# Evaluation of outcomes reported in randomized controlled trials for herbal remedies for adults with chronic hepatitis C

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Running title: Herbal remedies for adults with chronic hepatitis C.

**Abstract** *Background:* Herbal remedies have been widely utilized in treating chronic hepatitis C (CHC) worldwide. Selecting appropriate outcomes to reflect both beneficial and harmful effects is a crucial step in designing randomized controlled trials (RCTs). This study evaluated the outcomes reported in RCTs on herbal remedies for CHC with comparison to the core outcomes recommended by the Cochrane Hepato-Biliary Group (CHBG), to check the consistency of the outcomes and to provide recommendation for future researches.

*Methods:* A systematic literature search was conducted in Western and Chinese databases to identify RCTs on herbal remedies for adults with CHC. For each trial, all the outcomes reported in the results section were collected. Comparison between trial outcomes and CHBG core outcomes were evaluated and summarized with descriptive statistics.

*Results:* A total of 116 RCTs involving 9154 participants were included; 27 outcomes were identified. Commonly reported outcomes included alanine aminotransferase (64 trials, 55.2%), adverse events (58 trials, 50.0%), and end-of-treatment virological response (50 trials, 43.1%). All trials indicated that the herbal remedies under investigation had a positive effect and was markedly more effective than the control. Nearly half of the trials reported that the combination of herbal medicine and antiviral drugs could ameliorate adverse events. Very few trials reported primary core outcomes relating survival and quality of life. The most frequently reported core outcomes are non-serious adverse events (54 trials, 46.6%), viral response (27 trials, 23.3%), and biochemical response (24 trials, 20.7%).

*Conclusion:* The variation and inconsistency in trial outcomes impedes research synthesis efforts, and indicate the need for comparable outcomes through the development of core outcome sets in CHC. The low concordance of outcome reporting could be improved by following CHBG core outcomes recommendation.

**KEYWORDS**
Chronic hepatitis C;
Herbal;
Core outcome set;
Randomized controlled trial;
Cochrane Hepato-Biliary Group

# 1.0 Introduction

Hepatitis C virus (HCV) affects an estimated 180 million people globally,[1] and is a known cause for chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[2,3] As in many other conditions, patients with HCV infection often seek complementary and alternative medicine (CAM) when they have experienced dissatisfaction or drug resistance to conventional therapy.[4] Herbal intervention is a popular CAM therapy being frequently and widely used in Asia,[5] and is playing an important role in CHC management in China. Herbal remedies include single herbal extracts (e.g., silymarin, oxymatrine), which usually extracted from native plants, and multiple-herbal formulas (e.g., classical formula, prescription modification according to the pattern identification, self-created herbal prescription from individual hospital). It could be administered in tablet, capsule, pill, decoction, or injection. Over recent decades, herbal remedies have been commonly used worldwide to treat various liver diseases in clinical practice due to their anti-inflammatory and antifibrotic effects, long-lasting liver protection after treatment, low cost, natural way of healing, and few adverse events.[6,7] There has also been a substantial increase in effectiveness and efficacy studies of herbal remedy displaying hepato-protective effects against hepatitis C.[8,9] The volume of publications indicate high scientific interest in this field. When stakeholders seek guidance from clinical research to make evidence-based decisions, the outcomes reported could become an essential role in drawing a more forceful and persuasive conclusion.[10–12] Ideally, a meta-analysis will help answer the question of what is the best herbal remedy for CHC, or what are the significant beneficial or harmful effects. This requires the same outcome reporting and measurements. However, previously published literature in herbal remedies for CHC highlighted the lack of uniform outcome reporting and measurements in research data.[13,14]

The variations in outcome reporting limits research transparency, and may be misleading due to incomparability of trials, favoring ineffective interventions or underestimating adverse events. This contributes to the waste identified in research.[15] It is crucial to accurately measure and report the outcomes in a more consistent and comparable way.[16,17] The aforesaid issue can be solved by the establishment of a core outcome set (COS), which is a set of minimum agreed and standardized collection of outcomes that should be measured and reported for a specific clinical area for all trials.[18] COS has been endorsed as a mean to collect the outcomes in a more comparable way and to reduce outcome heterogeneity, as well as to increase the relevance of research and reduce research waste through the involvement of key stakeholders (e.g., health-care professionals, trialists, patients) in its development.[19] Currently, there is no

consensus among these stakeholders in what and how outcomes should be measured and reported in CHC randomized controlled trials (RCTs). But core outcomes for CHC recommended by Cochrane Hepato-Biliary Group (CHBG) is available online; Eight core outcomes have been recommended for use in systematic reviews (SRs) of CHC randomized clinical trials: all-cause mortality or hepatitis C-related morbidity, health-related quality of life (QoL), serious adverse events (that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect), mortality due to hepatitis C-related liver disease, non-serious adverse events (any untoward medical occurrence in a participant or clinical investigation participant that does not meet the above criteria for a serious adverse event is defined as a non-serious adverse events), number of participants without histological improvement, number of participants without sustained virological response (SVR), and number of participants without normalization of transaminases.[20] Obviously, the core outcomes recommended by CHBG is helpful for Cochrane SRs or other SRs in standardizing in the selection of outcomes for the summary of finding tables which summarize the evidence for important and critical outcomes.[21]

Nevertheless, unlike conventional intervention (e.g., interferon, direct antiviral agents) mainly focused in virological response and disease activity, herbal intervention addressed long-term adverse effects and QoL.[22,23] Our study aimed to summarize and display the outcomes reported in RCTs using herbal remedies for CHC, with comparison to CHBG core outcomes, and to serve as a basis for the future development of COS of integrity of conventional and herbal interventions on treatment of CHC.

# 2.0 Methods

### 2.1 Search strategy

We conducted a literature search of the following electronic databases: Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, BIOSIS, SinoMed, China Network Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), and Wanfang Database, from their inception date onwards until August 29, 2018.

Our search strategy included the MeSH headings chronic hepatitis C, herbal medicine, Chinese medicine, silymarin, glycyrrhizin, oxymatrine, and plant materials. The reference lists of included studies were also searched for additional studies that may not be identified through database searches. SRs were cross-checked for missing studies. The full search strategy is presented in Supplementary Data 1.

### 2.2 Eligibility criteria and study selection

Eligible criteria were predetermined: (i) RCTs irrespective of blinding, language, year, and publication status; (ii) RCT was designed to compare herbal remedy with no intervention, placebo, non-specific interventions (vitamins), antiviral drugs either

recommended in guidelines (e.g. interferon, ribavirin, and direct antiviral agents),[22,24–26] or commonly used drugs in clinical practice with potential antiviral effects. Co-interventions were allowed in the experimental and control groups provided that the co-interventions were administered equally to all the intervention groups of a trial; (iii) target population were adults with CHC, concomitant diseases such as cirrhosis, severe fibrosis, and hepatocellular carcinoma were also included; (iv) reporting at least one outcome.

Two authors (SBL and YXS) independently screened titles and abstracts for inclusion of potentially eligible studies. For multiple publications of the same trial, only the largest study with most data was included. The two authors resolved any difference in opinion through discussion. A third author (YQY) enabled a consensus when a disagreement still persisted.

### 2.3 Data collection and management

Two authors (SBL and YXS) independently performed data extraction for eligible trials using a pre-piloted data collection form. The publication language, sample size, age, herbal interventions were collected to present the general characteristics of the included trials. Both dichotomous data and continuous data as reported anywhere in the article's results text, tables, or figures were collected.

Serum HCV RNA levels measured at various time points, including rapid virological response (RVR), early virological response (EVR), end-of-treatment virological response (ETVR), sustained virological response (SVR), were collected respectively as reported in the trials. Disagreements were resolved through discussion, or a third author (YQY) arbitrated if a variable was unclear.

For each trial, we displayed all the outcomes reported in the results section, and presented the consistency between trial outcomes and CHBG core outcomes. We counted the number of core outcomes reported in each trial, and the proportion of trials that measured each core outcome. Additionally, the percentage of overlap in core outcomes in the RCTs and CHBG recommendations were reported.

### 2.4 Assessment of methodological quality

Two authors (YQY and NL) independently assessed the methodological quality in the included trials using the Cochrane "Risk of bias" tool.[27] This includes six main aspects: allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective data reporting, and other bias. We classified methodological quality as at overall low risk of bias only if all of the risk of bias sources described above were classified as at low risk of bias. We classified methodological quality as at overall high risk of bias if any of the risk of bias sources described above were classified as unclear risk of bias or high risk of bias.

## 3.0 Results

As shown in Fig. 1, we identified 1726 publications; after duplication, 1320 records remained and were included for screening. Title and abstract screening resulted in the inclusion of 308 studies for full-text screening.

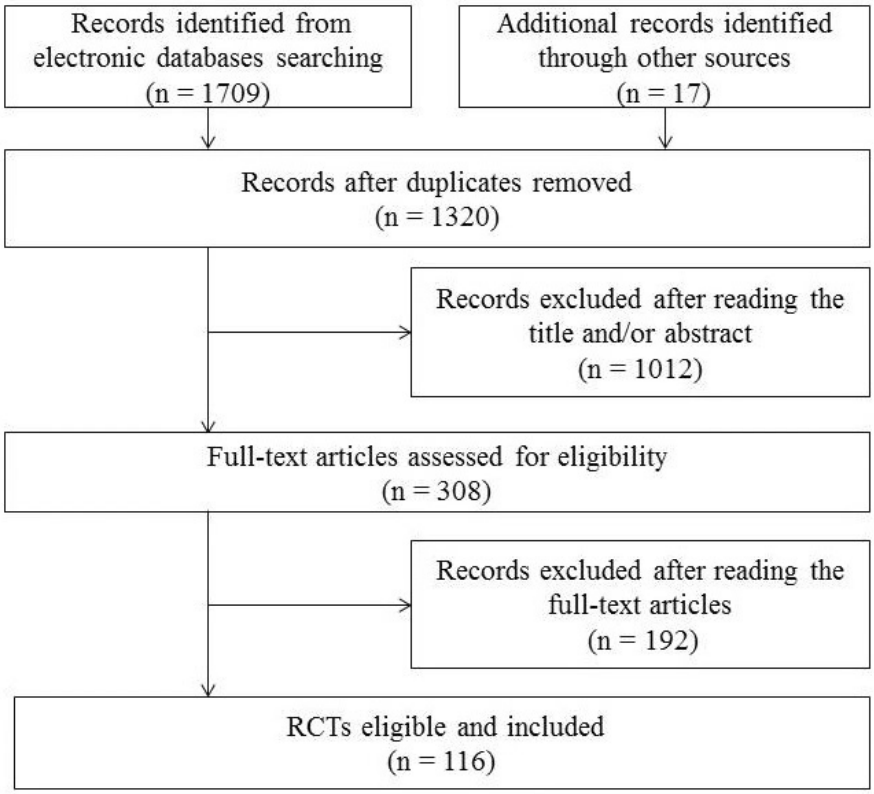


**Figure 1** Flow diagram of literature search.

### 3.1 General characteristics

One hundred and sixteen RCTs, reporting data from 9154 adult participants were included ranging from 18 to 79 years old. The first RCT for herbal intervention for chronic hepatitis C was published in 1993. There were 15 (12.9%) studies published in English, four of which were on Chinese medicine formulas, one was on Japanese herbal formula, and 10 were on herbal extracts. The rest were published in Chinese, 69 of which were on Chinese medicine formulas, and 32 were on herbal extracts. The included herbal remedies could be divided into three main categories: Chinese medicine formula (73 trials, 62.9%), Japanese herbal medicine (1 trial, 0.9%), and single herbal extract (42 trials, 36.2%) (Supplementary Data 2).

### 3.2 Risk of bias

The risk of bias of included trials is summarized in Table 1. Following the Cochrane "Risk of bias" tool assessment, the majority of trials are poorly designed and with low-quality methodology. All included RCTs were classified as trials with overall high risk of bias.

**Table 1** The risk of bias of included studies.

| Domains | Low (%) | High (%) | Unclear (%) |
|---|---|---|---|
| Allocation sequence generation | 21 (18.1) | 95 (81.9) | 0 |
| Allocation concealment | 3 (2.59) | 112 (96.55%) | 1 (0.86) |
| Blinding | 16 (13.79) | 95 (81.9) | 5 (4.31) |
| Incomplete outcome data | 18 (15.52) | 7 (6.03) | 91 (78.45) |
| Selective data reporting | 110 (94.83) | 1 (0.86) | 5 (4.31) |
| Other bias | 113 (97.41) | 3 (2.59) | 0 |

### 3.3 Outcomes reported in the included RCTs

A total of 27 unique outcomes were identified, and were inconsistently reported and measured among the 116 RCRs. Continuous variables were presented as mean with/without standard deviation, and dichotomous variables were described as number or percentage. We summarized all the reported outcomes and presented the results with descriptive statistics (Table 2).

**Table 2** Outcomes reported in 116 trials evaluating herbal remedy for CHC.

| Outcomes | Number of RCTs (%) |
|---|---|
| Total bilirubin | 22 (19.0) |
| Albumin | 5 (4.3) |
| Viral load | 22 (19.0) |
| Rapid virological response | 2 (1.7) |
| Early virological response | 20 (17.2) |
| End-of-treatment virological response | 50 (43.1) |
| Sustained virological response | 27 (23.3) |
| Haluronic acid | 23 (19.8) |
| Human laminin | 22 (19.0) |
| Procollagen III | 23 (19.8) |
| Collagen type IV | 18 (15.5) |
| Historical activity index | 2 (1.7) |
| Abdominal ultra-sonograms | 6 (5.1) |
| Quantitative serum ALT levels | 64 (55.2) |
| Normalization rate of ALT | 23 (19.8) |
| Quantitative serum AST levels | 43 (37.1) |
| Normalization rate of AST | 6 (5.2) |
| Liver fibrosis SSS score | 1 (0.9) |
| Health-related quality of life | 7 (6.0) |
| Non-serious adverse events | 58 (50.0) |
| Serious adverse events | 4 (3.4) |
| Mortality | 2 (1.7) |
| Hematological tests | 17 (14.7) |

| | |
|---|---|
| Immunological tests | 4 (3.4) |
| Pharmacokinetics | 1 (0.9) |
| Clinical symptoms | 16 (13.8) |
| Kidney function tests | 3 (2.6) |

**Abbreviations:** ALT: alanine aminotransferase, AST: aspartate aminotransferase, SSS: semiquantitative scoring system.

Commonly reported outcomes included quantitative serum alanine aminotransferase (ALT) level (64 trials, 55.2%), type and number of participants with adverse events (58 trials, 50%), number of participants achieved ETVR (50 trials, 43.1%), quantitative serum aspartate aminotransferase (AST) level (43 trials, 37.1%), number of participants achieved SVR (27 trials, 23.3%), and number of participants with normalization of ALT level (23 trials, 19.8%). The least reported outcomes (≤five trials) were albumin (five trials, 4.3%), serious adverse events (four trials, 3.4%), immunological tests (four trials, 3.4%), kidney function tests (three trials, 2.6%), RVR (two trials, 1.7%), historical activity index (two trials, 1.7%), liver fibrosis semiquantitative scoring system score (one trial, 0.9%), mortality (one trial, 0.9%), and pharmacokinetics (one trial, 0.9%).

Serious adverse events were reported in four English-published trials (3.4%), including death from hepatocellular carcinoma (n = 1), withdrew because of severe irritability (n = 3), and withdraw because of severe depression (n = 8), respectively. One trial indicates there were no serious adverse events (n = 0). QoL was reported by seven trials published in English (6%) using seven different outcome measures including Quality of Life Questionnaire (HQLQ), the Short-Form 36 (SF-36), Self-rating Depression Scale (SDS), the Center for Epidemiologic Studies-Depression (CES-D) Scale, self-administered quality-of-life WHOQOL-BREEF, Chronic Liver Disease Questionnaire (CLDQ), and The Arizona Sexual Experience Scale (ASEX). The term “therapeutic efficacy”, described as a “compound outcome”, was reported in 39 trials (33.6%), and the measurements were found to be variable. Some trials defined the “therapeutic efficacy” as the elimination of clinical symptoms plus the normalization of biochemical response; some defined the “therapeutic efficacy” as loss of detectable HCV RNA (and/or serum anti-HCV) plus normalization of serum ALT level; some used self-defined scoring systems.

All trials indicated that herbal intervention had a positive effect and were significantly more effective than the control group. Nearly half of the trials reported that the combination of herbal remedy and antiviral drugs can alleviate adverse events (e.g., alleviate myelosuppression); 23 trials (19.8%) reported that herbal intervention can delay the progression of liver fibrosis; seven trials (6.0%) used patient reported outcomes, and showed herbal intervention greatly improved clinical symptoms (e.g., fatigue, abdominal distention).

### 3.4 Comparison with CHBG core outcomes

Tables 3 and 4 presented the comparison between outcomes reported in RCTs and outcomes recommended by CHBG. Nearly one-third of the trials reported none of the

eight CHBG core outcomes; 46 trials (39.7%) only reported one of the CHBG core outcomes; 23 trials (19.8%) reported two of the CHGB core outcomes; six trials (5.2%) reported three of the CHBG core outcomes; four trials (3.4%) reported four of the CHBG core outcomes, which was the biggest number of CHGB core outcomes reported among the included 116 trials. The most frequently reported core outcome by trialists is non-serious adverse events (54 trials, 46.6%). Although most of the trials reported serum HCV RNA load, but only in 27 trials (23.3%), HCV RNA was measured at 12 and 24 weeks after end of treatment and reported in dichotomous data as CHBG defined. The third frequently reported core outcome was the number of participants without normalization of transaminases (24 trials, 20.7%). Three primary core outcomes, all-cause mortality/hepatitis C-related morbidity, health-related QoL, and serious adverse events were reported in two trials, seven trials, and four trials respectively. Two trials reported the number of participants without histological improvement, and both of them were measured with historical activity index. None of the trials reported hepatitis C-related mortality.

**Table 3** Number of trials reported on the CHBG core outcome.

| CHBG core outcomes | Trials (%) |
|---|---|
| All-cause mortality or hepatitis C-related morbidity | 2 (1.7) |
| Health-related quality of life | 7 (6.0) |
| Serious adverse events | 4 (3.4) |
| Mortality due to hepatitis C-related liver disease | 0 (0) |
| Non-serious adverse events | 54 (46.6) |
| Number of participants without histological improvement | 2 (1.7) |
| Number of participants without sustained virological response | 27 (23.3) |
| Number of participants without normalisation of transaminases | 24 (20.7) |

CHBG: Cochrane Hepato-Biliary Group.

**Table 4** Number of CHBG core outcome reported in RCTs.

| Number of CHBG core outcomes | Trials (%) |
|---|---|
| Number of trials reported zero core outcome | 37 (31.9) |
| Number of trials reported one core outcome | 46 (39.7) |
| Number of trials reported two core outcome | 23 (19.8) |
| Number of trials reported three core outcome | 6 (5.2) |
| Number of trials reported four core outcome | 4 (3.4) |

CHBG: Cochrane Hepato-Biliary Group.

# 4.0 Discussion

## 4.1 Main findings

With the development of evidence-based medicine and the establishment of the Oxford Evidence Pyramid, SRs, meta-analyses, and RCTs have become the best source of evidence for modern medical guidelines and clinical practice. The published RCTs on

herbal remedy for CHC showed the methodological quality are overall poor, and a huge heterogeneity of the outcome reporting and measurements, which may limit the between-study comparison and delay the progress of evidence collection.

Many Chinese trials used composite outcomes based on patient reported questionnaires about efficacy or symptoms relief, all with varying definitions. Different trialists encompassed the same concept (e.g. therapeutic efficacy) with different components, leading to variation in the definition criteria. Moreover, these composite outcomes lack reliability, and therefore they are not accepted internationally. The heterogeneity between definitions and the unreliability of composite outcomes make it difficult to synthesize and compare the beneficial and harmful effects, thus the RCT results could not be meta-analyzed, or the RCT results for different interventions could not be compared horizontally. Only seven English-published trials used international scale to measure QoL. The advantages of traditional Chinese medicine such as improving clinical symptoms, QoL, and reduce side-effects were not well reflected in the included trials. Obvious discrepancies between outcomes reported in RCTs and core outcomes recommended by CHBG for SRs were observed. Outcomes in the randomized trials on CHC should be primarily related to survival and disease progression according to CHBG, but the majority of current trials failed to comprehensively addressed mortality, liver-related morbidity, or QoL.

The lack of consensus regarding the measurement and reporting of outcomes affect trial design, conduct, and analysis.[28] Therefore, it is necessary to establish the minimum outcomes that conforms to the characteristics of traditional Chinese medicine (e.g., herbal remedy), and to develop a COS that should be collected in a standardized way and reported consistently in any publications.[29,30] COS has been internationally regarded as a means to reduce outcome heterogeneity, thus to reduce research waste among similar studies.

### 4.2 Strength and limitations

Our study used a robust search strategy to collect outcomes reported internationally and nationally in RCTs of herbal remedy for CHC. To our knowledge, this is the first study to systematically overview the outcomes reported in trials and compare them with the core outcomes recommended by CHBG. This study can serve as a basis for developing a COS for clinical trials and researchers for CHC and herbal remedies.

There are limitations that should be considered when interpreting these results. First, we included published RCTs, but did not include outcomes reported from unpublished trials and observational studies. Second, we focused on trials evaluating herbal remedies, but did not evaluate outcomes reported using other pharmacological interventions. Third, many of the included trials ambiguously defined composite outcomes, making it difficult to make judgments about whether differences were accurately presented.

### 4.3 Implication for practice and research

Trialists and journal editors should be reminded that most individual RCTs may well

be incorporated into subsequent SRs. Outcomes that did not reflect the priority of stakeholder groups or did not match internationally recommended core outcomes, may not always matter when interpreting a single trial result, but can have significant impact when synthesizing data of multiple randomized trials (e.g. meta-analysis).[31]

Protocols should be made publicly available.[32,33] Prespecified outcomes can help protect against data dredging, in which only positive or favorable outcomes are reported, while negative or unfavorable outcomes are obscured.[18] We suggest that journal editors be more vigilant and mandatory about registration policies when they receive the RCT submission. This may help alleviate the heterogeneity of future outcome reporting.

It is important to acknowledge the therapeutic advantages of herbal remedy and antiviral drugs. The long-term effect in anti-inflammatory and liver protecting relates to functional items (e.g., physiological symptoms) and composite measures of QoL.[34] Internationally recognized QoL scales (e.g., SF-36, CLDQ) should be measured and reported instead of patient reported questionnaires designed by individual trialists/hospitals.

The Cochrane SRs form the highest level of evidence and are the most valuable source of information for health interventions. Therefore, until a COS is finalized, we encourage trialists and researchers select prespecified outcomes with reference to the core outcomes recommended by CHBG. This will be effective in improving the scientific possibility of comparing and summarizing outcomes from different trials and will maximize the research contribution of SRs and meta-analyses.

Core outcomes are a recommended set of minimum outcomes that should be reported. However, it should be acknowledged that trialists and researchers, depending on the scope and the objective of the study, are not limited to report only these core outcomes.

## 5.0 Conclusion

The variation in outcomes measurements and reporting leads to multidirectional research, and makes the combination and comparability of the results impossible because of outcome heterogeneity. There is an urgent need for accurate reporting and measurement of consistent comparable outcomes through the development of a COS in CHC. The low concordance of outcome reporting could be improved by following the core outcome recommendation from CHBG.

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**Conflicts of interest**

The authors report no competing interest.

**CRediT authorship contribution statement**

**Yuqian Yan:** Conceptualization, methodology, formal analysis, and writing − original draft. **Jianping Liu:** Conceptualization, supervision, funding acquisition, and writing − review & editing. **Ning Liang:** Data curation, methodology, formal analysis, and writing − review & editing. **Shibing Liang:** Investigation and data curation. **Yuxin Sun:** Investigation and data curation. **Nicola Robinson:** Conceptualization and writing − review & editing.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at

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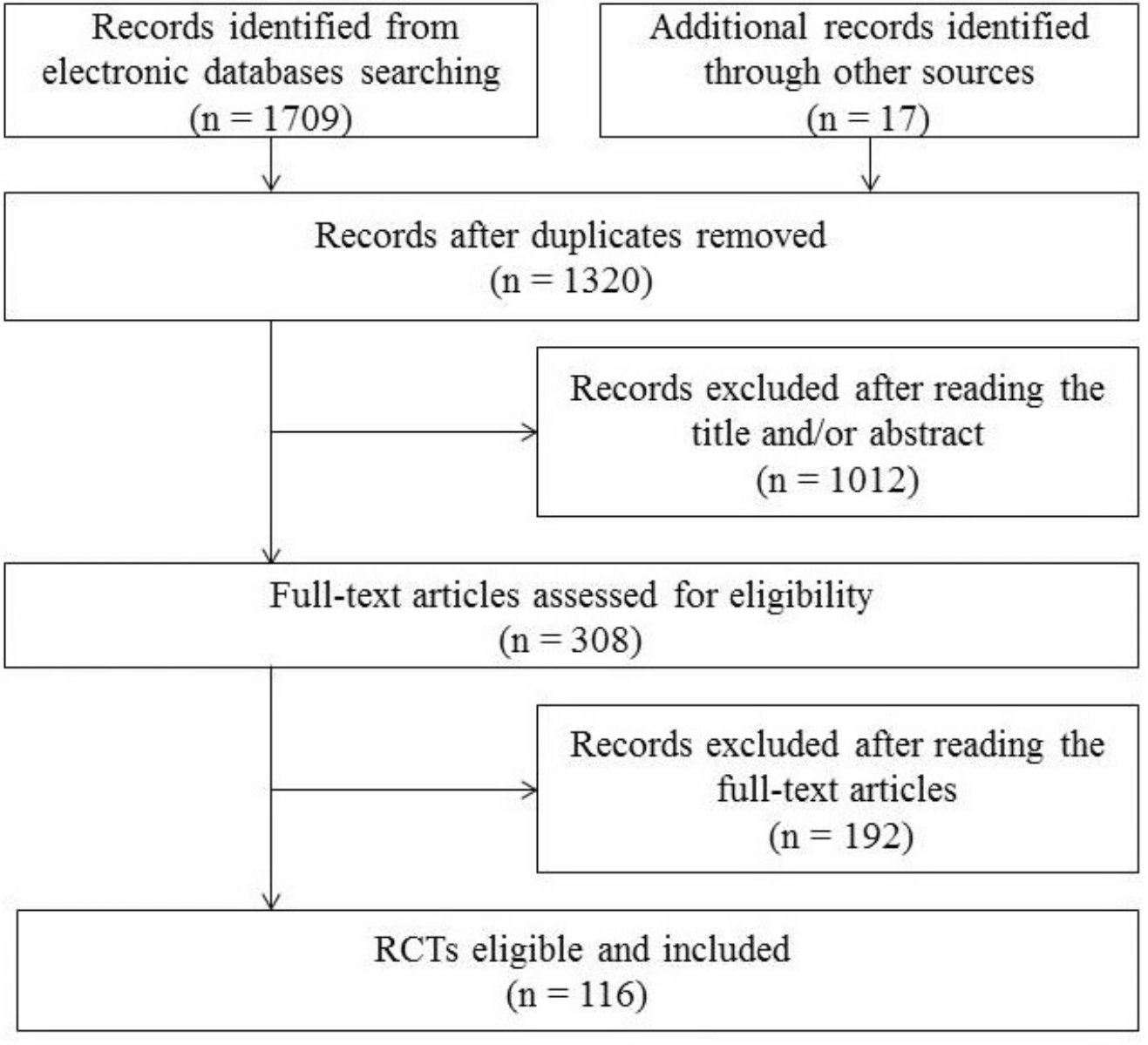
Records identified from electronic databases searching (n = 1709)
Additional records identified through other sources (n = 17)
Records after duplicates removed (n = 1320)
Records excluded after reading the title and/or abstract (n = 1012)
Full-text articles assessed for eligibility (n = 308)
Records excluded after reading the full-text articles (n = 192)
RCTs eligible and included (n = 116)

| Category | Herbal remedies | RCTs (%) |
|---|---|---|
| Chinese medicine formula | TCM decoction without name | 28 (24.1) |
| | *Binggan Heji* Decoction | 3 (2.9) |
| | *Xiao Chai Hu* Decoction | 3 (2.9) |
| | *Song Zhi* Pill | 3 (2.9) |
| | *Diqin Guben* Oral Liquid | 3 (2.9) |
| | *Chaihu Shugan* Powder | 3 (2.9) |
| | *Er Gu* Decoction | 2 (1.7) |
| | *Fufang Danshen* Tablet | 2 (1.7) |
| | *Qishen Erlian* Decoction | 2 (1.7) |
| | *Qi Zhu* Granule | 2 (1.7) |
| | *Jianpi Moji* Decoction | 2 (1.7) |
| | *Anluo Huaxian* Pill | 1 (0.9) |
| | *Baogan Fugan* Pill | 1 (0.9) |
| | *Bing Gan* Granule | 1 (0.9) |
| | *Binggan Yihao* Decoction | 1 (0.9) |
| | *Gan Shu* Capsule | 1 (0.9) |
| | *Shenqi Fugan* Capsule | 1 (0.9) |
| | *Chai Shao Liu Jun Zi* Decoction | 1 (0.9) |
| | *Dahuang Shuchong* Pill | 1 (0.9) |
| | *Fuzhen Huayu* Capsule | 1 (0.9) |
| | *Yin Chen Hao* Decoction | 1 (0.9) |
| | *Shu Gan* Capsule | 1 (0.9) |
| | *Li Gan Long* Granule | 1 (0.9) |
| | *Hu Gan Ning* Tablet | 1 (0.9) |
| | *Shugan Jianpi* Decoction | 1 (0.9) |
| | *Jianpi Huoxue* Decoction | 1 (0.9) |
| | *Jianpi Bushen* Decoction | 1 (0.9) |
| | *Jiedu Huagan* Decoction | 1 (0.9) |
| | *Ganpi Tiaobu* Decoction | 1 (0.9) |
| | CH100 Tablet | 1 (0.9) |
| | *Kuan Sin Yin* Decoction | 1 (0.9) |
| Japanese herbal medicine | Ninjinyoeito Granule | 1 (0.9) |
| Single herbal extract | Oxymatrine Capsule | 5 (4.3) |
| | Oxymatrine Injection | 19 (16.4) |
| | Glycyrrhizin Tablet | 2 (1.7) |
| | Glycyrrhizin Injection | 7 (6) |
| | Glycyrrhizin Capsule | 1 (0.9) |
| | Silymarin Tablet | 5 (4.3) |
| | Silibinin Capsule | 2 (1.7) |
| | Silibinin Injection | 1 (0.9) |

**Supplementary Table 2** Herbal remedies in the included RCTs.

TCM: traditional Chinese medicine.

**Table 1** The risk of bias of included studies.

| Domains | Low (%) | High (%) | Unclear (%) |
|---|---|---|---|
| Allocation sequence generation | 21 (18.1) | 95 (81.9) | 0 |
| Allocation concealment | 3 (2.59) | 112 (96.55%) | 1 (0.86) |
| Blinding | 16 (13.79) | 95 (81.9) | 5 (4.31) |
| Incomplete outcome data | 18 (15.52) | 7 (6.03) | 91 (78.45) |
| Selective data reporting | 110 (94.83) | 1 (0.86) | 5 (4.31) |
| Other bias | 113 (97.41)2 | 3 (2.59) | 0 |

**Table 2** Outcomes reported in 116 trials evaluating herbal remedy for CHC.

| Outcomes | Number of RCTs (%) |
|---|---|
| Total bilirubin | 22 (19.0) |
| Albumin | 5 (4.3) |
| Viral load | 22 (19.0) |
| Rapid virological response | 2 (1.7) |
| Early virological response | 20 (17.2) |
| End-of-treatment virological response | 50 (43.1) |
| Sustained virological response | 27 (23.3) |
| Haluronic acid | 23 (19.8) |
| Human laminin | 22 (19.0) |
| Procollagen III | 23 (19.8) |
| Collagen type IV | 18 (15.5) |
| Historical activity index | 2 (1.7) |
| Abdominal ultra-sonograms | 6 (5.1) |
| Quantitative serum ALT levels | 64 (55.2) |
| Normalization rate of ALT | 23 (19.8) |
| Quantitative serum AST levels | 43 (37.1) |
| Normalization rate of AST | 6 (5.2) |
| Liver fibrosis SSS score | 1 (0.9) |
| Health-related quality of life | 7 (6.0) |
| Non-serious adverse events | 58 (50.0) |
| Serious adverse events | 4 (3.4) |
| Mortality | 2 (1.7) |
| Hematological tests | 17 (14.7) |
| Immunological tests | 4 (3.4) |
| Pharmacokinetics | 1 (0.9) |
| Clinical symptoms | 16 (13.8) |
| Kidney function tests | 3 (2.6) |

**Abbreviations:** ALT: alanine aminotransferase, AST: aspartate aminotransferase, SSS: semiquantitative scoring system.

**Table 3** Number of trials reported on the CHBG core outcome.

| CHBG core outcomes | Trials (%) |
|---|---|
| All-cause mortality or hepatitis C-related morbidity | 2 (1.7) |
| Health-related quality of life | 7 (6.0) |
| Serious adverse events | 4 (3.4) |
| Mortality due to hepatitis C-related liver disease | 0 (0) |
| Non-serious adverse events | 54 (46.6) |
| Number of participants without histological improvement | 2 (1.7) |
| Number of participants without sustained virological response | 27 (23.3) |
| Number of participants without normalisation of transaminases | 24 (20.7) |

CHBG: Cochrane Hepato-Biliary Group.

**Table 4** Number of CHBG core outcome reported in RCTs.

| Number of CHBG core outcomes | Trials (%) |
|---|---|
| Number of trials reported zero core outcome | 37 (31.9) |
| Number of trials reported one core outcome | 46 (39.7) |
| Number of trials reported two core outcome | 23 (19.8) |
| Number of trials reported three core outcome | 6 (5.2) |
| Number of trials reported four core outcome | 4 (3.4) |

CHBG: Cochrane Hepato-Biliary Group.