REVIEW
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Histological efficacy of traditional Chinese medicine plus entecavir therapy for HBV-related liver fibrosis

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Cheng-Hai Liu, Zheng-Xin Li conceived and critically revised the manuscript. Ting-Ting Zhu, Yun-Kai Dai, Feng Xing collected literatures, analyzed the data and prepared the manuscript. Xin Sun and Zhi-Min Zhao Conducted critical revisions of the manuscript. Ting-Ting Zhu and Yun-Kai Dai contributed equally to this work. All authors have read and approved the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HA, hyaluronic acid; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; IV-C, collagen C Type IV; OR, odds ratio; RCTs, randomized controlled trials; TCM, Traditional Chinese medicine.

Citation

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Abstract

Background/Aims: Traditional Chinese medicine (TCM) combined with antiviral therapy has been proven to be effective for liver fibrosis due to chronic hepatitis B (CHB) in clinical practice in China. However, the robust evidence is limited, and the validity of results has been controversial in the past. The current study is to evaluate the efficacy and safety of the combination therapy of TCM plus entecavir (ETV) in the management of HBV-associated liver fibrosis or cirrhosis. **Methods:** Seven electronic databases were searched from inception to 10 August 2021. Primary outcome of this study was the regression of liver fibrosis; the secondary outcomes were a necro-inflammatory improvement, alanine aminotransferase (ALT), HBV DNA undetectable rate, HBeAg loss and HBeAg seroconversion. All the trials included were assessed by the Cochrane risk-of-bias tool. **Results:** It showed that TCM plus ETV attenuated liver fibrosis or cirrhosis in chronic hepatitis B patients as compared to ETV monotherapy(OR = 1.65; 95% CI: 1.29~2.11; $P <$ 0.000,1). There is no statistical difference between TCM plus ETV and ETV in histological activity index, HBV DNA undetectable rate, HBeAg loss, HBeAg seroconversion and adverse events($P < 0.05$). **Conclusion:** The comprehensive evaluation showed that TCM combined with ETV treatment was safe for the patients with CHB, and better promoted the regression of liver fibrosis than ETV monotherapy. However, the standardized, rigorously designed, and large-scale randomized controlled trials (RCTs) were needed for further validation.

Keywords: traditional Chinese medicine; entecavir; HBV-related fibrosis or cirrhosis; meta-analysis; randomized controlled trials

Introduction

Liver fibrosis is a pathological process of abnormal connective tissue hyperplasia which is characterized by excessive accumulation of extracellular matrix, thereby leading to persistently destroying the physiological architecture of the liver [1–3]. Many etiologies, such as hepatitis virus, and non-alcoholic and alcoholic fatty liver disease, could develop liver fibrosis [4]. Hepatitis B virus (HBV) infection is a major etiology in China and Asia, promoting the pathological process [5]. According to the epidemiological survey results, over 350 million people are suffering from chronic hepatitis B (CHB) worldwide. Persistent HBV infection can lead to liver fibrosis, even hepatocellular carcinoma (HCC). Therefore, timely diagnosis and treatment of liver fibrosis should be considered for CHB patients. Currently, etiological treatment is the main strategy of anti-liver fibrosis, the antiviral treatment is a main etiological regimen for HBV or hepatitis C virus-caused chronic hepatitis, including interferon-based therapies and several nucleos(t)ide analogues. Clinically, nucleos(t)ide analogues such as entecavir, adefovir dipivoxil, tenofovir disoproxil and tenofovir alafenamide are mainly used to treat CHB related liver fibrosis, whose therapeutic mechanisms mainly involve the suppression of HBV-DNA replication [6–8]. Anti-viral drugs could regress liver fibrosis, but its efficacy was limited. Many patients remain hepatic fibrosis when HBV DNA were under detectable level after enough duration of anti-viral treatment. The ideal strategy for treating CHB with liver fibrosis should be conducted anti-viral combined with anti-fibrotic agents. Although many anti-fibrotic drugs have shown underlying effects in animal experiments, their clinical effects have been absent [9, 10]. Therefore, most Chinese and Asian sufferers put their eyes into complementary and alternative medicine. In China, Traditional Chinese medicine (TCM) has proven to be effective in the management of liver fibrosis due to its unique superiorities. So far, it has formed the "Guidelines for Diagnosis and Treatment of Liver Fibrosis with Integrated Traditional Chinese and Western Medicine" and "Consensus Opinions on Diagnosis and Treatment of Liver Fibrosis with Integrated Traditional Chinese and Western Medicine" [11, 12]. For instance, Chinese patent medicines such as Fuzheng Huayu capsules, Biejia Ruangan tablets, and Anluo Huaxian pills are all recommended for the treatment of liver fibrosis or cirrhosis. There are some published clinical studies using the combination therapy of TCM and nucleos(t)ide analogues [13–16].

Early publications are limited to small retrospective experiences and few prospective trials. Many studies evaluated the efficacy and safety without histological outcomes but only by observing the serum liver fibrotic markers, liver function, and adverse events. This may lead to a problem: Is combination therapy effective and safe enough to be practiced clinically? In recent years, many studies adopted RCT design and histological evaluation to report clinical outcomes, but there is still a lack of meta-analysis or systematic review to assess the regression of liver fibrosis after antiviral and TCM therapy. Therefore, we are about to conduct this meta-analysis to address this issue. It can offer some guidelines for the clinical application of related drugs.

Materials and methods

Search strategies

We performed a systematic and comprehensive literature search of multiple electronic databases including Cochrane Library, SpringerLink, EMBASE, Cochrane, Wanfang Data, China National Knowledge Infrastructure, Chinese Biomedicine Database, and Chinese Scientific Journals Database. The including search terms were as follows: "liver fibrosis", "hepatitis fibrosis", "liver cirrhosis", "hepatitis cirrhosis", "Traditional Chinese Medicine", "antiviral drugs", "Fuzheng Huayu", "Anluo Huaxian", "Biejia Ruangan", "entecavir", "randomized controlled trials", "prospective cohort study" in English or Chinese. The dates of studies ranged from the establishment of databases to 25 December 2023.

Inclusion criteria

Two review authors independently extracted data according to the selected criteria, The inclusion criteria were as follows:

(1) RCT;

(2) Persistent serum hepatitis B surface antigen (HBsAg) positive for ≥ 6 months, and (or) HBV DNA positive;

(3) Treatment-naïve for antiviral therapy;

(4) HBV-related cirrhosis was diagnosed according to definite diagnostic criteria, and liver biopsy-confirmed chronic hepatitis B with fibrosis stage ≥ F1;

(5) Treatment groups received Traditional Chinese medicine combined with routine medicine, and contro groups were only treated with routine medicine (Antivirals plus placebo or antivirals alone). Treatment course ≥ 48weeks;

(6) A semi-quantitative assessment of histopathology must be adopted. Fibrotic stages were evaluated with the Ishak system [17]. All participants received twice liver biopsies before and after treatment.

Exclusion criteria

Items of exclusion criteria included: (a) Overlapped published articles and incomplete data in studies, or data could not be analyzed. (b) Review, animal experiments and other non-clinical research literature. (c) Hepatitis B overlapped with other hepatitis virus infections. (d) There are significant differences between the treatment and the control groups involving age, gender, course of disease, and liver fibrosis stage.

Data extraction and quality assessment

Data extraction was independently conducted by two reviewers. The general information of the retrieved articles was extracted, including first author, publication year, sample size, gender, age, treatment course, intervention applied in two groups, and outcome measures. Detailed method information including random sequence generation, blinding, allocation concealment, description of withdrawal or dropout, follow-up periods, and adverse events. We used the Jadad scale to initially screen the literature and evaluated methodological quality using the Cochrane Collaboration's risk of bias tool [18, 19].

Data analysis

RevMan 5.3 software provided by Cochrane Collaboration would be used for statistical analysis.

Heterogeneity test. Heterogeneity was statistically assessed by Cochrane's Q test and I^2 test. When there was no significant heterogeneity ($P \geq 0.05$, $I^2 \leq 50\%$), a fixed effect model was adopted. If noticeable heterogeneity existed ($I^2 > 50\%$ or $P < 0.05$), a random effect model was used.

Analysis of outcome indicators. Odds ratio (OR) was adopted in dichotomous variables, such as clinical efficacy rate, improvements of necro-inflammation, HBV DNA undetectable rate, HBeAg loss, and HBeAg seroconversion, whereas mean difference was applied in continuous variables such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, γ–glutamyl transpeptidase, procollagen III protein, hyaluronic acid (HA), laminin, Collagen C Type IV (IV-C), HBsAg (hepatitis B surface antigen) seroconversion, collagen parameters and liver stiffness measurement. The funnel plot was adopted to analyze the publication bias of enrolled researchers.

Sensitivity analysis. Sensitivity analysis was performed using Stata version 13.0 software to verify the robustness of results and explain the source of heterogeneity in each RCT.

Results

Study characteristics

A total of 9,324 potential trials were screened by the search strategies. 8,170 studies were excluded after screening the titles and abstracts. Based on the criteria of this meta-analysis, 5 articles with a total of

1,606 participants meeting the eligibility were ultimately included [20–24]. The flow chart of the literature search process is shown in Figure 1. All of the identified studies were conducted in China, three of them were published in the Chinese language [22–24], and the others were published in the English language [20, 21]. The ages of participants were from 18 to 65 years old. The types of intervention were classified as ETV (N = 5) and combined treatment (TCM + ETV) (N = 5). TCM was prepared as tablets (N = 2) and pills (N = 1). The range of intervention duration in the studies ranged from 48 to 78 weeks. All selected RCTs reported histological responses at the end of the treatment. Table 1 describes the characteristics of the included studies. The Source and quality control measures of 5 trials are presented in Table 2, and the components are extracted in Table 3.

Methodological quality

We used the Cochrane risk of bias tool to make an appraisal of the methodological quality of the included trials. A description of methodological quality can be checked in Table 4. Four studies used randomization codes generated by computer [20–22, 24], the

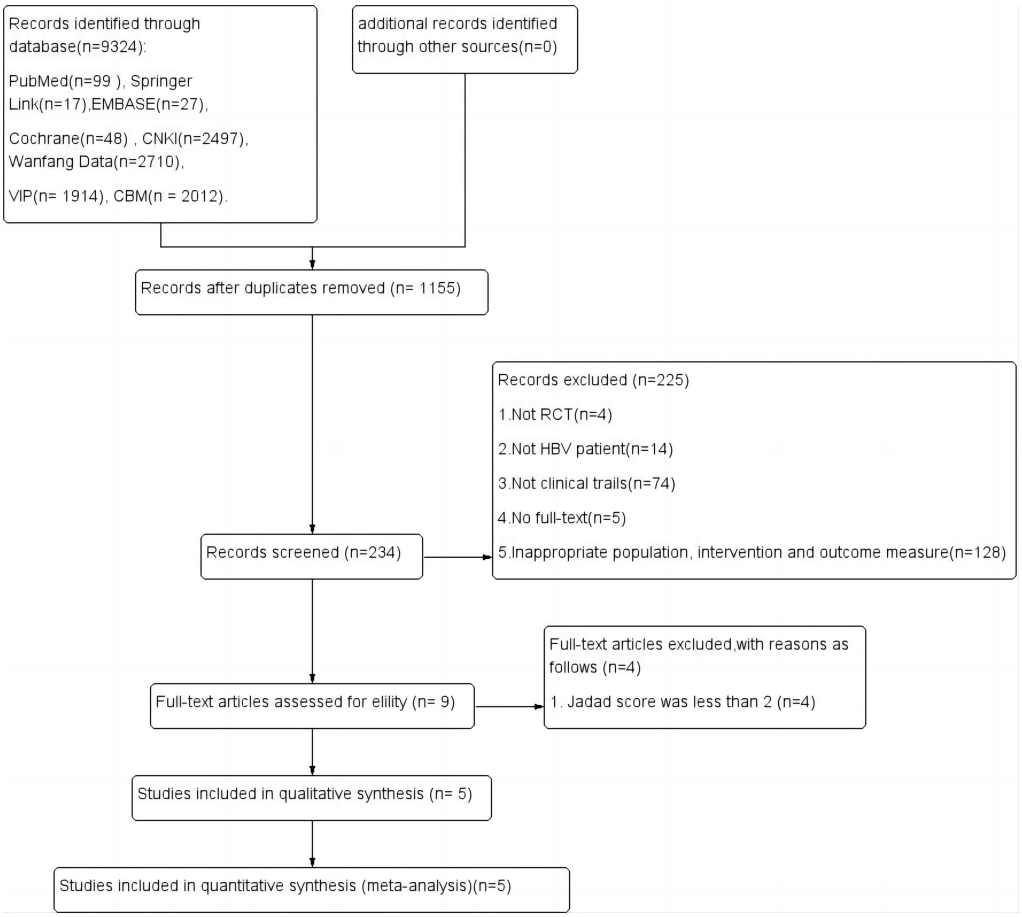

Figure 1 Flow chart of study selection process

Table 1 Characteristics of included studies

Included study (year)	Country	Patients (T/C)	Gender (Male/Female)	Age	Intervention	Treatment courses (weeks)	Outcome measure
Gui HL, 2020	China	22/24	T: 15/10 C: 19/7	T: 44.48 ± 10.31 C: 42.46 ± 11.39	T: FZHY + ETV C: ETV + placebo	48	1 + 2 + 3 + 11 + 12 + 13 + 14
Rong GH, 2020	China	358/347	T: 243/115 C: 241/106	T: 42.2 ± 9.8 C: 42.4 ± 10.1	T: BJRG + ETV C: ETV + placebo	72	1 + 2 + 3 + 10 + 11 + 13
Xu YF, 2020	China	18/26	T: 14/18 C: 26/8	T: 43.33 ± 10.79 C: 42.81 ± 9.32	T: FZHY + ETV C: ETV + placebo	48	1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 + 12 + 13
Miao L, 2019	China	142/77	T: 107/35 C: 16/61	T: 39.13 ± 10.39 C: 37.91 ± 11.08	T:ALHX + ETV C:ETV	78	1 + 2 + 3 + 11 + 12 + 13
Li SS, 2019	China	24/35	T: 19/8 C: 23/14	T: 42.89 ± 7.9 C: 40.7 ± 8.5	T: BJRG + ETV C: ETV + placebo	72	1 + 2 + 3 + 4 + 13 + 15

FZHY, Fuzheng Huayu; BJRG: Biejia Ruangan; ALHX: Anluo Huaxian; ETV: entecavir; 1 = regression of liver fibrosis; 2 = histological improvement; 3 = alanine aminotransferase(ALT); 4 = aspartate aminotransferase (AST); 5 = total bilirubin (TBIL); 6 = procollagen III protein (PC III); 7 = hyaluronic acid (HA); 8 = laminin (LN); 9 = Collagen C Type IV (IV-C); 10 = HBsAg seroconversion; 11 = HBeAg seroconversion; 12 = HBeAg loss; 13 = HBV DNA undetectable rate; 14 = collagen parameters; 15 = liver stiffness measurement (LSM).

Table 2 The source and quality control measures of included studies

Study	Formulation	Source	Quality control reported? (Y/N)	Chemical analysis reported? (Y/N)
Gui et al., 2020 [20]	Fuzheng Huayu tablet	Shanghai Huanghai Pharmaceutical Co., Ltd.	Y-National Medical Products Administration	N
Rong et al., 2020 [21]	Biejia-Ruangan tablet	Inner Mongolia Furi Medicine Co., Ltd.	Y-National Medical Products Administration	N
Xu et al., 2020 [22]	Fuzheng Huayu tablet	Shanghai Huanghai Pharmaceutical Co., Ltd.	Y-National Medical Products Administration	N
Miao et al., 2019 [23]	Anluohuaxian pill	Senlong Pharmaceutical Co., Ltd.	Y-National Medical Products Administration	N
Li et al., 2019 [24]	Biejia-Ruangan tablet	Inner Mongolia Furi Medicine Co., Ltd.	Y-National Medical Products Administration	N

Table 3 The ingredients of each formula in the included trials

Author	Formulation	Ingredients of each formula		
		Chinese name	Latin name	English name
Gui et al., 2020 [20] Xu et al., 2020 [22]	Fuzheng Huayu tablet	Danshen	*Salviae Miltiorrhizae Radix et Rhizoma*	Dan-Shen Root
		Dongchongxiacao	*Cordyceps*	Chinese Caterpillar Fungus
		Taoren	*Persicae Semen*	Peach Seed
		Songhuafen	*Pini Pollen*	Pine pollen
		Jiaogulan	*Gynostemma pentaphyllum* (Thunb.) Makino	Fiveleaf Gynostemma Herb
		Wuweizi	*Schisandrae Chinensis Fructus*	Chinese Magnolcavine Fruit
		Biejia	*Trionycis Carapax*	Turtle Carapace
		Ezhu	*Curcumae Rhizoma*	Acruginous Turmeric Rhizome
		Chishao	*Paeoniae Radix Rubra*	Red paeony root
		Danggui	*Angelicae Sinensis Radix*	Chinese Angelica
Rong et al., 2020 [21] Li et al., 2019 [24]	Biejia-Ruangan tablet	Sanqi	*Notoginseng Radix*	Sanchi
		Dangshen	*Codonopsis Radix*	Tangshen
		Huangqi	*Astragali Radix*	Milkvetch Root
		Ziheche	*Placenta Hominis*	Dried Human Placenta
		Dongchongxiacao	*Cordyceps*	Chinese Caterpillar Fungus
		Banlangen	*Isatidis Radix*	Root of Indigowoad
		Lianqiao	*Forsythiae Fructus*	Weeping Forsythia Capsule
		Dihuang	*Rehmanniae Radix*	Rehmannia Glutinosa
		Sanqi	*Notoginseng Radix*	Sanchi
		Shuizhi	*Hirudo*	Leech
		Jiangcan	*Bombyx Batryticatus*	Stiff Silkworm
		Dilong	*Pheretima*	Earthworm
		Baizhu	*Atractylodis Macrocephalae Rhizoma*	Largehead Atractylodes Rh
Miao et al., 2019 [23]	Anluohuaxian pill	Yujin	*Curcumae Radix*	Aromatic Turmeric Root - tuber
		Niuhuang	*Bovis Calculus*	Bezoar
		Walengzi	*Concha Arcae*	Clam shell
		Mudanpi	*Moutan Cortex*	Tree Peony Bark
		Dahuang	*Rhei Radix et Rhizoma*	Rhubarb root and rhizome
		Shengmaiya	*Fructus Hordei Germinatus*	Malt
		Jineijin	*Galli Gigeriae Endothelium Corneum*	Chicken's Gizzard - membrane
		Shuiniujiao	*Cornu Bubali*	Buffalo Horn

other mentioned the word "randomization " without describing the specific process [23]. What's more, four studies mentioned double blinding or allocation conceal [20–22, 24], and the other adopted open-label [23]. In addition, two trials reported dropout or withdrawal but only one of them reported whether they had used intention-to-treat analysis [20, 21]. Overall, Jadad scores of these publications ranged from 2 to 5 points, four of the trials were considered as high-quality [20–22, 24], and the other trial was regarded as low-quality [23]. The majority of the studies were rated low risk for selection bias, performance bias, and detection bias. An assessment of the methodological quality of each selected trial was summarized in Table 2. And the accordingly assessment is shown in Figure 2.

Primary outcome

Regression of liver fibrosis. Histological comparison was performed in 5 trials in which 564 patients were assigned to experiment groups (TCM plus ETV) while 509 patients were assigned to control groups

(ETV monotherapy) . The regression of liver fibrosis was defined as a reduction of ≥ 1 point than the baseline by the Ishak fibrosis stage system [25, 26]. The result showed that TCM plus ETV significantly improved significant improvement of fibrosis as compared to ETV (OR (Total) = 1.65; 95% CI: 1.29, 2.11; $P < 0.000,1$) (see Figure 3). No heterogeneity was observed ($\chi^2 = 2.45$, $P = 0.65$, $I^2 = 0\%$). Potential publication bias was identified by funnel plot analysis in Figure 4.We also did sensitivity analysis to analyze the source of heterogeneity accordingly and found that Rong's research may be the main influence on the results (see Figure 5)

Figure 2 Risk of bias summary and graph

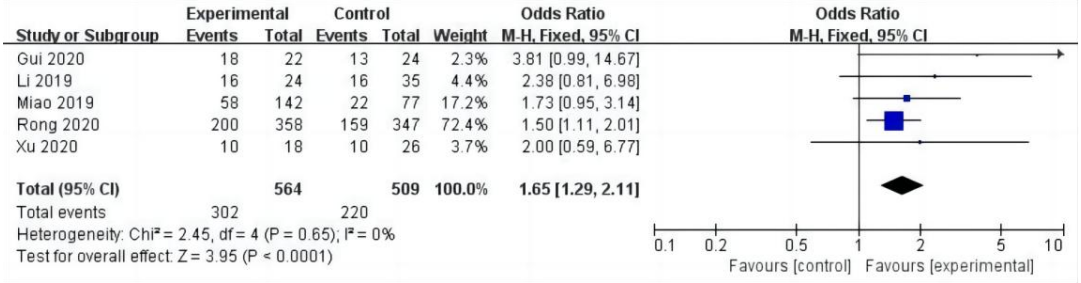

Figure 3 Forest plot of primary outcomes

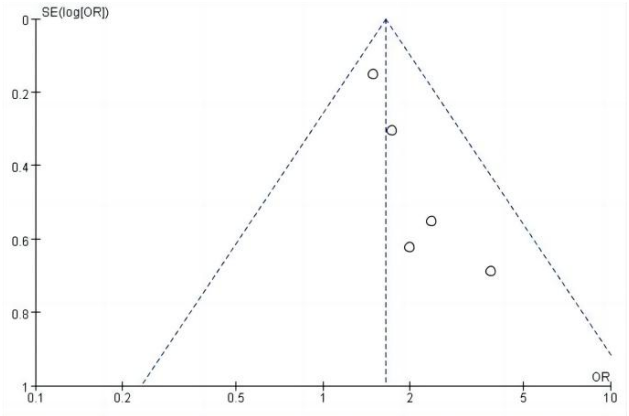

Figure 4 Funnel plot of primary outcomes

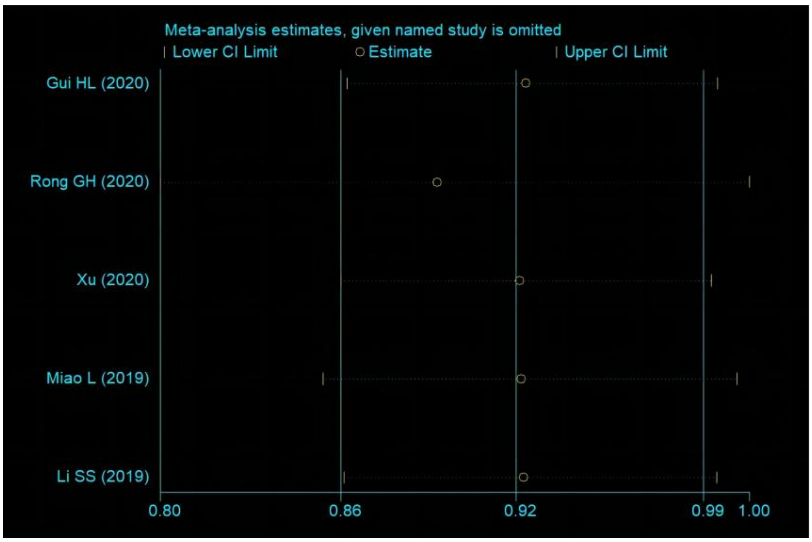

Figure 5 Sensitivity analysis of clinical efficacy

Secondary outcomes

Histological necro-inflammatory improvement

Four studies [20–23] reported the improvement of necroinflammatory. Moreover, necro-inflammatory activity was assessed by a modified Knodell histological activity index score, the necroinflammatory improvement was defined as a reduction of ≥ 2 points than the baseline in the Knodell necroinflammatory score [27, 28]. As shown in the forest plot (see Figure 6), no statistically significant difference was found in either group. Interestingly, two studies showed that TCM combined with ETV can improve histological necro-inflammation [20,22]. Therefore, large samples are required to verify the findings.

Serum liver function

All included trials reported ALT [20–24]. Two reported AST [22, 24] and one reported total bilirubin [24]. Results of qualitative analysis indicated that there was no significant difference in biochemical endpoints in each study.

Virological indicators

Although all studies [20–24] reported serum HBV DNA undetectable rate, the forest plots (see Figure 7) revealed that the rate of undetectable serum HBV DNA had no significant difference between the two groups. Three studies reported HBeAg seroconversion [20, 21, 23]. The forest plot of the rate of serum HBeAg seroconversion using random effect models showed no statistically significant difference in Figure 8. Three of those described HBeAg loss [20, 22, 23], but the forest plot (Figure 9) showed that the difference between the two groups was not statistically significant. One reported HBsAg seroconversion [21]. What's depressing is that no patient in this study developed HBsAg seroconversion. So large-scale RCTs are warranted to provide more robust evidence to support the efficacy.

Serum fibrosis indicators

Only one of the included studies reported serum fibrosis indicators [22], which was composed of procollagen III protein, HA, laminin, and IV-C. Compared to entecavir alone, we found that TCM plus entecavir therapy can improve patients' serum fibrosis indicators.

Collagen parameters

In the included trials, only one evaluated the changes in different collagen parameters from portal, septal and fiber areas via dual-photon microscopy [20]. The study showed collagen parameters were significantly improved in the combination group, supporting the importance of septa resorption in fibrosis regression.

Liver stiffness measurement

Because only one trial reported the use of transient elastography to measure liver stiffness [24], the item was only qualitatively analyzed. However in the improvement of liver stiffness, the treatment groups were potentially superior to the control groups.

Adverse events

In this meta-analysis, one reported no noticeable adverse effects during the treatment course except that one patient developed HCC [20]. The other one reported no different adverse effects between the experiment and control groups, which indicated an excellent safety profile [21].

Discussion

In this meta-analysis, participants with HBV fibrosis received who TCM + ETV treatment had better efficacy and alleviations in Ishak fibrosis stage (a decrease of Ishak score ≥1) than in ETV monotherapy. The evaluation results showed no significant difference in the improvement of biochemical, virologic responses, serologic responses, and histological necroinflammation between the two groups at the same time. These findings suggested that TCM + ETV may have the same benefits on anti-viral and hepatic inflammation as ETV. However it provided convincing evidence to support that TCM can be applied as an effective adjuvant to improve HBV-related fibrosis or cirrhosis.

Current studies do not fully understand the pathogenesis of HBV fibrosis. Most attention has been focused on hepatic stellate cell and myofibroblast responses, given their critical roles in extracellular matrix production. Liver injury provokes a complex multicellular response involving other resident cells, such as hepatocytes, macrophages, sinusoidal endothelial cells, and different immune cell families [29–31]. Entecavir is a nucleoside analogue of 2'-deoxyguanosine, inhibiting replication of the hepatitis B virus from intracellular triphosphate. Entecavir is phosphorylated intracellularly where it acts by competing with guanosine for uptake by the HBV DNA polymerase and incorporation into the growing HBV DNA molecule, leading to inhibition of polymerase activity and chain termination. Entecavir lowers HBV DNA levels and leads to improvements in serum aminotransferase levels in the majority of patients [32]. Viral replication is now recognized as a key driver of liver injury and disease progression. Now the main goal of treating chronic HBV infection has been shifted to the suppression of HBV replication under undetectable levels [33, 34]. Several researches have shown that long-term entecavir therapy is beneficial for sustained improvement in liver histology, regression of advanced

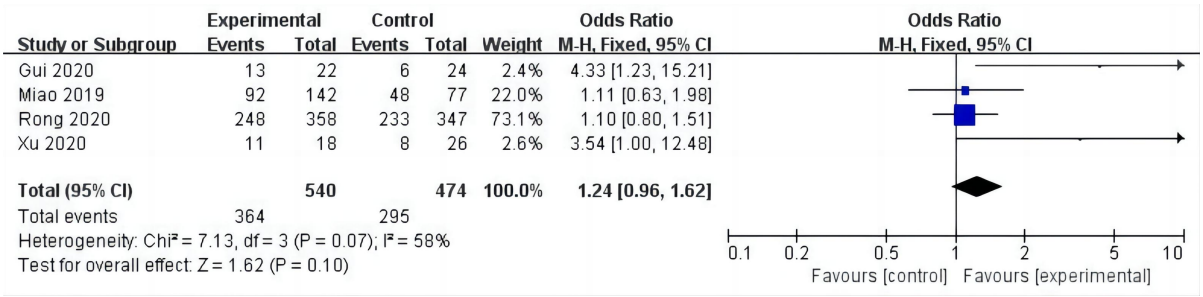

Figure 6 Forest plot of improvements in necro-inflammatory

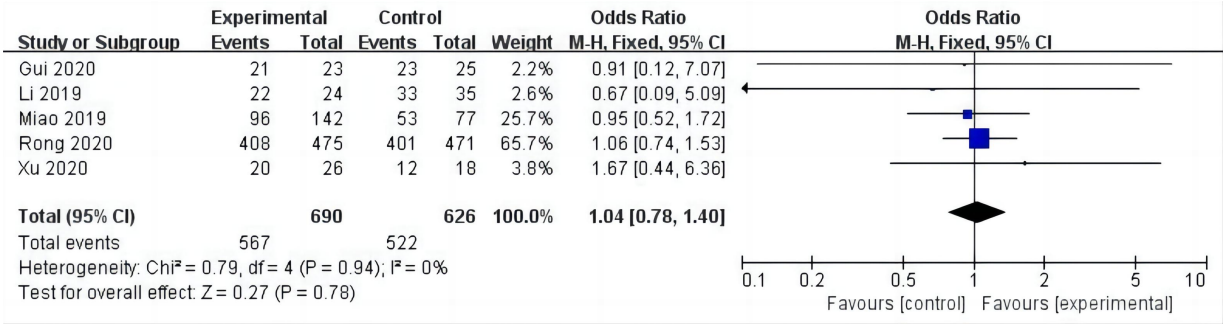

Figure 7 Forest plot of improvement in HBV DNA undetectable rate

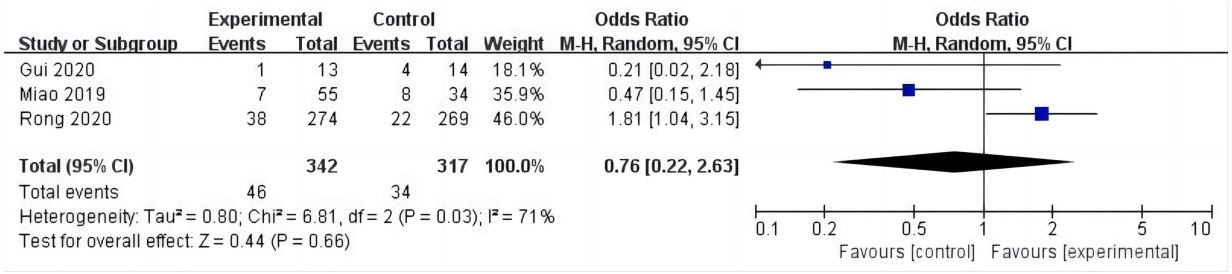

Figure 8 Forest plot of improvement in HBeAg seroconversion

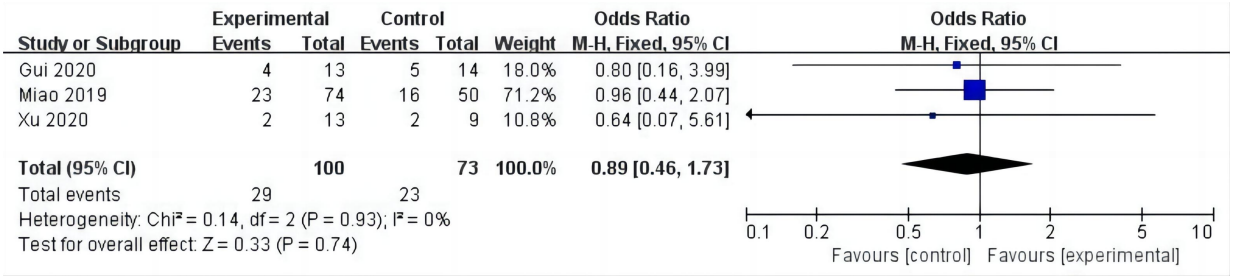

Figure 9 Forest plot of improvement in HBeAg loss

fibrosis, and even reversal of cirrhosis, especially reduction in Ishak fibrosis score to 4 or less and HBV DNA serum levels, and the other antiviral drugs have reached the same conclusion [28,35–37]. Some studies showed that about 1/3 of patients still fail to improve liver fibrosis, or even develop HCC while receiving 5- to 10- year antiviral therapy [26,38]. In addition, almost one-third of patients reached detectable low-level HBV DNA after entecavir therapy for 78 weeks, but incomplete virologic response and low-level viremia could elicit a higher risk of liver fibrosis progression [39]. Adjunctive administration of antifibrotic agents would be useful for patients with HBV infection when coupled with an effective treatment.

Nowadays, many researchers have found that TCM can relieve or even reverse CHB-related liver fibrosis. Experimental data have proved that the mechanism of anti-fibrosis of TCMs involves anti-peroxidation damage and apoptosis of hepatocytes, inhibition of hepatic stellate cell activation, and improvement of hepatic sinusoidal capillarization [40–45]. Clinical trials have demonstrated that liver fibrosis decreased significantly and the inflammatory activity was improved after treatment, as well as a decrease in HA, LM, P-III-P, and IV-C content and improvement in serum albumin, ALT, AST, and γ-glutamyl transpeptidase, which confirmed the effectiveness of Fuzheng Huayu capsule [46]. Biejia Ruangan tablet has also ability to improve liver tissue fibrosis and inflammation, whose mechanism is connected with the inhibition of hepatic stellate cells activation and promotion of apoptosis of activated hepatic stellate cells [43, 47]. Overall, TCM can be used as a multi-targeted treatment for HBV fibrosis and deserves further exploration regardless of clinical or animal trials.

This meta-analysis also has a few potential limitations. In the first place, all trials were conducted in China. It was hard to validate the

efficacy of TCM applied to non-Asian. Secondly, blinding was inadequate in the included studies. One study was an open randomized trial [23]. This reduced the evidence quality. Next, since the small number of included literature, it is impossible to compare different Chinese medicines currently. We hope that more relevant clinical research published in the future, and the most effective anti-fibrosis herb will be explored. The fourth point is that sample sizes were small in three studies. Only three trials [20, 21, 23] were multi-center, and the other study used a stratified analysis of the fibrotic stage [23], causing an inability to truly reflect general trends. Fifth, only two studies [20, 21] reported dropouts. One study reported dropouts without intention-to-treat analysis, which could lead to bias in evaluating the clinical efficacy. Although the TCM drugs were different in each study, which will make the quality less convincing. However, the experimental drugs were composed of TCM, we aimed to put them under the category of TCM and compare the efficacy of TCM combined ETV therapy with ETV monotherapy. We also added sensitivity analysis to analyze the source of heterogeneity accordingly and found that Rong's research may be the main influence on the results. Even so, included studies adopted histological evaluation, and four of them with blinding. This meta-analysis still provides a reference for clinical. Additionally, large samples with multi-center RCTs should be conducted to further stronger evidence that TCM has an advantage in the management of HBV-related liver fibrosis in clinical applications in the future.

Conclusions

In brief, this meta-analysis could provide evidence for the efficacy and safety of TCM in treating patients with hepatitis B-related fibrosis. Nevertheless, further standardized, rigorously designed, and large-scale RCTs are required to provide more convincing and solid evidence.

References

1. Schuppan D, Ruehl M, Somasundaram R, Hahn EG. Matrix as a Modulator of Hepatic Fibrogenesis. *Semin Liver Dis.* 2001;21(3):351–372. Available at: http://doi.org/10.1055/s-2001-17556
2. Wynn T. Cellular and molecular mechanisms of fibrosis. *J Pathol.* 2007;214(2):199–210. Available at: http://doi.org/10.1002/path.2277
3. Friedman SL. Mechanisms of Hepatic Fibrogenesis. *Gastroenterology.* 2008;134(6):1655–69. Available at: http://doi.org/10.1053/j.gastro.2008.03.003
4. Bataller R, Brenner DA. Liver fibrosis. *J Clin Invest.* 2005;115(2):209-218. Available at: http://doi.org/10.1172/JCI24282
5. Wang F, Fan J, Zhang Z, Gao B, Wang H. The global burden of liver disease: The major impact of China. *Hepatology.* 2014;60(6):2099–2108. Available at: http://doi.org/10.1002/hep.27406
6. Sundaram V, Kowdley K. Management of chronic hepatitis B infection. *BMJ.* 2015;351(oct213):h4263–h4263. Available at: http://doi.org/10.1136/bmj.h4263
7. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B. *Hepatology.* 2018;67(4):1560–1599. Available at: http://doi.org/10.1002/hep.29800
8. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017; 67(2): 370-398. Available at: http://doi.org/10.1016/j.jhep.2017.03.021
9. Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. *Cells.* 2020;9(4):875. Available at: http://doi.org/10.3390/cells9040875
10. Schuppan D, Ashfaq-Khan M, Yang AT, Kim YO. Liver fibrosis: Direct antifibrotic agents and targeted therapies. *Matrix Biol.* 2018;68–69:435–51. Available at: http://doi.org/10.1016/j.matbio.2018.04.006
11. Liver Disease Committee, Chinese Association of Integrative Medicine. Guidelines for the diagnosis and treatment of liver fibrosis with integrated traditional Chinese and Western medicine (2019 edition). *Zhonghua Gan Zang Bing Za Zhi.* 2019; 27(7): 144-1449.
12. Chinese Society of Integrated Traditional and Western Medicine Digestive System Diseases Committee.Consensus on the diagnosis and treatment of liver fibrosis with integrated Chinese and Western medicine. *Chin J Integ Trad West Med*. 2017; 25:895-900.
13. Huang ZJ, Zeng CP. The therapy of entecavir combined with Anluo Huaxian capsule on HBeAg positive chronic hepatitis B-related liver fibrosis in 134 cases , *Chin J Integr Tradit West Med Liver Dis.* 2016; 26:74-75.
14. Chen HB. Clinical effect of entecavir combined with Dahuang Zhechong pills in the treatment of hepatitis B liver fibrosis, *Clin Res Pract.* 2018; 3: 133-134. Available at: http://doi.org/10.19347/j.cnki.2096-1413.201805065.
15. Chen Y, Yang YP. The role of traditional Chinese medicine in blocking and reversing hepatic fibrosis: current status, hope, and challenge, *J Clin Hepatol.* 2018; 34(4): 689-693. Available at: http://doi.org/10.3969/j.issn.1001-5256.2018.04.002.
16. Zhang YH, Guo WQ, Guo PJ. The effect of adefovir dioxin combined with Anluo Huaxian pills on hepatic fibrosis indexes in patients with chronic hepatitis B, *Chin Hepatol* 2013; 18:620-622. Available at: http://doi.org/10.14000/j.cnki.issn.1008-1704.2013.09.006
17. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol.* 1995;22(6):696–99. Available at: http://doi.org/10.1016/0168-8278(95)80226-6
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*.1996; 17(1): 1-12. Available at: http://doi.org/10.1016/0197-2456(95)00134-4
19. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–60. Available at: http://doi.org/10.1136/bmj.327.7414.557
20. Gui H, Zhao C, Wang Y, et al. Histological Outcome of Fuzheng Huayu plus Entecavir Combination Therapy in Chronic Hepatitis B Patients with Significant Liver Fibrosis. *J Clin Transl Hepatol.* 2020;8(3):1–8. Available at: http://doi.org/10.14218/JCTH.2020.00004
21. Rong G, Chen Y, Yu Z, et al. Synergistic Effect of Biejia-Ruangan on Fibrosis Regression in Patients With Chronic Hepatitis B Treated With Entecavir: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial.*J Infect Dis.* 2020;225(6):1091–99. Available at: http://doi.org/10.1093/infdis/jiaa266
22. Xu YF, Zhao ZM, Zhang YY, et al. Single center observation of fibrosis improvement about Fuzheng Huayu combined with entecavir in the treatment of hepatitis B cirrhosis patients, *Chin J Integr Trad West Med Dig.* 2020; 28: 909-913.
23. Miao L, Yang WN, Dong XQ, et al. Combined anluohuaxianwan and entecavir treatment significantly improve the improvement rate of liver fibrosis in patients with chronic hepatitis B virus infection. *Zhonghua Gan Zang Bing Za Zhi*. 2019; 27(7): 521-526. Available at: https://pubmed.ncbi.nlm.nih.gov/31357778/
24. Li SS, Chen Y, Qu JH, et al. Clinical effect evaluation of entecavir combined with compound biejia ruangan tablet on chronic hepatitis B hepatic fibrosis, *Infect Dis Info*. 2019; 32: 119-121. Available at: http://doi.org/10.3969/j.issn.1007-8134.2019.02.005.
25. Ishak K, Baptista A, Bianchi L, et al. Histological grading and

staging of chronic hepatitis. *J Hepatol.* 1995;22(6):696–99. Available at: http://doi.org/10.1016/0168-8278(95)80226-6
26. Chang TT, Liaw YF, Wu SS, et al. Long-Term Entecavir Therapy Results in the Reversal of Fibrosis/Cirrhosis and Continued Histological Improvement in Patients with Chronic Hepatitis B†,‡. *Hepatology.* 2010;52(3):886–93. Available at: http://doi.org/10.1002/hep.23785
27. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis†. *Hepatology.* 1981;1(5):431–35. Available at: http://doi.org/10.1002/hep.1840010511
28. Xu Y. Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis. *WJG.* 2015;21(25):7869. Available at: http://doi.org/10.3748/wjg.v21.i25.7869
29. Lee YA, Wallace MC, Friedman SL. Pathobiology of liver fibrosis: a translational success story. *Gut.* 2015;64(5):830–41. Available at: http://doi.org/10.1136/gutjnl-2014-306842
30. Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. *Mol Asp Med.* 2019;65:37–55. Available at: http://doi.org/10.1016/j.mam.2018.09.002
31. Karlmark KR, Weiskirchen R, Zimmermann HW, et al. Hepatic recruitment of the inflammatory Gr1+ monocyte subset upon liver injury promotes hepatic fibrosis #. *Hepatology.* 2009;50(1):261–74. Available at: http://doi.org/10.1002/hep.22950
32. Lee HW, Park JY, Ahn SH. An evaluation of entecavir for the treatment of chronic hepatitis B infection in adults. *Expert Rev Gastroent.* 2016;10(2):177–86. Available at: http://doi.org/10.1586/17474124.2016.1125781
33. Chen CJ. Risk of Hepatocellular Carcinoma Across a Biological Gradient of Serum Hepatitis B Virus DNA Level. *JAMA.* 2006;295(1):65. Available at: http://doi.org/10.1001/jama.295.1.65
34. Iloeje UH, Yang H, Su J, Jen C, You S, Chen C. Predicting Cirrhosis Risk Based on the Level of Circulating Hepatitis B Viral Load. *Gastroenterology.* 2006;130(3):678–86. Available at: http://doi.org/10.1053/j.gastro.2005.11.016
35. Schiff ER, Lee SS, Chao YC, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol.* 2011; 9(3): 274-276. Available at: https://doi.org/10.1016/j.cgh.2010.11.040
36. Kose S, Tatar B, Gül S, Pala E. The effect of long-term entecavir therapy on liver histopathology in patients with chronic viral hepatitis B. *Acta Clin Belg.* 2016;71(4):244–49. Available at: http://doi.org/10.1080/17843286.2015.1118183
37. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *The Lancet.* 2013;381(9865):468–75. Available at: http://doi.org/10.1016/S0140-6736(12)61425-1
38. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut.* 2011;60(8):1109-1116. Available at: https://doi.org/10.1136/gut.2010.221846
39. Sun YM, Wu XN, Zhou JL, et al. Persistent Low Level of Hepatitis B Virus Promotes Fibrosis Progression During Therapy. *Clin Gastroenterol Hepatol.* 2020; 18(11): 2582-2591. Available at: https://doi.org/10.1016/j.cgh.2020.03.001
40. Liu H, Lv J, Zhao Z, et al. Fuzhenghuayu Decoction ameliorates hepatic fibrosis by attenuating experimental sinusoidal capillarization and liver angiogenesis. *Sci Rep.* 2019;9(1). Available at: http://doi.org/10.1038/s41598-019-54663-4
41. Pan Q, Wang YQ, Li GM, Duan XY, Fan JG. Fuzheng Huayu Recipe Ameliorates Liver Fibrosis by Restoring Balance between Epithelial-to-Mesenchymal Transition and Mesenchymal-to-Epithelial Transition in Hepatic Stellate Cells. *BioMed Res Int.* 2015;2015:1–11. Available at: http://doi.org/10.1155/2015/935903
42. Cheng Q, Li N, Chen M, et al. Fuzheng Huayu inhibits carbon tetrachloride-induced liver fibrosis in mice through activating hepatic NK cells. *J Ethnopharmacol.* 2013;145(1):175–81. Available at: http://doi.org/10.1016/j.jep.2012.10.047
43. Guo SG. Influence of serum collected from rat perfused with compoundBiejiaruangandrug on hepatic stellate cells. *WJG.* 2004;10(10):1487. Available at: http://doi.org/10.3748/wjg.v10.i10.1487
44. Wang L, Lu w, Gao YH, et al. Effect of Anluohuaxianwan on the expression of matrix metalloproteina ses and their inhibitors in rat liver with fibrosis. *Chin J Hepatol.* 2019; 27: 267-273. Available at: https://doi.org/10.3760/cma.j.issn.l007-3418.2019.04.006.
45. Tan XH, Li CQ, Zou SR, et al. Inhibitory effect of anluohuaxianwan on experimental hepatic fibrosis in rats. *Zhonghua Gan Zang Bing Za Zhi.* 2010; 18(1): 9-12. Available at: https://doi.org/10.3760/cma.j.issn.1007-3418.2010.01.003
46. Liu P. Multicenter clinical study on Fuzhenghuayu capsule against liver fibrosis due to chronic hepatitis B. *WJG.* 2005;11(19):2892. Available at: http://doi.org/10.3748/wjg.v11.i19.2892
47. Zhou GD, LI WS, Zhao JM, et al. Clinical pathological study on the mechanism of effect of Fufangbiejiaruanganpian in treatment of liver fibrosis. *Med J Chin PLA.* 2004; 29: 563-564. Available at: https://doi.org/10.3321/j.issn:0577-7402.2004.07.003.