the best therapeutics was the highest in eight therapies. In addition, according to the result, this study indicated that the proportion of medicine used is different from the traditional proportion of Yinchenhao decoction. Therefore, the dose of IP-f might be a beneficial therapeutic method for the clinical medication of ICP.

**CONCLUSION**

According to the result of our research, the intervention plans of combination medication were generally better than UDCA alone in terms of improving pruritus and the level of TBA, ALT, and AST. However, IP-a was better than IP-d in terms of improving the level of ALT. Furthermore, the probability that IP-f [the similar prescription of Yinchenhao decoction 2 (A. capillaris Thumb $>15$ g, Gardenia $>9$ g, and Rhubarb $<5$ g) + UDCA] was the best therapeutics was the highest in eight therapies. In addition, according to the result, this study indicated that the proportion of medicine used is different from the traditional proportion of Yinchenhao decoction. Therefore, the dose of IP-f might be a beneficial therapeutic method for the clinical medication of ICP.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

**AUTHOR CONTRIBUTIONS**

YJ conducted data analysis and drafted the manuscript. HL and DS designed the study, interpreted the results, and drafted the manuscript. PY and NX collected the data, and assessed the methodological quality of included studies. YC and WZ assisted with the design of PICOs and interpreted the results. QH conceived the study and reflected on the study implementation. JW provided the methodological guidance and revised the manuscript. YL strictly modified the proof version. XM and YZ conceived the study, designed the PICOs, and interpreted the study results. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found at: https://www.frontiersin.org/articles/10.3389/fphar.2021.774884/full#supplementary-material
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