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Review Article

Chinese herbal medicine for drug-induced liver injury in patients with HIV/AIDS: A systematic review of randomized controlled trials

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ABSTRACT

Background: To explore the effectiveness and safety of Chinese herbal medicine (CHM) for drug-induced liver injury (DILI) in patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).

Methods: A systematic search was made of eight databases (Pubmed, Cochrane Library, Web of Science, Embase, CNKI, Wanfang, VIP, Sinomed) and two trial registries (WHO ICTRP, ClinicalTrials.gov) from inception to September 2022. The effect size was presented as risk ratio (RR) or mean difference (MD) with their 95% confidence interval (CI). The Cochrane Risk of Bias and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tools were used for quality appraisal.

Results: Ten randomized controlled trials (RCTs) involving 732 participants were included. Comparing CHM alone with routine treatment, the CHM group showed lower aspartate aminotransferase (MD=-11.47 U/L, 95%CI[-13.05, -9.89], low certainty), lower alanine aminotransferase (MD=-2.68 U/L, 95%CI[-4.27, -1.08], low certainty), lower total bilirubin (MD=-4.31 mmol/L, 95%CI[-5.66, -2.96], low certainty), lower bilirubin direct (MD=-3.19 mmol/L, 95%CI[-3.87, -2.51], low certainty), and higher effective rate (assessed by symptoms and liver indicators) (RR=1.13, 95%CI[1.06, 1.20], low certainty). A significant difference was also found in CHM plus routine treatment versus routine treatment in the previous outcomes. No significant difference was found on helper T cells among these comparisons. Only one RCT reported safety of CHM and found no adverse reaction during the trial.

Conclusions: CHM may improve the liver function indices and effective rate for HIV/AIDS patients with DILI. However, the sample size was small and quality was low. Larger-samples of high-quality trials are needed.

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1. Introduction

Acquired immunodeficiency syndrome (AIDS) is an immune system disease caused by infection with human immunodeficiency virus (HIV). After HIV invading the human body, their main cellular target is helper T lymphocytes (CD4+ cells), where they reproduce by fusing with target cells and infecting B lymphocytes, macrophages, Langerhans cells, etc.[1] During the reproduction of HIV, the host cells are destroyed constantly, especially the CD4+ cells. By damaging the immune system, HIV interferes with the body's ability to fight disease and infection, resulting in various complications.[2,3] There are three stages for people with HIV: acute HIV infection, chronic HIV infection, and AIDS. Progression to AIDS is the most severe phase of HIV infection, which may result in fatal infections or cancer.[1] Although a lot of research has been con-

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ducted in this field, HIV disease continues to be a serious global public health risk.[4]

Due to the various antiviral and anti-infection medications taken by HIV patients, liver damage has become the main reason for stopping highly active antiretroviral therapy (HAART). This should not be neglected as it can develop into acute liver failure and result in the need for a liver transplant.[5] If insufficient attention is paid to the progression of liver damage, it can be a life-threatening factor for patients with HIV/AIDS.[6,7] Liver damage or liver failure happens when the toxins destroy or damage the normal structure of liver cells, which then affects cell metabolism and function. The common factors related to HIV with liver injury are those induced by specific drugs, autoimmunity, and alcohol use. Drug-induced liver injury (DILI) results from the use of both prescription and non-prescription medication by HIV patients.[5,8] Antiretroviral therapy (ART) induced liver injury, is mainly induced by four mechanisms, mitochondrial toxicity, metabolic host-mediated injury, immune reconstitution, and hypersensitivity reactions.[9] DILI has to be considered a serious problem because the nature of the disease is unpredictable and probably fatal.[5]

Modern medicine treats this condition mainly by stopping the administration of any suspicious drugs and taking western drugs to protect the liver, reduce enzyme levels, and promote liver cell repairment.[10] Although this treatment can have short-term effects, there are problems of suffering a relapse after stopping drugs, drug resistance with constant treatment and high costs still exist. Characterized by syndrome differentiation and treatment, and the concept of holism, Chinese Herbal Medicine (CHM) may be helpful for relieving liver damage and may provide benefits by slowing the progression of the disease.[11,12] For HIV patients with DILI, there are no current systematic reviews of CHM treatment, so this review aimed to provide an evaluation and meta-analysis of the published clinical studies to explore the effectiveness and safety of CHM for HIV/AIDS patients with DILI.

2. Methods

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020[13] (**Appendix 1**). However, the protocol has not been registered at a registry.

2.1. Eligibility criteria

The eligibility criteria for inclusion in the systematic review were as follows: 1) All randomized controlled trials (RCTs); 2) Population with HIV infection, HIV-related disease, or AIDS, and diagnosed as drug-induced liver injury after receiving antiretroviral therapy were included. Considering HIV/AIDS complicated by hepatitis B or hepatitis C may affect AIDS disease progression and the liver function indices[14,15], patients co-infected with hepatitis B virus or hepatitis C virus were excluded; 3) The intervention of CHM should be used alone or as adjunctive therapy, without limitation of the dosage forms of CHM, including decoctions, granules, powders, injections, and other possible CHM preparations. Anti-infective drugs and symptomatic treatment could be applied based on individual needs if necessary. 4) Compared with placebo, routine treatment, or CHM combined with routine treatment. Routine treatment refers to hepatoprotective treatment and symptomatic treatment for DILI in people with HIV/AIDS, such as Glutataione, Compound Glycyrrhizin or Inosine Injection. 5) Primary outcomes were indices of liver function, like aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBiL), bilirubin direct (DBiL); secondary outcomes include recurrence rate/effective rate, quality of life, CD4+ T cell count, and safety. Effective rate equals (cases with effectiveness)/n *100%. It was regarded as effective when the liver indices reduced significantly, for example, from severe (ALT or AST>200 U/L) reduced to moderate DILI (80 U/L<ALT or AST≤200 U/L), or from moderate to mild DILI (40 U/L<ALT or AST≤80 U/L)[16,17], and symptoms disappeared or improved significantly. 6) Unclear ingredients, dosage, or treatment courses of the therapy would be excluded. 7) If the same trial is published in several articles, only one article with the most comprehensive data reporting would be included.

2.2. Search strategy

Systematic literature research was conducted in four English databases, including PubMed, Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science; four Chinese databases, including China National Knowledge Infrastructure (CNKI), Wanfang database, Chinese Scientific Journal Database (VIP) and Chinese biomedical literature database (CBM); and two trial registers, including World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, from inception to September 7, 2022.

The search strategies were designed under the training and guidance of information specialists and evidence-based medicine expertise, and presented in **Appendix 2**.

2.3. Data collection

After removing duplicates of the identified studies, two authors (Hou WB, Zheng RX) screened the studies independently. The first round of screening was based on reading titles and abstracts, subsequently followed by full-text screening. Any differences were decided by a third author (Li J). Once all included studies were confirmed, details of the publication, study methodology, diagnostic criteria, eligibility criteria, baseline data of participants, intervention methods, treatment course, outcome measurements, outcome data, and all related information were extracted.

2.4. Assessment of risk of bias

The Cochrane Risk of Bias (ROB) was adopted to evaluate the methodological quality of included RCTs[18] by two authors independently (Zhang XW, Hou WB). We assessed the risk of bias from the seven domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, and each domain was judged as “low”, “unclear”, or “high”. The results of the assessment were presented in a risk of bias graph.

2.5. Data analysis and synthesis

All data were recorded in RevMan Software (version 5.4.1).[19] For dichotomous variables, the risk ratio (RR) with 95% confidence intervals (CI) was calculated. For continuous variables, the mean difference (MD) with 95% CI, or standardized mean difference (SMD) for different measurement units was calculated. We used I^2 test and P value for heterogeneity. If $I^2 \leq 30\%$ and $P \geq 0.10$ had occurred, which means low heterogeneity, then the fixed-effect model would have been applied; if $I^2 > 30\%$ or $P < 0.10$ had occurred, which means statistically significant heterogeneity, then the random effects model would have been applied. In addition, considering this review included various dosage forms of CHM, and the potential high heterogeneity was inevitable, so we applied random effects model for all the outcomes. If the data failed to meet the condition of meta-analysis, they would be described narratively.

If the heterogeneity was significant, the subgroup analysis was done according to the CHM formulas, the route of administration, and the course of treatment.

We planned to identify the potential publication bias by conducting a funnel plot if there were more than 10 trials pooled in one meta-analysis.[20] But in this review, there were too few trials to judge the asymmetry of the funnel plot for each outcome.

2.6. Certainty of the evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[21] was used to grade the quality of each outcome. For RCTs, the certainty of evidence started as high, and downgraded based on five domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. The risk of bias was assessed by the results of ROB assessment; the inconsistency was determined by the heterogeneity of meta-analysis, and downgraded if there was high heterogeneity without reasonable explanations; the indirectness was up to the applicability of the study questions of the included RCTs, whether to answer the estimate of effect directly; the imprecision was determined by the CIs and sample size; the publication bias was assessed by the funnel plot or reported funding resources. According to the results of the five domains, the evidence was finally graded as “high” (not downgraded), “moderate” (downgraded by one level), “low” (downgraded by two levels), or “very low” certainty (downgraded by more than two levels). All the outcomes reported by at least two trials were graded and presented as the “summary of findings” table.

3. Results

3.1. Characteristics of the included studies

A total of 4467 articles were identified from the eight databases and other sources. We included 10 clinical trials involving 732 participants in total. The screening process is given in Fig. 1. One trial used the placebo as the control group[22], and the others compared with routine treatment. The study using a placebo was not pooled in the quantitative synthesis.

The ten included studies were all published in Chinese and recruited Chinese participants. The sample size ranged from 40 to 150 (median 60). All RCTs recruited HIV/AIDS patients with antiretroviral therapy-induced liver damage. Among the included RCTs, one study compared CHM with placebo[22], five studies compared CHM alone with routine treatment,[23-27] three studies compared CHM plus routine treatment with routine treatment,[28-30] and one three-arm study compared CHM alone, CHM plus routine treatment with routine treatment.[31] The characteristics of included 10 studies are displayed in Table 1.

3.2. Risk of bias within studies

The included RCTs had a high risk of bias in at least one domain for the outcomes, so the overall risk of bias was all assessed as high (Fig. 2). The randomization process of these included studies was mainly unclear, among which only three RCTs[25,27,30] used random number tables, and the other RCTs just mentioned “random” without the specific method. The allocation concealment of all the RCTs had an unclear risk of bias, as no studies reported the details of randomization or the way of concealment. The performance bias and detection bias in the majority of trials were high, due to the different properties of decoction and drugs, and self-assessment symptoms. Due to no blinding or incomplete blinding during the study or outcome assessment, the participants, researchers, and outcome assessors are very likely to be influenced by the lack of blinding. In addition, most RCTs used clinical symptoms to judge the effective rate, which was pooled in the results of this review. As the symptoms were subjectively assessed by the patients and practitioners themselves, bias was inevitable. For the attrition bias, all the RCTs reported data completely without missing or dropping out during the trial, which all assessed as low risk of bias. The reporting bias was low in most trials. Although most protocols were not available, it was clear that the published reports included all expected outcomes. Only one RCT[31] seemed to report outcomes selectively, which only reported the effective rate without any objective index. As for ‘other bias’, four studies[22,24,28,29] did not report eligibility criteria clearly, so they were evaluated as high risk of bias. Other studies all reported eligibility criteria, comparative baseline, and no clear conflict of interest.

3.3. Effect of interventions

Based on the intervention and outcomes, the meta-analysis was done on ALT, AST, TBiL, DBil, effective rate and CD4+ in CHM vs. routine treatment, and ALT, AST, TBiL, effective rate in CHM plus routine treatment vs. routine treatment.

3.3.1. Primary outcomes

3.3.1.1. Liver function: AST (Fig. 3). For the comparison of CHM versus routine treatment, five RCTs reported AST.[23-27] Although three RCTs[23,24,26] reported taking decoction with several ingredients as a basic prescription and modifying according to syndromes, one RCT[25] taking modified Hua Gan Decoction and Yinchenhao Decoction, and one taking Shenqi Gankang Capsules[27], the majority of compounds in these trials were the same. Overall, compared with routine treatment, the CHM group was more likely to have lower AST (MD=-11.47U/L, 95%CI [-13.05, -9.89]), and the effect showed a significant difference (P<0.00001) (Fig. 3A).

For the RCTs comparing CHM plus routine treatment with routine treatment, three RCTs reported AST.[28-30] The result showed that CHM plus treatment was significantly better in reducing AST when compared with routine treatment (MD=-21.69 U/L, 95%CI [-41.34, -2.05], P=0.03) (Fig. 3B).

The RCT with placebo as a comparison[22] did not report this index.

3.3.1.2. Liver function: ALT. For the RCT with placebo as comparison[22], both intervention group and control group were treated by HAART, and participants in the intervention group were prescribed with Chinese San Huang decoction, compared with "sham decoction" of same package and flavor as placebo. After 12 months of treatment, ALT decreased from 22±10.3 U/L to 21±10.3 U/L in the intervention group, and changed from 27±10.3 U/L to 32±13.0 U/L in control group, which indicated better improvement in the intervention group (P<0.05).

For the RCTs compared CHM with routine treatment, the same five RCTs[23-27] also reported ALT. According to the result of meta-analysis, the CHM group have significantly lower ALT when compared with the control group (MD=-2.68U/L, 95%CI [-4.27, -1.08]) (Fig. 4A).

When compared with routine treatment,[28-30] CHM plus routine treatment was significantly better in reducing ALT (MD=-19.02 U/L, 95%CI [-32.09, -5.94], P=0.0008, 3 RCTs) (Fig. 4B).

3.3.1.3. Liver function: TBiL. For the RCTs compared CHM with routine treatment, the same five RCTs[23-27] also reported TBiL. After pooling the data, the CHM group showed lower TBiL when compared with the control group (MD=-4.31 mmol/L, 95%CI [-5.66, -2.96], P<0.00001) (Fig. 5A). When CHM plus routine treatment

Table 1
Characteristics of included trials.

Study ID	Study types	N	Gender (male/female)		Age (years old)		Course of disease		ART	Intervention		Duration (weeks)	Outcomes
			T	C	T	C	T	C		T	C		
Hong ZS 2012	RCT	40	NR	NR	35.85±5.06	34.47±6.76	6.73±3.71 years	7.65±3.52 years	HAART	San Huang decoction	placebo	52	ALT, symptoms score[3]
Kong XE 2020	RCT	50	13/12	15/10	37.39±4.11	36.21±3.06	NR	NR	ART	Prescribed Herbal Decoction[4]	GSH	4	ALT, AST, TBiL, DBil, effective rate[2], CD4+
Wang CX 2019	RCT	60	17/13	17/13	37.5±3.8	38.7±3.2	NR	17.4±2.6 months	HAART	Prescribed Herbal Decoction[4]	GSH	4	ALT, AST, TBiL, DBil, effective rate[2], symptoms score[3], CD4+
Wang BH 2018	RCT	80	26/14	25/15	38.5±3.9	38.7±3.7	16.2±3.0 months	16.4±3.2 months	HAART	Hua Gan Decoction+Yinchenhao Decoction	GSH	4	ALT, AST, TBiL, DBil, effective rate[2], symptoms score[3], CD4+
Qiu TS 2011	RCT	100	27/23	26/24	20-60	20-60	NR	NR	HAART	Xiao Yao Powder+routine treatment[1]	routine treatment[1]	1.5	ALT, AST, TBiL, effective rate[2]
Xing YL 2010	RCT	72	22/14	21/15	51.48±15.66	50.56±14.38	5.37±1.86 years	5.67±1.09 years	ART	Huangqi Injection+Danshen Injection+GSH	GSH	4	ALT, AST, TBiL, effective rate[2], symptoms score[3], safety events
Xiong WB 2011	three-arm RCT	60	T1:11/9 T2:10/10	11/9	T1: 31.4±8.9 T2: 31.1±9.0	30.2±9.7	T1: 39.5±3.0 days T2: 39.5±3.5 days	40.5±2.5 days	HAART	T1: Huangliang Wendan Decoction T2: Huangliang Wendan Decoction+CG	CG	8	effective rate[2]
Pan JZ 2022	RCT	60	36/24		49.38±10.24		NR	NR	HAART	Baishao Hugan Granules+GSH	GSH	4	ALT, AST, TBiL, DBil, symptoms score[3], CD4+, IL-4, IL-10
Luo YD 2021	RCT	150	58/17	60/15	40.12±2.38	40.13±2.37	5.23±0.27 years	5.24±0.26 years	ART	Shenqi Gankang Capsules	GSH	4	ALT, AST, TBiL, DBil, effective rate[2], patients' satisfaction rate
Xi RH 2021	RCT	60	16/14	15/15	46.32±2.21	44.23±2.11	NR	NR	ART	Prescribed Herbal Decoction[4]	CG	4	ALT, AST, TBiL, DBil, effective rate[2], CD4+

Notes:
[1] routine treatment, including inosine injection, Vitamin B6 injection, glucurolactone injection, symptomatic treatment, supportive care, etc..
[2] effective rate, (cases with effectiveness)/n *100%. For the patients, when the liver index have improved or symptoms relieved or disappear regarded as cases with effectiveness.
[3] symptoms score, the change of traditional Chinese medicine symptoms scores, including anorexia, nausea and vomiting, dry mouth, bitter taste in mouth, abdominal distention, hypochondriac pain and mental fatigue, etc. The score based on the severity of symptoms: absence of symptoms 0, mild 1, moderate 2, severe 3, with 100 as full marks. The higher scores represented the severer symptoms.
[4] prescribed herbal decoction: *Massa Medicata Fermentata Usta* (Shenqu) 10g, *Gardeniae Fructus Frictus* (Zhizi) 5g, *Setariae Fructus Germinatus* (Guya) 15g, *Myristicae Semen* (Roudoukou) 15g, *Paeoniae Radix Alba* (Baishao) 20g, *Artemisiae Scopariae Herba* (Yinchen) 20g, *Polygonati Odorati Rhizoma* (Yuzhu) 20g, *Polygonati Rhizoma* (Huangjing) 20g, *Astragali Radix Fricta* (Huangqi) 30g, or combined with *Mume Fructus* (Wumei) 10g, *Angelicae Sinensis Radix* (Danggui) 15g, *Angelicae Sinensis Radix* (Chaihu) 15g, *Adenophorae seu Glehniae Radix* (Shashen) 30g, *Toosendan Fructus Frictus* (Chuanlianzi) 5g. The herbs were modified according to syndrome differentiation.Abbreviation: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; GSH, Glutataione; DG, Diammonium Glycyrrhizinate; CG, Compound Glycyrrhizin; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; DBiL, bilirubin direct

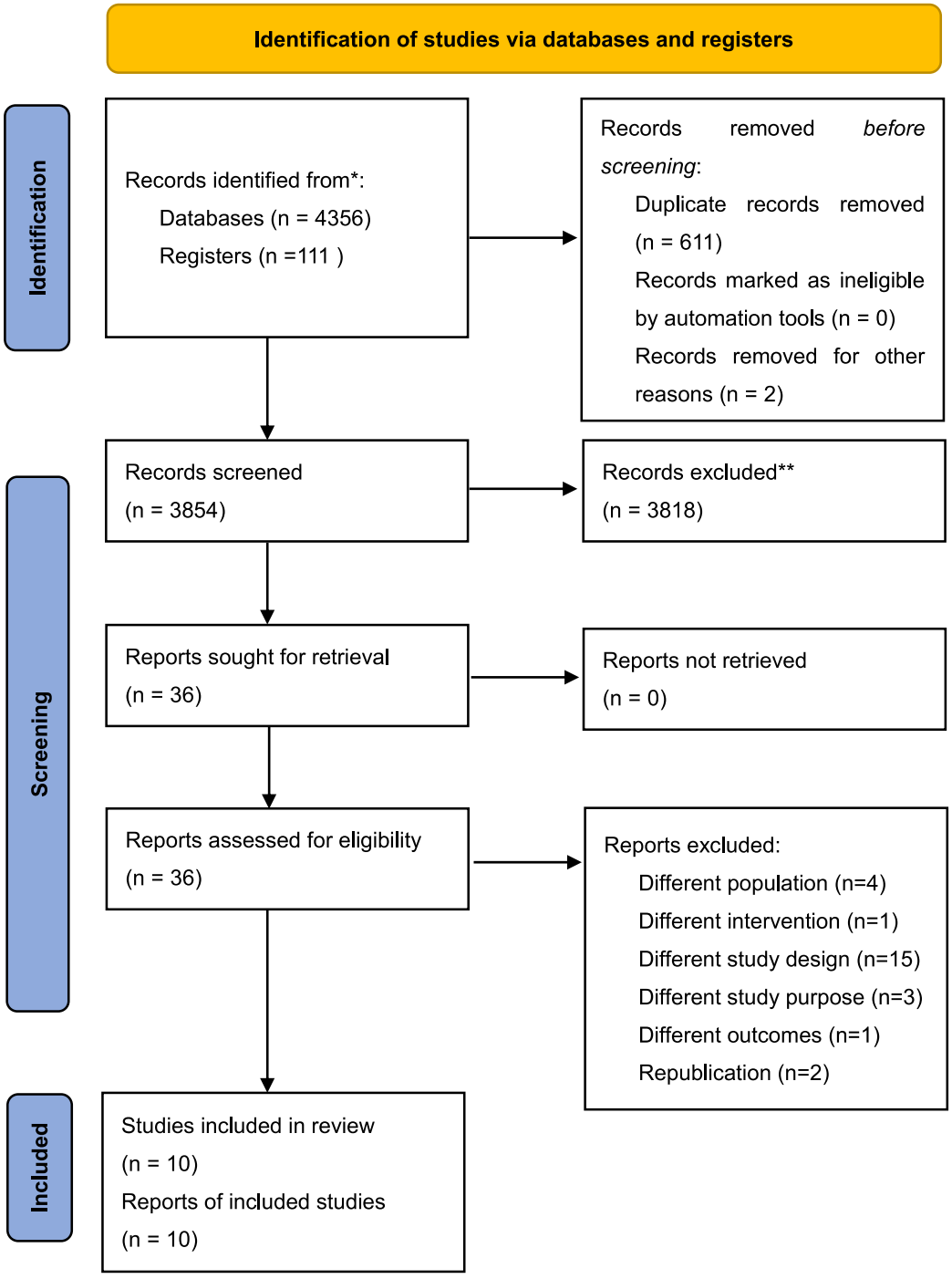


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow chart of literature searching and screening.

compared with routine treatemtn,[28-30] the result also showed significant lower TBiL in CHM group than that in routine treatment group (MD=-6.33 mmol/L, 95%CI [-9.68, -2.98], P=0.0002) (Fig. 5B).

The included RCT with placebo as comparison[22] did not report this outcome.

3.3.1.4. Liver function: DBiL. For the RCTs comparing CHM with routine treatment, the same five RCTs[23-27] also reported DBiL. According to the results of the meta-analysis, the CHM group seemed to have lower DBiL when compared with the control group (MD=-3.19 mmol/L, 95%CI [-3.87, -2.51]), but there was no significant difference (P<0.00001). (Fig. 6)

The RCTs comparing CHM plus routine treatment with routine treatment, and the RCT compared with placebo did not report this index.

3.3.2. Secondary outcomes

3.3.2.1. Recurrence rate/effective rate. For the RCTs which compared CHM with routine treatment, no trials reported the recurrence of DILI, but six RCTs[23-27,31] reported effective rate. After analyzing, the CHM group appeared to show higher effectiveness than the control group (RR=1.13, 95%CI [1.06, 1.20], P=0.0001). (Fig. 7A)

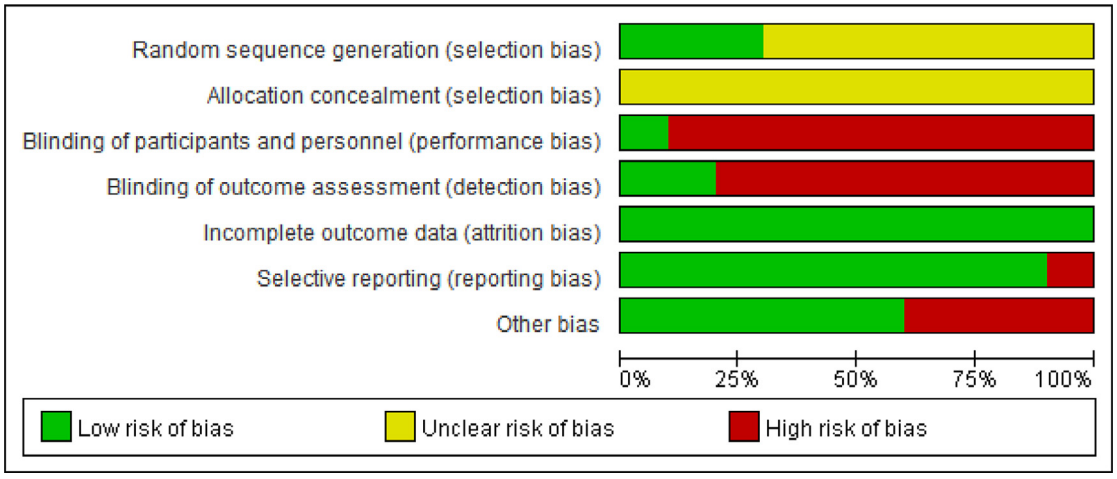
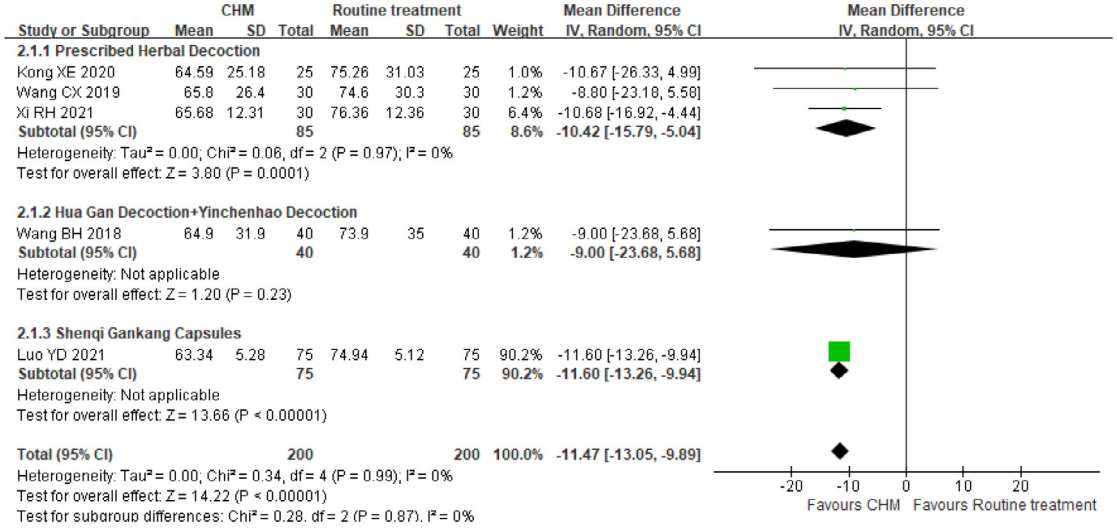
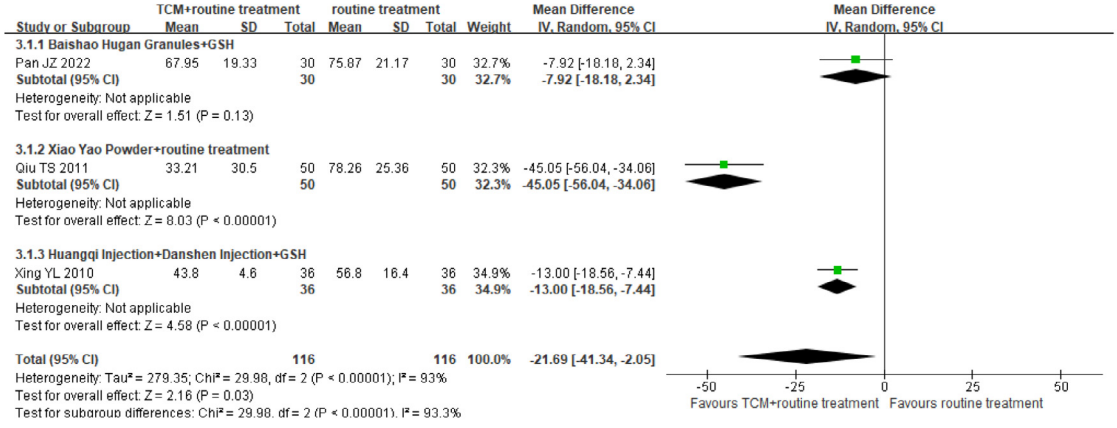


Fig. 2. Risk of bias graph of the included RCTs.

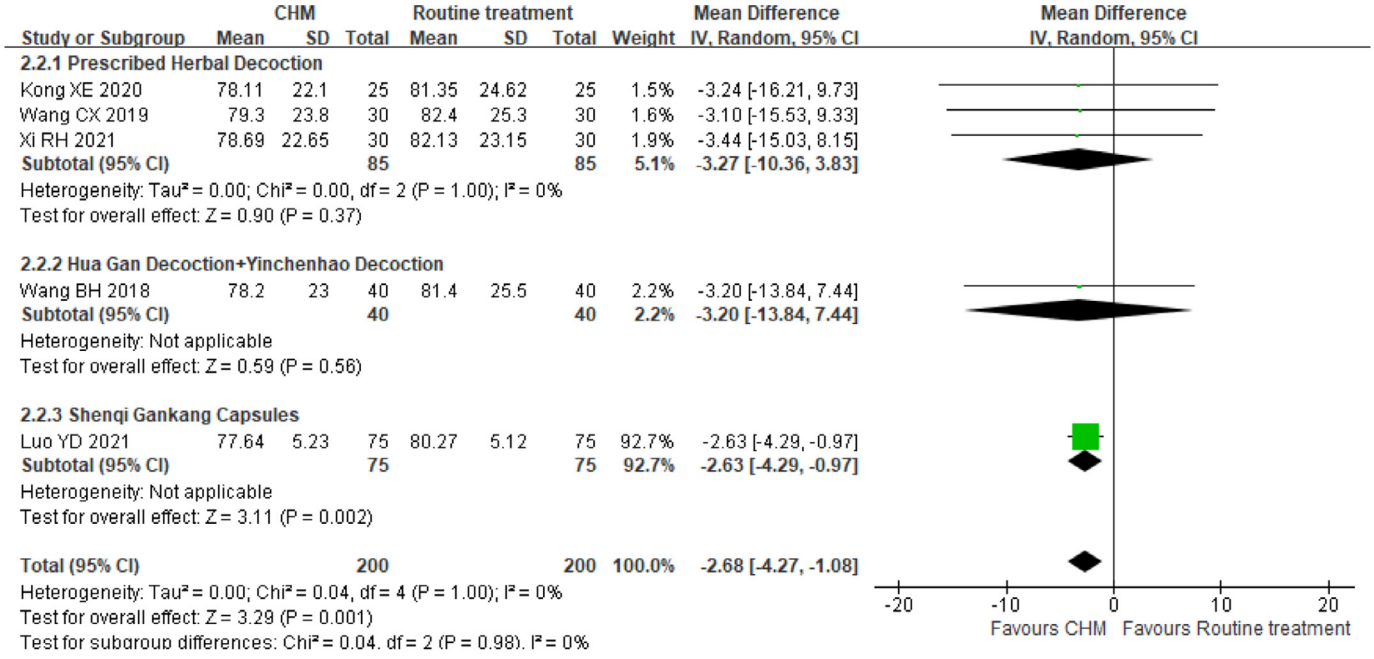


(A) Comparison: CHM vs. Routine treatment



(B) Comparison: CHM plus routine treatment vs. Routine treatment

Fig. 3. Forest plot of AST (U/L) after Chinese herbal medicine treatment.



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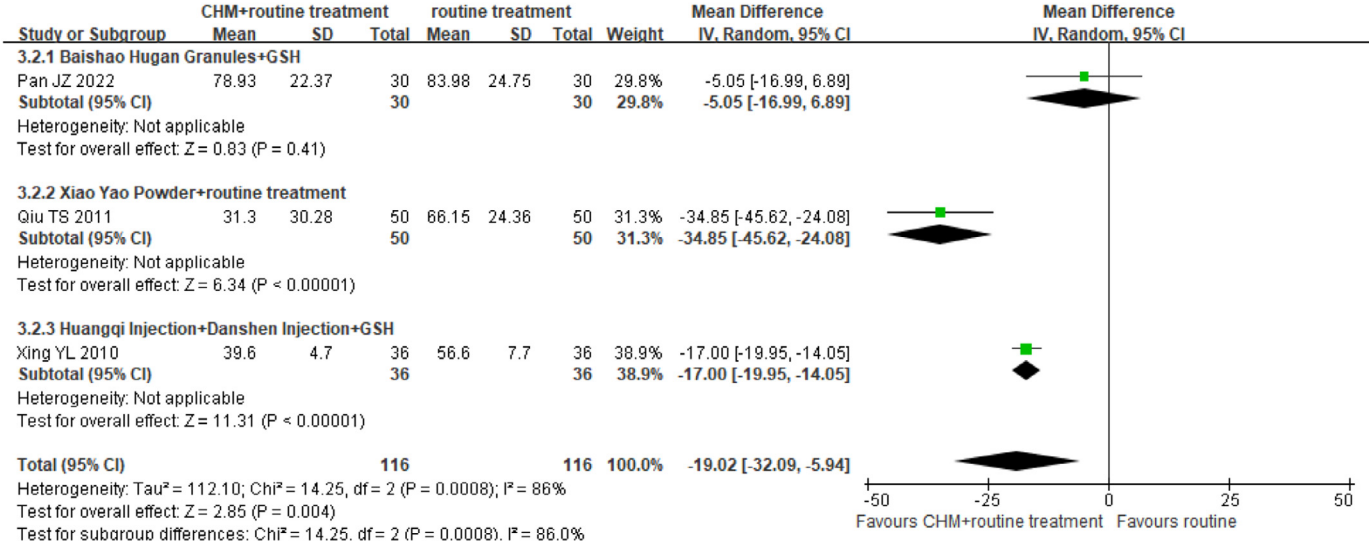
(A) Comparison: CHM vs. Routine treatment



(B) Comparison: CHM plus routine treatment vs. Routine treatment

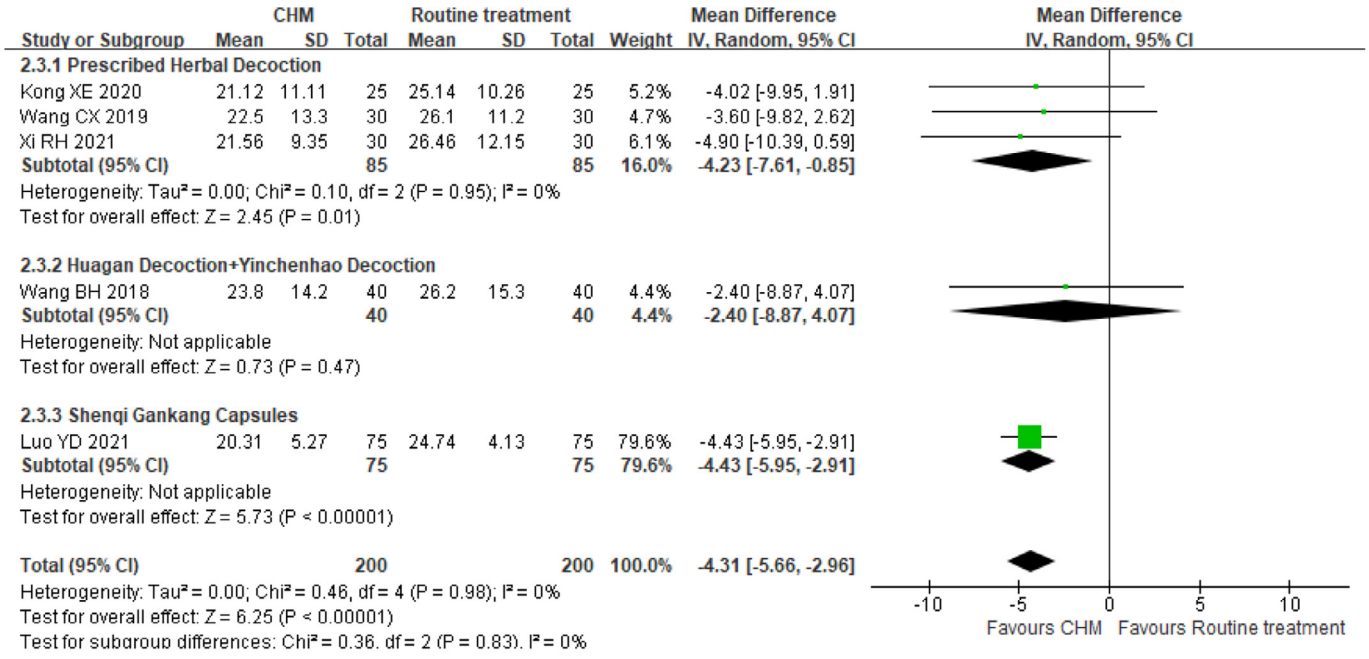
Fig. 4. Forest plot of ALT (U/L) after Chinese herbal medicine treatment.

For the RCTs comparing CHM plus routine treatment with routine treatment, three RCTs[28-30] reported the effective rate. According to the results of the meta-analysis, the intervention group had a higher effective rate when compared with the control group (RR=1.33, 95%CI [1.12, 1.58]), as there was a significant difference between groups (P=0.001). (Fig. 7B)

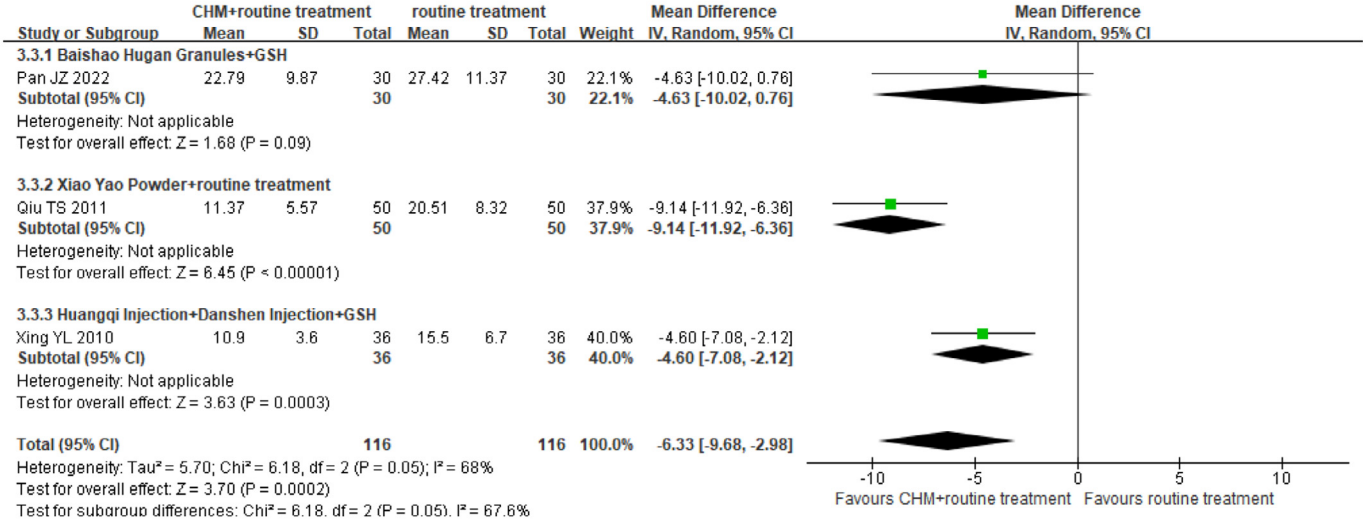
The RCT with placebo as a comparison[22] did not report this index.

3.3.2.2. Quality of life. No trials evaluated changes in the quality of life for patients.

3.3.2.3. CD4+ T cell. Four RCTs[23-26] were included in the comparison of CHM with routine treatment and reported changes in CD4+ counts, but no significant difference was shown for any group (MD=3.04 mm^{-3}, 95%CI [-47.49, 53.58], P=0.91) (Fig. 8). The tri-



(A) Comparison: CHM vs. Routine treatment



(B) Comparison: CHM plus routine treatment vs. Routine treatment

Fig. 5. Forest plot of TBiL (mmol/L) after Chinese herbal medicine treatment.

als comparing CHM plus routine treatment with routine treatment, and the RCT compared with placebo did not report this index.

3.3.2.4. Safety. Only one RCT[29] reported no drug-related adverse reactions, and no abnormal index was shown on routine blood, urine tests, and electrocardiograms. The other trials did not mention the safety of treatment.

3.3.3. Subgroup analysis

For the comparison of CHM plus routine treatment with routine treatment, the included studies applied both oral and intravenous intervention, and the course of CHM treatment varied, so we conducted additional subgroup analysis on AST, ALT, TBiL, and effective rate by the route of administration and the course of CHM treatment. The course of CHM treatment seems to have a closer

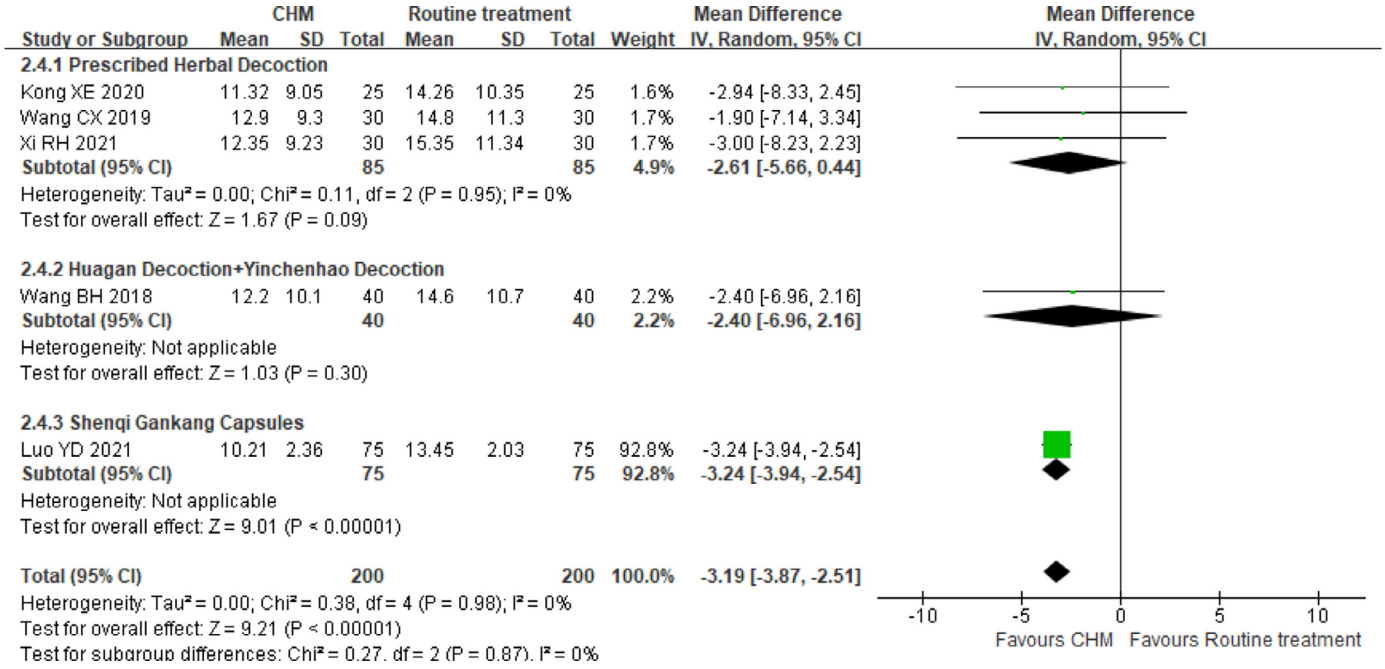


Fig. 6. Forest plot comparing CHM treatment with routine treatment on DBiL (mmol/L).

relationship with these outcomes than the route of administration. (**Appendix 3**)

3.4. Certainty of evidence

Categorized by intervention, control, and outcomes, the overall certainty of the evidence was graded. Due to the limited reporting on methodology and small sample size, the certainty of the evidence was mostly low (Table 2, Table 3). Therefore, we have to be cautious when illustrating results.

4. Discussion

4.1. Summary of evidence

This review identified 10 trials involving 732 participants. In studies of CHM vs. Routine treatment, significant differences between intervention and control groups were shown for AST, ALT, TBiL, DBiL, and effective rate. For the other type of comparisons, CHM plus routine treatment was significantly better for liver function indicators and effective rate when compared with routine treatment. However, no significant difference was found for CD4+ based on the data from four RCTs, which compared CHM alone with routine treatment. These findings suggest that CHM has the potential to improve liver function and enhance the effectiveness rate for HIV/AIDS patients with DILI, but no improvement was found for CD4+. The risk of bias mainly resulted from underreported allocation concealment, incomplete blinding during the study and subjective outcome assessment. According to the GRADE tool, most of the evidence were assessed as low certainty, which were mainly due to the inadequate description of the randomization method, and the fact that the protocol was unavailable or there was no protocol. Meanwhile, the small sample size also affected the certainty of result.

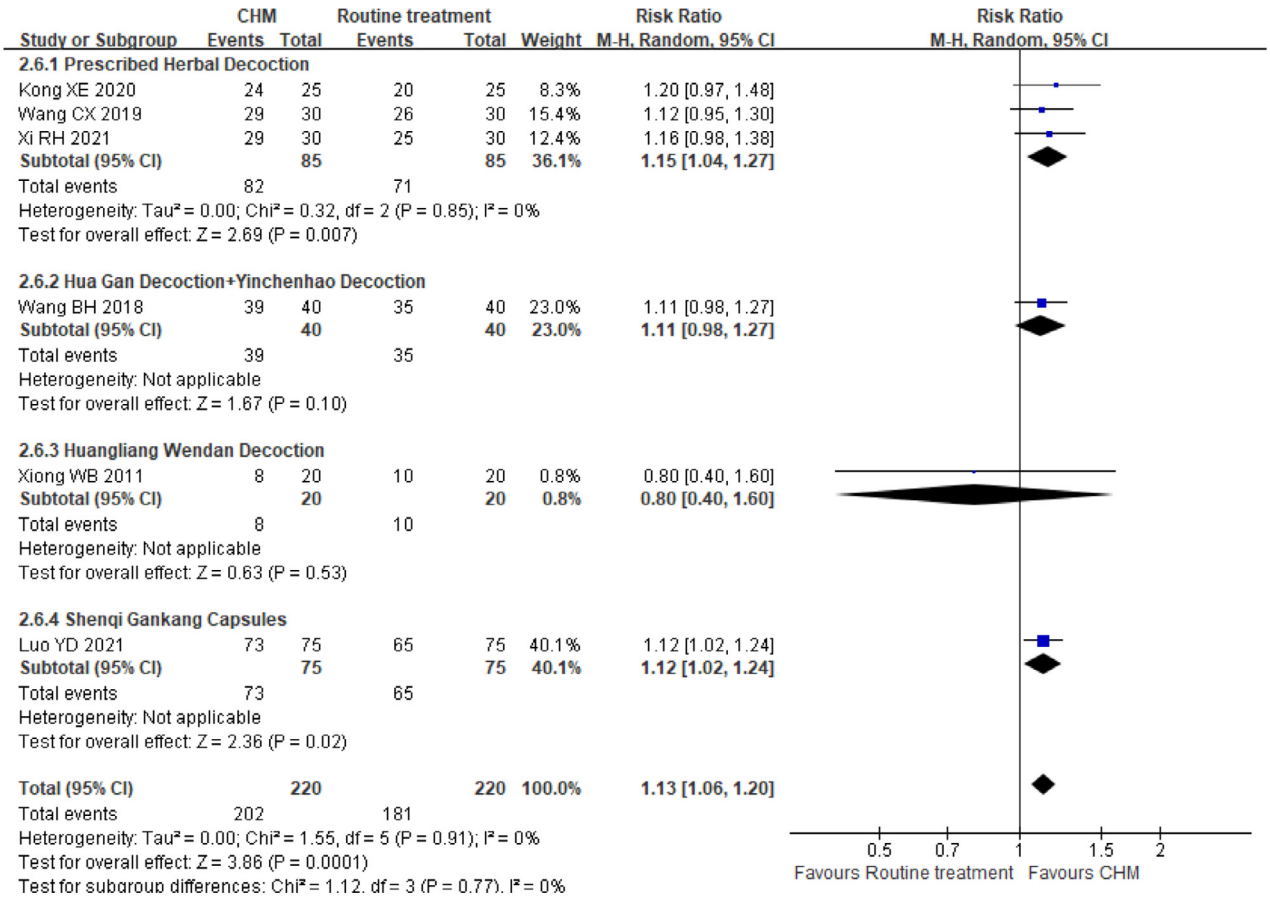
4.2. Comparison with other studies

There were several systematic reviews that explored the effectiveness of Chinese medicine for HIV/AIDS, and several reviews assessed CHM for HIV/AIDS with complications, but no study reviewed CHM for DILI with HIV/AIDS. A Cochrane review of herbal medicine for HIV/AIDS published in 2005[32] identified nine RCTs of CHM for patients with HIV or AIDS, which found that evidence was insufficient to support CHM for HIV infection or AIDS. Another systematic review included 12 RCTs of TCM for HIV/AIDS involving 881 participants[33], which found that TCM interventions were better in reducing plasma viral load when compared with placebo, but worse when compared with conventional western therapy. The limited number and quality of evidence may affect the result, which was not contradictory to our findings. Recently, though a huge number of trials of CHM for HIV/AIDS have been conducted, and more people choosing CHM as their therapy, the evidence was still too little to support a high-confidence conclusion.[34-37] Some reviews focused on complications of HIV/AIDS, including oral mucosa lesions, and depression,[38,39] which showed CHM may have advantages in improving the symptoms of patients with HIV/AIDS. But the evidence was limited, so they had low confidence in the results. In addition, numerous studies on HIV have been done and have been conducted around the world, and reviews on CHM seldom provide a definite conclusion although most trials report a positive result.[34,40,41] The current studies supported that more high-quality trials on CHM for HIV/AIDS were needed.

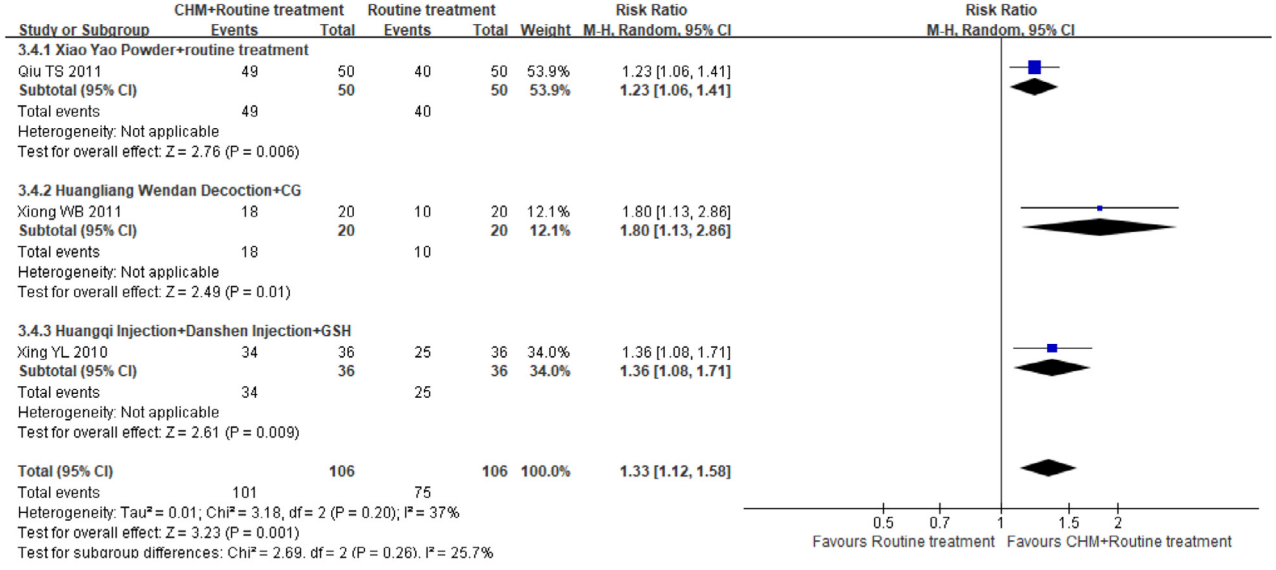
For the effect of CHM on the trend of CD4+ T cell counts for patients with HIV/AIDS, a cohort study[42] involving 721 participants found CHM can increase the CD4+ level rapidly when the baseline <350 cells/mL, and the effect of CHM is related to the initial level. But when the baseline ≥350 cells/mL, no significant difference was found between CHM plus antiretroviral therapy with antiretroviral therapy. The CD4+ level of the trials included in our review are varied, which may explain the reason for no significant difference between CHM and routine treatment.

4.3. Strengths and limitations

To our knowledge, it is the first systematic review to evaluate the effectiveness and safety of CHM for HIV/AIDS with DILI. Also, a comprehensive search of both English and Chinese databases was conducted to identify all the RCTs, and there was detailed and



(A) Comparison: CHM vs. Routine treatment



(B) Comparison: CHM plus routine treatment vs. Routine treatment

Fig. 7. Forest plot of effective rate after Chinese herbal medicine treatment.

Table 2
Certainty of the evidence of treatment for drug-induced liver injury in patients with HIV/AIDS according to GRADE, comparison: CHM vs. routine treatment.

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHM	routine treatment	Relative (95% CI)	Absolute (95% CI)	
AST (U/L)											
5	RCTs	serious	not serious	not serious	serious	none	200	200	-	MD 11.47 lower* (13.05 lower to 9.89 lower)	⊕⊕◯◯ Low
ALT (U/L)											
5	RCTs	serious	not serious	not serious	serious	none	200	200	-	MD 2.68 lower* (4.27 lower to 1.08 lower)	⊕⊕◯◯ Low
TBiL (mmol/L)											
5	RCTs	serious	not serious	not serious	serious	none	200	200	-	MD 4.31 lower* (5.66 lower to 2.96 lower)	⊕⊕◯◯ Low
DBiL (mmol/L)											
5	RCTs	serious	not serious	not serious	serious	none	200	200	-	MD 3.19 lower* (3.87 lower to 2.51 lower)	⊕⊕◯◯ Low
CD4+ (mm^{-3})											
4	RCTs	serious	not serious	not serious	very serious	none	125	125	-	MD 3.04 higher (47.49 lower to 53.58 higher)	⊕◯◯◯ Very low
Effective rate											
6	RCTs	serious	not serious	not serious	serious	none	202/220 (91.8%)	181/220 (82.3%)	RR 1.13 (1.06 to 1.20)	107 more per 1,000* (from 49 more to 165 more)	⊕⊕◯◯ Low

Notes: *represents significant difference (P<0.05); GRADE: Grading of Recommendations, Assessment, Development and Evaluations; CHM: Chinese herbal medicine; CI: confidence interval; MD: mean difference; RR: risk ratio.

Table 3
Certainty of the evidence of treatment for drug-induced liver injury in patients with HIV/AIDS according to GRADE, comparison: CHM plus routine treatment vs. routine treatment.

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHM+routine treatment	routine treatment	Relative (95% CI)	Absolute (95% CI)	
AST (U/L)											
3	randomized trials	serious	serious	not serious	serious	none	116	116	-	MD 21.69 lower* (41.34 lower to 2.05 lower)	⊕◯◯◯ Very low
ALT (U/L)											
3	randomized trials	serious	serious	not serious	serious	none	116	116	-	MD 19.02 lower* (32.09 lower to 5.94 lower)	⊕◯◯◯ Very low
TBiL (mmol/L)											
3	randomized trials	serious	serious	not serious	serious	none	116	116	-	MD 6.33 lower* (9.68 lower to 2.98 lower)	⊕◯◯◯ Very low
Effective rate											
3	randomized trials	serious	not serious	not serious	serious	none	101/106 (95.3%)	75/106 (70.8%)	RR 1.33 (1.12 to 1.58)	**233** more per 1,000* (from 85 more to 410 more)	⊕⊕◯◯ Low

Notes: *represents significant difference (P<0.05); GRADE: Grading of Recommendations, Assessment, Development and Evaluations; CHM: Chinese herbal medicine; CI: confidence interval; MD: mean difference; RR: risk ratio.

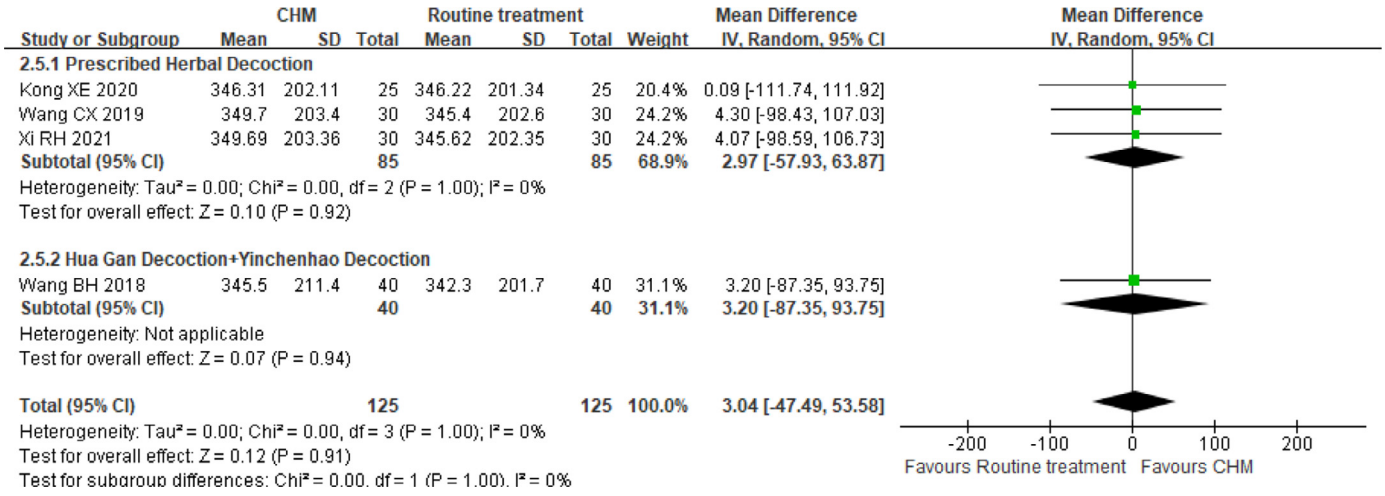


Fig. 8. Forest plot comparing CHM treatment with routine treatment on CD4+(mm^{-3}).

transparent reporting on the methodology to allow replicate easily.

However, although we drafted a protocol before conducting this review, it is the major limitation that the protocol of this review was not registered in any registry, which may affect the judgement on the deviation between the protocol and the final report. Regarding the limitation of the included evidence, firstly, the included studies were all published in Chinese and recruited Chinese participants, so the generalizability of the findings was limited. Secondly, considering the number and sample size of the included evidence with the same comparisons, only a few trials could be pooled for meta-analysis. Funnel plots were not carried out to evaluate publication bias as few studies could be included. Besides, the certainty of evidence has to downgrade due to the small sample size. Thirdly, most included trials had weak methodologies incorporating the high or unclear risk of bias and incomplete reporting, which affected our confidence in the results.

4.4. Implications

Due to the diverse ingredients used in CHM and the use of syndrome differentiation in individualized treatment, there was insufficient homogenous evidence to pool and analyze. More evidence would contribute to the studies on the effectiveness of CHM and expand the research such as the interaction relationship between CHM and routine treatment. Therefore, large-sample size, multicenter and high-quality trials of CHM for DILI in patients with HIV/AIDS should be conducted. It is recommended for researchers to refer to the CONSORT checklist[43] when drafting the RCTs.

4.5. Conclusions

CHM may help improve the liver function indicators and enhance the effective rate in patients with HIV/AIDS, but this evidence should be practiced with caution due to the limited sample size and inadequate reporting of the methodology.

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CRediT authorship contribution statement

Xiao-wen Zhang: Data curation, Writing – original draft, Writing – review & editing. **Jing Li:** Resources, Project administration. **Wen-bin Hou:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Yue Jiang:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Ruo-xiang Zheng:** Formal analysis, Investigation, Data curation, Writing – review & editing. **De-hao Xu:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Chen Shen:** Writing – review & editing. **Nicola Robinson:** Methodology, Writing – review & editing, Supervision, Funding acquisition. **Jian-ping Liu:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition.

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Ethical statement

Ethical approval and inform consent were not required.

Data availability

All data retrieved from the published articles were included in this article.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2022.100918.

Supplement 1. PRISMA checklist.
Supplement 2. Search Strategies.
Supplement 3. Additional subgroup analysis.

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