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Galaxy Publication

Assessing the Effectiveness of Traditional Chinese Medicine as Neoadjuvant Therapy for Lowering Hepatocellular Carcinoma Risk in Patients with Hepatitis B-Induced Cirrhosis: A Systematic Review and Meta-Analysis

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ABSTRACT

Traditional Chinese Medicine (TCM) has been applied at all stages of hepatocellular carcinoma (HCC) management, including prior to tumor development. Nonetheless, its effectiveness in lowering the risk of HCC among patients with hepatitis B-related cirrhosis remains uncertain. This study aims to systematically evaluate this issue. Relevant studies were retrieved from PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, SinoMed, VIP, and WanFang databases. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated, and heterogeneity across studies was assessed. The risk of bias was evaluated using the Cochrane Collaboration's tool. A total of 10 studies involving 2,702 patients were included. The findings indicated that TCM combined with conventional therapy significantly lowered HCC incidence in patients with post-hepatitis B cirrhosis at 1-, 3-, and 5-year follow-ups. The preventive benefit was observed primarily in patients with compensated cirrhosis, whereas it was not significant in decompensated cirrhosis. Additionally, TCM was associated with improved liver function and better virological outcomes. Integration of TCM with standard therapy shows potential in reducing HCC risk among patients with hepatitis B-related cirrhosis, likely through improvements in liver function and viral response. However, further high-quality randomized controlled trials are needed to confirm these effects and provide more robust evidence.

Keywords: Meta-analysis, HBV-Related cirrhosis, Traditional Chinese medicine, Hepatocellular carcinoma

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Introduction

Hepatitis B virus (HBV) infection remains a significant global health challenge, with approximately 296 million individuals living with chronic infection and 820,000 deaths reported worldwide in 2019 [1]. A frequent complication of chronic HBV infection is hepatitis B-related cirrhosis, with hepatocellular carcinoma (HCC) being the leading cause of liver-related mortality among patients with compensated cirrhosis [2]. The prognosis of HCC is generally poor, as reflected by its low five-year survival rates due to high recurrence and metastasis [3, 4]. Patients with cirrhosis are known to have a markedly increased risk of developing HCC compared with those without cirrhosis [5]. Despite this, standardized strategies to reduce HCC incidence in individuals with HBV-related cirrhosis are lacking, highlighting the need for effective preventive interventions.

Advanced HCC is associated with a particularly unfavorable prognosis [6], typically presenting with extrahepatic spread or macrovascular invasion. At this stage, systemic therapies remain the cornerstone of management, provided liver function is adequate and performance status allows [7]. Recent years have seen remarkable advancements in systemic treatment for HCC, including targeted therapies, immunotherapies, and their combined approaches, which have significantly improved survival outcomes and are now widely implemented in advanced cases [8–10].

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Traditional Chinese Medicine (TCM) has been integrated into healthcare for over three millennia, encompassing a holistic array of interventions such as herbal formulations, acupuncture, moxibustion, cupping, massage, and therapeutic exercises [11, 12]. According to TCM principles, disease arises from disruptions in the body's equilibrium, including imbalances between Yin and Yang. Therapeutic strategies aim to restore harmony through tailored herbal combinations [13–15]. As a complementary approach, TCM has played an important role in managing liver cirrhosis [16]. Several clinical studies have reported that TCM may help prevent HCC development in patients with HBV-related cirrhosis [17, 18]; however, its role as a neoadjuvant therapy for HCC prevention remains unclear.

Currently, there is a lack of systematic and comprehensive assessment of the available evidence. Therefore, this study aims to perform a systematic review and meta-analysis to evaluate the clinical efficacy of TCM in preventing HCC among patients with chronic HBV-related cirrhosis and to explore potential underlying mechanisms.

Materials and Methods

This review followed the methodological guidance outlined in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1. The review protocol was prospectively registered in PROSPERO (registration number CRD42023447915) [19].

Search strategy

A comprehensive literature search was undertaken across multiple electronic databases—including PubMed, EMBASE, the Cochrane Library, Web of Science, SinoMed, CNKI, VIP, and WanFang Data—from their inception until May 2023. The search approach was developed using the PICOS framework. The Population (P) included individuals with liver fibrosis resulting from HBV infection. The Intervention (I) consisted of Traditional Chinese Medicines (TCMs), compared either with placebo or with no therapeutic intervention, with the requirement that any accompanying treatments be identical between groups aside from the TCM regimen. The Comparator (C) involved standard Western medical therapy, such as antiviral agents, hepatoprotective drugs, and supportive care. The Outcome (O) of interest was the incidence of hepatocellular carcinoma (HCC). Only Randomized Controlled Trials (S) were eligible for inclusion. A full example of the search syntax, based on the PubMed query, is presented in **Table 1**.

Table 1. Search strategy on PubMed.

Search	PUBMED
#1	"hepatitis B virus" [All Fields] OR "cirrhosis" [All Fields] OR "liver cirrhosis" [All Fields] OR "hepatic cirrhosis" [All Fields] OR "hepatocirrhosis" [All Fields] OR "viral cirrhosis" [All Fields] OR "hepatitis B cirrhosis" [All Fields] OR "hepatitis b virus related cirrhosis" [All Fields] OR "hepatitis b virus related cirrhosis" [All Fields] OR "HBV－cirrhosis" [All Fields] OR "HBV－C" [Title/Abstract]
#2	"Liver cirrhosis" [All Fields] OR "hepatitis B virus" [MeSH Terms]
#3	#1 or #2
#4	((((((((((Medicine, Chinese Traditional [MeSH Terms]) OR (Traditional Chinese Medicine [Title/Abstract])) OR (Chung I Hsueh [Title/Abstract])) OR (Traditional Medicine, Chinese [Title/Abstract])) OR (Zhong Yi Xue [Title/Abstract])) OR (Chinese Traditional Medicine [Title/Abstract])) OR (Chinese Medicine, Traditional [Title/Abstract])) OR (Traditional Tongue Diagnosis [Title/Abstract])) OR (Tongue Diagnoses, Traditional [Title/Abstract])) OR (Traditional Tongue Diagnoses [Title/Abstract])) OR (Traditional Tongue Assessment [Title/Abstract])) OR (Tongue Assessment, Traditional [Title/Abstract])) OR (Traditional Tongue Assessments [Title/Abstract])
#5	#3 and #4

Inclusion criteria

Studies were considered eligible if they satisfied the following: (1) the experimental group received traditional Chinese medicine (TCM) for patients with HBV-induced liver cirrhosis; (2) the control group was treated with conventional Western medicine only; (3) the study was designed as a randomized controlled trial (RCT); and (4) the outcome included the development of primary liver cancer.

Exclusion criteria

Studies were excluded if they reported incomplete or missing data, or if they were non-randomized in nature, including quasi-RCTs, animal experiments, protocols, conference abstracts, case reports, or correspondence.

Study selection

All retrieved articles were imported into EndNote for management and initial screening. Two reviewers (A. Tu and P. Zarghami) first removed duplicates and excluded studies based on titles, including non-RCTs, review articles, conference papers, protocols, and correspondence. Next, abstracts were independently examined by both reviewers to assess eligibility and further eliminate irrelevant studies. The full texts of the remaining articles were then reviewed in detail to confirm inclusion. Any disagreements between reviewers were resolved through discussion, with a third reviewer (J. Wang) making the final decision when necessary.

Data extraction

Two reviewers independently collected data from the included studies using a standardized form, recording information such as: (1) author, (2) country of study, (3) publication year, (4) participants' mean age, (5) sample size, (6) details of TCM and control interventions, and (7) study outcomes.

Data analysis

Analyses were conducted using RevMan version 5.4. Continuous data were expressed as mean ± standard deviation (SD), and binary outcomes were reported as relative risk (RR) with 95% confidence intervals (CI), reflecting the ratio of event incidence between treatment and control groups. For continuous outcomes, standardized mean difference (SMD) was calculated by dividing the mean difference between groups by the pooled SD and presented with 95% CI. To account for heterogeneity, a random-effects model was applied when I^2 exceeded 50%, while a fixed-effects model was used for I^2 below 50%.

Risk of bias assessment

Two reviewers independently evaluated the risk of bias in each RCT using the Cochrane Handbook version 5.1.0 tool [20], assessing seven domains: random sequence generation, allocation concealment, blinding of participants, blinding of personnel, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was rated as low, high, or unclear risk. Any disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer made the final judgment.

Results and Discussion

Study retrieval

The initial search yielded 6,830 articles. After removing 2,391 duplicates, 4,120 records were excluded following title and abstract screening. Full-text assessment excluded 309 articles for reasons including non-RCT design (n = 49), conference abstracts (n = 21), interventions outside the scope of this review (n = 17), and outcomes not including cancer incidence (n = 222). Ultimately, 10 RCTs met the inclusion criteria [17, 18, 21–28]. The study selection process is summarized in **Figure 1.**

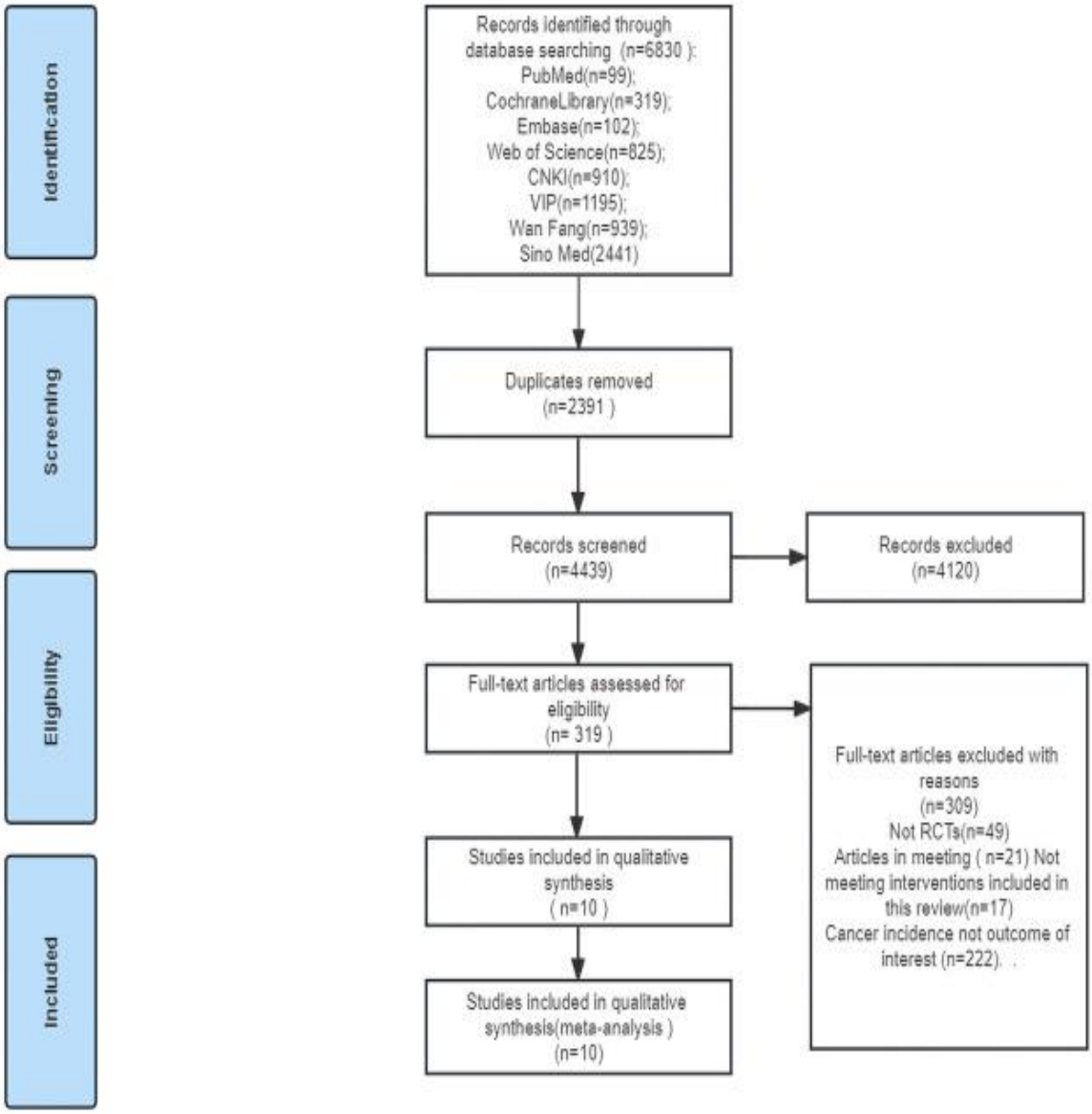


Figure 1. Flowchart illustrating the literature selection process for the meta-analysis.

Basic characteristics of the included studies

A total of ten randomized controlled trials published from 2013 to 2023 were eligible for inclusion, comprising 2,702 participants—1,340 allocated to the control arm and 1,362 to the intervention arm. All enrolled individuals had a confirmed diagnosis of chronic hepatitis B–related liver fibrosis, established using recognized diagnostic standards in certified medical institutions. Participants in the control group received standard Western medical therapy, whereas those in the intervention group were treated with the same conventional regimen supplemented with Traditional Chinese Medicine. Of the identified studies, five assessed outcomes related to hepatic function [18, 23–25, 27], while three evaluated virological responses [22, 23, 28]. **Table 2** provides a detailed overview of the characteristics of each included trial.

Table 2. Characteristics of the studies.

Author	Country	Year	Age [mean (SD)]	Total/male/female	Intervention	Outcome
Yang	China	2023	T:49.58 (14.07） C:49.65（14.54）	T:71/53/18 C:71/57/14	Po. BLRG Tablet (tid) Length of Intervention: 5 years	IR

Xu	China	2021	T:53.2 (6.5) C:51.7 (6.8)	T: 150/88/62 C: 150/100/50	Po.FZHY Capsule (2g.tid).or ALHX Pills (6g.bid).or BJRG Tablets (2g.tid) Length of Intervention: 3 years	IR
Xing	China	2023	T: 49.37 (13.87) C: 49.06 (9.45)	T: 160/126/34 C: 80/58/22	Po.RG Granule (bid) Length of Intervention: 48 weeks	IR, istologic examination, liver function, and imageology examination
Tong	China	2013	T: 35–65 C: 36–65	T: 52/41/11 C: 50/40/10	Po.CPUL (100 ml bid) Length of Intervention: 3 years	IR,HBV－DNA, and antibodies
Shi	China	2020	T: 50.35 (12.67) C:49.7 (11.92)	T: 259/184/75 C: 259/168/91	Po.FZHY Capsule (1.5g.tid) Length of Intervention: At least 24 weeks	IR
Li	China	2017	T: 46.83 (12.62) C: 49.56 (14.82)	T: 82/69/13 C: 94/78/16	Po.BZYQ Pills (6g.bid) Length of Intervention:5 years	IR, liver function, complications, and safety assessment
Ji	China	2022	T: 42 (10.41) C: 42 (10.41)	T: 271/188/83 C: 257/178/79	Po.BJRG Tablets (2g.tid) Length of Intervention: At least 72 weeks	IR
Jia	China	2017	T: 55 (17) C: 55.2 (10)	T: 222/163/59 C: 291/194/97	Po.FZHY Capsule (1.5g.tid).or ALHX Pills (6g.bid). or BJRG Tablets (2g.tid). or HLSG Pills (2.2g.tid). Length of Intervention: At least 24 weeks	IR
Chen	China	2021	T: 54.3 (8.4) C: 55.3 (7.6)	T: 32/22/10 C: 30/19/11	Po.EZJD granule (bid) Length of Intervention: 48 weeks	IR, liver function, and liver fibrosis indicators
Chen	China	2023	T: 52.7 (9.61) C: 54.2 (9.41)	T: 71/54/17 C: 68/43/25	Po.YGJ (6.6g.tid) Length of Intervention: 24 weeks	IR, CTP, variceal bleeding liver function, mortality

Note: T: treatment group, C: control group, bid: bis in die, tid: ter in die, IR: HCC incidence rate, BLRG: Bielong Rugan tablet, FZHY: Fuzheng Huayu capsule, ALHX: Anluohuaxian pills, BJRG: Fufang Biejia Ruangan tablets, RG: Ruangan granule, CPUL: Compound Phyllanthus Urinaria L.

HBV－DNA: Hepatitis B virus DNA, FZHY: Fuzheng Huayu capsule, BZYQ: Buzhong Yiqi pills, HLSG:Heluo Shugan pills.

EZJD:Erzhu Jiedu Decoction granule, YGJ: Yanggan Jian, CTP: Child－Turcotte－Pugh class and score.

Outcome measures

Incidence of hepatocellular carcinoma

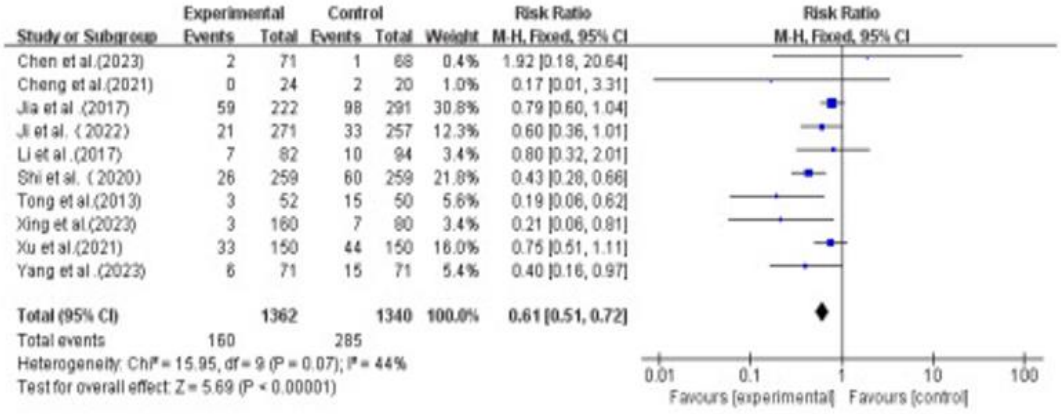
The analysis demonstrated that adding traditional Chinese medicine (TCM) to the treatment of patients with hepatitis B-related cirrhosis reduced the risk of HCC by 39% compared with the control group receiving only Western medicine (RR = 0.61, 95% CI [0.51–0.72], P < 0.01) **(Figure 2a)**, with low heterogeneity observed (I^2 = 44%).

Subgroup analyses based on follow-up duration revealed a consistent protective effect of TCM: at 1 year (RR = 0.22, 95% CI [0.09–0.56], P < 0.01), 3 years (RR = 0.36, 95% CI [0.24–0.55], P < 0.01), and 5 years (RR = 0.60, 95% CI [0.51–0.72], P < 0.01), patients receiving combined TCM and Western therapy had significantly lower HCC incidence compared with controls **(Figure 2b).**

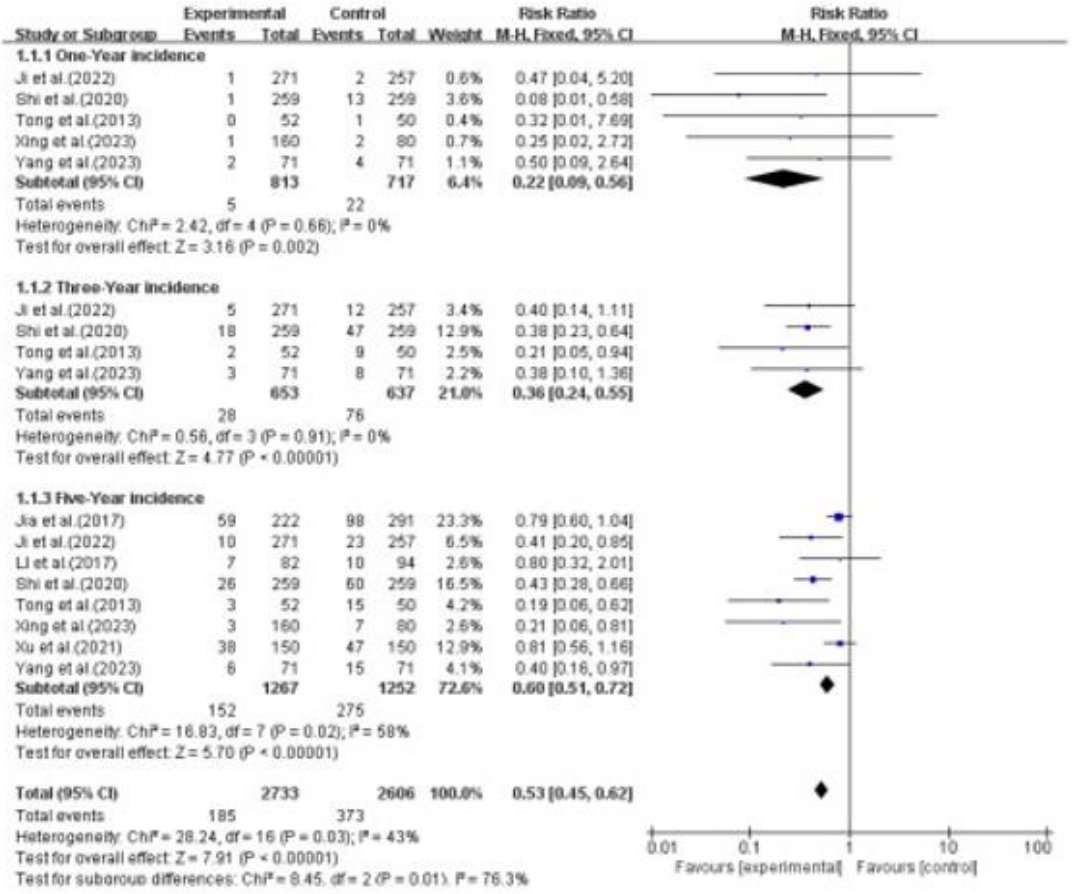
When stratified by cirrhosis stage, TCM showed a significant preventive effect in patients with compensated cirrhosis (RR = 0.58, 95% CI [0.43–0.78], P < 0.01). Conversely, no protective effect was observed in patients with decompensated cirrhosis (RR = 1.0, 95% CI [0.77–1.30], P = 0.99). The corresponding forest plots for compensated and decompensated stages are presented in **Figure 2c**.

Liver function

Five studies [18, 23–25, 27] including 899 participants reported liver function outcomes. The TCM group showed significant improvements, with ALT levels reduced (SMD = −1.70, 95% CI [−3.27 to −0.12], P < 0.05), AST levels decreased (SMD = −1.23, 95% CI [−2.18 to −0.29], P = 0.01), and albumin (ALB) levels increased (SMD = 1.23, 95% CI [0.72–1.74], P < 0.01). Forest plots depicting ALT, AST, and ALB outcomes are shown in **Figures 3a-3c**, respectively.



a)



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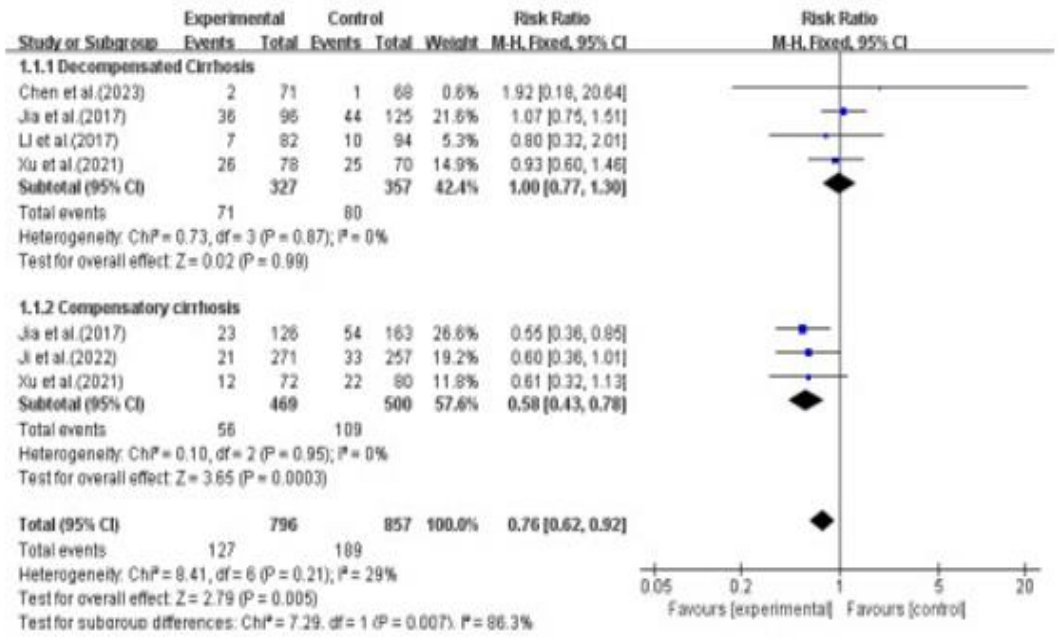
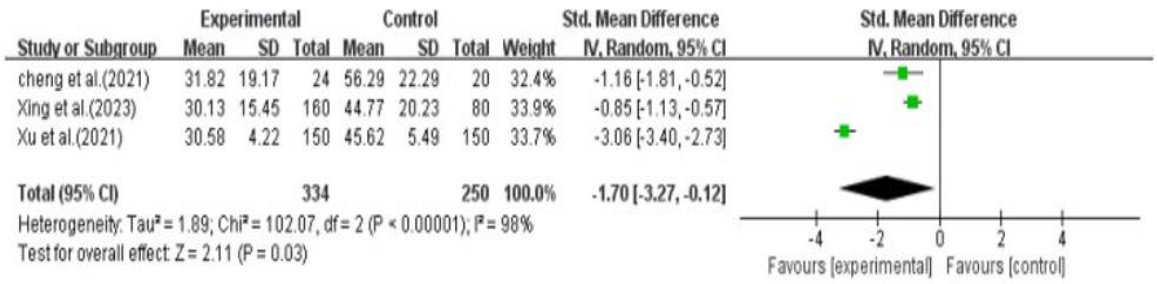
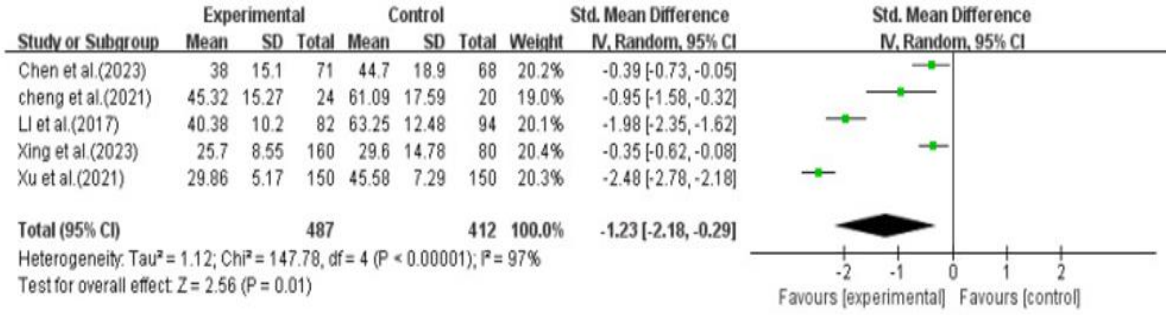


c)

Figure 2. Forest plots from the meta-analysis showing (a) overall HCC incidence, (b) HCC incidence at 1, 3, and 5 years, and (c) comparison between compensated and decompensated groups.



a)



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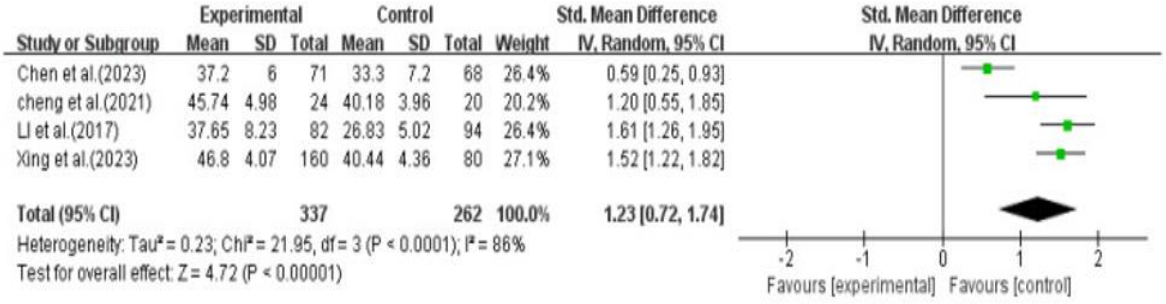

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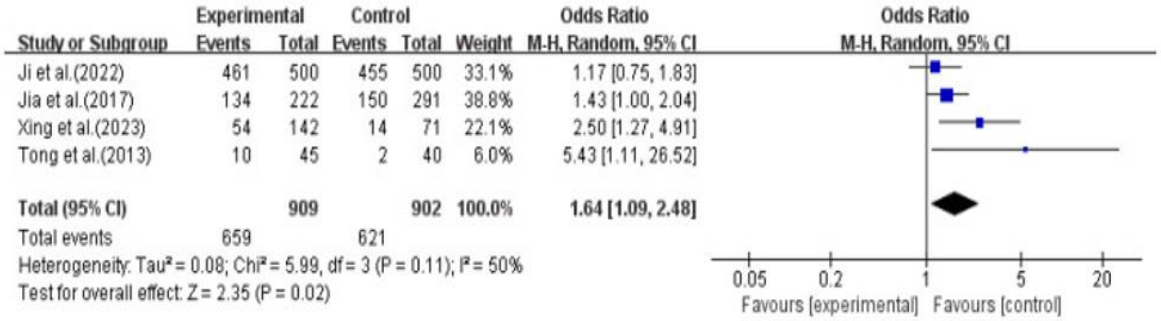


d)

Figure 3. Forest plots displaying ALT, AST, ALB levels, and virological response

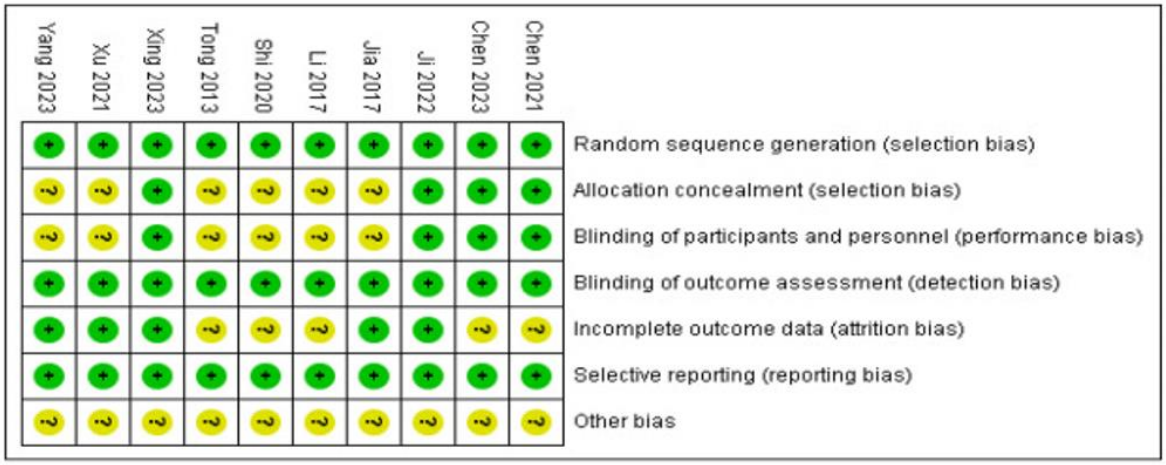
Virological response

The antiviral effects post-treatment were reported in four trials. Of the 902 participants in the control groups [17, 22, 23, 28], 621 achieved HBV-DNA clearance, whereas in the intervention groups, 659 of 909 patients tested negative for HBV-DNA after therapy, demonstrating that the combination of treatments was more effective than conventional Western medicine (OR = 1.64, 95% CI [1.09–2.48], P < 0.05, **Figure 3d**).

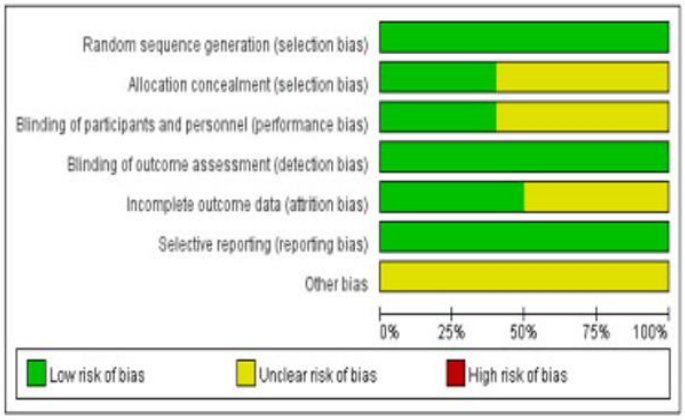
Risk of bias evaluation

Figures 4a and 4b summarizes the risk of bias for each included RCT. All trials were considered low-risk for random sequence generation and outcome assessor blinding. Four studies were judged low-risk for participant

and personnel blinding and allocation concealment, while the remainder were unclear. Regarding incomplete outcome reporting, only one study was low-risk, with the rest categorized as unclear. For other sources of bias, all studies were assessed as unclear.



a)



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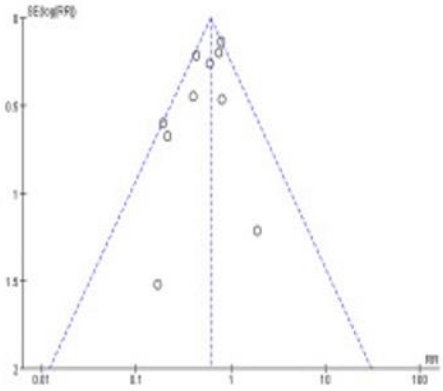

c)

Figure 4. Risk of bias assessment for the included studies.

Publication bias and sensitivity analysis

Publication bias was evaluated using funnel plots, which indicated no evidence of bias among the included studies **(Figure 4c)**. Sensitivity analyses of the primary outcomes showed that removing individual studies one at a time did not substantially alter the results, suggesting that the findings of this meta-analysis are robust and reliable.

Cirrhosis caused by HBV infection is a well-recognized independent risk factor for hepatocellular carcinoma (HCC), with 70%–90% of HCC cases developing in patients with underlying cirrhosis [29, 30]. Globally, HCC ranks as the fifth most common cancer and the third leading cause of cancer-related mortality, with over 850,000 new cases reported annually [31]. The progression from cirrhosis to HCC is complex and driven by multiple mechanisms, including viral genome integration, dysregulation of cellular signaling, epigenetic alterations, and other processes that promote uncontrolled hepatocyte proliferation and malignant transformation [29, 32–34]. Additionally, chronic inflammation, fibrosis, and alterations in the hepatic microenvironment facilitate immune tolerance and tumor evasion, further promoting carcinogenesis [35–37].

Efforts to prevent HCC have increasingly focused on controlling chronic hepatitis through antiviral therapy [38]. Evidence shows that long-term treatment with nucleoside analogues (NAs) can reduce HCC risk [39–41] by suppressing HBV replication and alleviating liver inflammation, thereby slowing cirrhosis progression and delaying the onset of HCC [41, 42]. However, prolonged NA therapy often leads to drug resistance [43, 44] and may be associated with adverse effects, particularly impacting bone and kidney health [45]. Moreover, antiviral therapy alone does not always fully prevent cirrhosis from advancing to HCC, as some patients develop HCC

even after achieving HBsAg loss [46], highlighting the urgent need for novel therapies, especially non-nucleoside agents.

Our findings indicate that traditional Chinese medicine (TCM), when used as an adjuvant therapy, can substantially reduce HCC risk. This aligns with previous research, such as the 15-year follow-up study by Tsai *et al*., which included 21,020 Taiwanese patients with chronic hepatitis B and reported that the combination of TCM and Western medicine reduced HCC risk by approximately 37% compared to Western medicine alone [47]. Subgroup analyses in our study revealed that TCM significantly decreased HCC incidence at 1, 3, and 5 years. Interestingly, we observed that longer TCM use did not always correspond to proportionally greater HCC risk reduction, which may reflect differences in study populations, methodologies, or complex interactions influencing TCM effectiveness [21]. Moreover, TCM appeared particularly effective in patients with compensated cirrhosis, while its impact was less pronounced in those with decompensated cirrhosis, likely due to advanced liver dysfunction and related complications affecting treatment response.

Biochemical markers including ALT, AST, and ALB showed marked improvement in the combination therapy group relative to controls, highlighting the beneficial effects of TCM on liver function [48, 49]. Despite significant heterogeneity among liver function indicators—potentially attributable to variations in baseline clinical characteristics and intervention protocols—the sensitivity analyses confirmed the stability of our meta-analytic results. Multiple clinical studies support TCM's hepatoprotective effects. For instance, a systematic review by Dai *et al.* reported consistent improvements in serum liver markers following TCM administration [50]. Additionally, various herbal compounds, such as curcumin and tanshinone, are recognized for reducing oxidative stress and inflammation, thereby mitigating hepatic injury [51–54], while silymarin exerts membrane-stabilizing and antioxidant effects that promote hepatocyte regeneration [55, 56].

Our findings further indicate that TCM can enhance the effects of antiviral therapy. Several studies have reported that combining traditional Chinese medicine with antiviral treatment is more effective than antiviral therapy alone [57, 58]. Moreover, evidence suggests that TCM combined with nucleoside analogues (NAs) may achieve viral suppression by modulating host immune responses [59, 60], thereby improving antiviral efficacy, reducing liver inflammation, and alleviating associated symptoms [60]. This immunomodulatory effect may play a critical role in slowing the progression of cirrhosis and lowering the risk of HCC. In patients with HBV-related HCC, persistent liver inflammation is a central driver of fibrosis and cirrhosis [61, 62]. Chronic viral infection exacerbates hepatic inflammation, which over time can cause extensive hepatocellular injury, leading to fibrosis, cirrhosis, and ultimately HCC development [63, 64]. When combined with standard antiviral and antifibrotic therapies, TCM can significantly improve liver function and enhance antiviral responses, thereby potentially delaying disease progression and reducing HCC incidence [65, 66].

This study highlights the promise of TCM in managing Hepatitis B-related cirrhosis. The growing body of clinical evidence underscores its potential as an adjunctive intervention, which may attract increasing attention in both research and clinical settings. Integrating TCM into formal guidelines for managing Hepatitis B-related cirrhosis could optimize patient outcomes and yield meaningful public health benefits by reducing the global burden of HCC.

Nevertheless, this meta-analysis has several limitations. First, there was considerable heterogeneity in TCM interventions across studies, including differences in herbal composition, dosage, and administration, which complicates identifying the specific components responsible for observed effects. Standardized formulations and clearly defined treatment protocols are needed. Second, all included studies were conducted in China, which may introduce regional bias. Third, some trials had unclear allocation concealment and blinding, potentially contributing to bias. Finally, the limited number of studies and sample sizes for liver function and virological outcomes may increase the risk of analytical bias, potentially limiting the accuracy of conclusions. Future research should focus on standardized intervention protocols, rigorous study designs, and diverse patient populations to enhance the reliability and generalizability of findings.

Conclusion

In summary, TCM as a neoadjuvant therapy shows promising potential in reducing HCC incidence among patients with HBV-related cirrhosis by improving liver function and enhancing viral clearance. This study provides valuable evidence supporting the integration of TCM into clinical practice for HCC prevention in this population.

However, the results should be interpreted cautiously, considering the study limitations, and further high-quality randomized controlled trials are needed to strengthen the evidence base and fill existing knowledge gaps.

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Conflict of Interest: None

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Ethics Statement: This study was approved by the Ethics Committee of the Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University (KY2021056/FS-01).

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