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Network meta-analysis of the compensatory effect of different Chinese herbal compounds combined with Entecavir in the treatment of hepatitis B cirrhosis

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Author contributions

Hui-Wen Zheng and Yang Zheng co-wrote the article, Tie-Jian Zhao provided the article ideas and revised and polished the article, Wen-Xing He and Can-Li Xu conducted literature search and data collation, Rui-Wen Xu and Jia-Xi He conducted literature screening, Jia-Hui Wang made the stata diagram.

Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

ALT, glutamic pyruvic transaminase; HA, hyaluronic acid; ETV, Entecavir.

Citation

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Abstract

Objective: To evaluate the efficacy and safety of different Chinese herbal compounds combined with Entecavir in the treatment of hepatitis B cirrhosis during the compensatory period by using mesh meta-analysis.

Methods: PubMed, CNKI, Wanfang and VIP databases were searched by computer, and the retrieval time was from the establishment of each database to October 5, 2022. According to inclusion and exclusion criteria, literature search was conducted independently by two researchers. RevMan5.4.1 software provided by Cochrane was used for evaluation, and Stata16.0 software was used for statistical analysis.

Results: A total of 34 RCTs were included, involving 16 TCM compounds and 1543 patients. The results of network meta-analysis showed that ALT indexes of liver function were listed as Yiqi Jiedu Tongluo Method > Luoshugan Tablet > Anluo Huaxian Wan > Qishenrugan Capsule > Qingganhuaji Decoction > Ganshuang Granules > Compound Biejia Rugan Tablet > Rougan Sanjie Decoction > Shugan Jianpi Decoction > Shenqi Fuzheng Huayu Decoction > Peituhua Decoction > Shugan Jianpi Huoxu prescription > Rhubarb Zhezhan Capsule combined with Entecavir treatment respectively; The order of HA index of liver fibrosis was Heluo Shugan Tablet > Shugan Jianpi Huoxui prescription > Anluo Huaxian Wan > Compound Biejia Ruangan Tablet > Rougan Sanjie Decoction > Ganshuang Granules > Danji Huoxui Decoction > Yiqi Jiedu Tongluo Method > Rhubarb Zhezhe Capsule > Fuzheng Huayu Table > Shugan Jianpi Decoction > Rougan Huayu Decoction > Peitu Huayu Decoction > Qingganhuaji Prescription > Shenqi Fuzheng Huayu prescription combined with Entecavir respectively; In order of adverse reactions from best to worst, Shuganjianpi Decoction, Qishenrugangan Capsule, Ganshuang Granules, Peituhuazhi Decoction, compound Biejiruganpian, and He Shugan Pian combined with entecavir, respectively; The effective rate of treatment was listed as Ganshuang Granules > Compound Biejia Ruangan Tablets > uoshugan Tablets > Rougansanjie Decoction > Rhubarb Zhezhe Capsules > Yiqi Jiedu Tongluo Method > Qingganhuaji prescription > Anluo Huaxia Wan > Shugan Jianpi Decoction > Fuzheng Huayu tablets > Peituhuazhi Decoction > Shenqi Fuzheng Huayu prescription combined with Entecavir respectively.

Conclusion: Entecavir combined with supplementing qi and detoxifying and dredging collages is the best method to recover ALT index of liver function during the compensation period for hepatitis B cirrhosis; Entecavir combination and Luoshugan tablet were the best treatment for HA index of hepatic fibrosis; Entecavir combined with Shuganjianpi Decoction was the best treatment for adverse reactions; The best treatment efficiency was Entecavir combined with Ganshuang granules.

Keywords: TCM compound; Hepatitis B cirrhosis compensatory period; Network meta-analysis; Entecavir; Randomized controlled trial

Introduction

Cirrhosis is a pathological stage characterized by chronic inflammation of the liver, diffuse fibrosis, pseudolobules, regenerating nodules, and vascular proliferation in and out of the liver. In our country, patients with cirrhosis of the liver are mainly caused by HBV infection [1]. There were no obvious symptoms in the compensatory stage, and the decompensated stage mainly included clinical stage 3–ascites and no bleeding, clinical stage 4–esophageal venous bleeding, and clinical stage 5–hepatorenal syndrome or cystic hematoma. The main complications of decompensated patients include endocrine disorders, hypothermic inflammatory anemia, prone to bleeding and digestive tract discomfort [2]. Therefore, early detection and treatment is the key to prevent cirrhosis. The key to the common treatment of liver cirrhosis in China is antiviral therapy. If

necessary, antiviral drugs should be given to protect the liver and nourish the liver. Entecavir (ETV) is a commonly used first-line drug against hepatitis B virus in modern clinical practice, but after many experiments, it was found that the efficacy of Entecavir has certain limitations. Modern scholars have found that Entecavir and Chinese herbal compound have different mechanisms of action in the treatment of hepatitis B cirrhosis. Compared with Entecavir alone, the combined use of both has more obvious effects on hepatitis B virus reduction and liver function recovery in patients [3]. There are more than ten kinds of TCM compounds commonly used in the clinical treatment of hepatitis B, each of which has different curative effects and advantages, but the comparison of curative effects of TCM compounds is still lacking. Based on network meta-analysis, this study compared the effectiveness of different Chinese herbal compounds combined with Entecavir in the treatment of hepatitis B cirrhosis during the compensatory period, providing favorable and reliable reference evidence for later clinical drug use.

Data and methods

Included literature
Randomized controlled trials (RCTS) published at home and abroad.

Research object
(1) The subjects included in the study should meet any of the following criteria for the compensation period of hepatitis B cirrhosis: Diagnostic criteria for the compensatory period of hepatitis B cirrhosis in the Guidelines for Diagnosis and Treatment of Cirrhosis; The diagnostic criteria for the compensatory period of hepatitis B cirrhosis in the Guidelines for the Diagnosis and Treatment of Cirrhosis; Chinese Guidelines on The Management of Liver Cirrhosis. (2) There was no significant difference in gender, age and nationality of patients in the same study, and they were comparable.

Intervention measure
The experimental group was treated with Chinese herbal compound combined with entecavir. The control group was treated with entecavir alone. The dose of entecavir and the number of times of administration were the same in the two groups. The experimental course of 2 groups was 6 months.

Exclusion criteria
① republished papers; ② the type of research is not RCTS and the quality of the paper is poor; ③ the subjects did not meet the diagnostic criteria for hepatitis B cirrhosis; ④ literatures with non-standard data or incomplete data cannot be obtained; ⑤ the course of treatment is less than 6 months or more.

Literature retrieval strategy
Chinese and English databases were searched by computer, including CNKI, WanFang, VIP, PubMed, Web of Science and Cochrane databases. Chinese and English databases were searched by computer, including CNKI, WanFang, VIP, PubMed, Web of Science and Cochrane databases. The key words are adjusted according to the characteristics of each database. The search terms in Chinese database were “Hepatitis B cirrhosis compensation period”, “hepatitis B cirrhosis compensation period”, “Entecavir”, “TCM compound", “random”, etc. The search terms in the citation database are “Compensation period of hepatitis B cirrhosis”, “Entecavir”, “Chinese medicine compound” and “random”. The search strategy is a combination of subject words and free words.

Literature selection process and quality evaluation
Literature search screening and evaluation were carried out independently and synchronously by two researchers. Literature preliminary screening was conducted by reading literature titles and abstracts, and irrelevant literature was removed without careful reading of the original text. According to the inclusion and exclusion criteria of literature, the inconsistent literature was excluded to determine the final inclusion of literature. In case of disagreement, discuss or find a third researcher to decide. Basic data of literature were extracted, including first author, year of publication, sample size, gender, age, intervention measures, course of treatment, outcome indicators, etc., and Excel2016 was used to sort out the extracted data. Literature quality analysis was carried out by two researchers, and in case of disagreement, the third researcher participated in the negotiation. The RevMan5.4.1 software provided by Cochrane was used for evaluation.

Statistical analysis
Using the software Stata16.0, a network meta-analysis was conducted based on the random effects model of the frequencics framework. In this study, odds ratio (OR) was used as the effect index and mean deviation (MD) was used as the measurement data. Interval estimation was performed using 95% confidence intervals (CI). For each outcome indicator, the efficacy of the interventions was ranked using the surface under the cumulative ranking (SUCRA) value.

Result

Literature search and screening results
According to the specified search strategy, the initial number of retrieved literatures was 2851. EndNoteX9 software was used to review and delete the literatures, and 1,986 literatures were obtained. After reading the abstract and the full text, a total of 34 literatures were finally included, all of which were Chinese literatures, as shown in Figure 1.

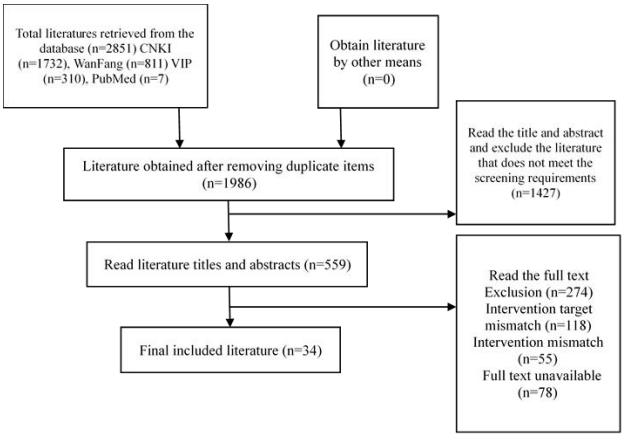

Figure 1 Screening process of included references

Basic features included in the study
A total of 34 studies were included, all of which were two-arm studies. With a total sample size of 1543, the maximum sample size of a single study was 278 [11] and the minimum sample size was 50 [33]. It involves 16 kinds of Chinese patent medicines: Dan Ji Huoxue Decoction, compound Biejia Ruangan Tablet, Qi Shen Ruangan Capsule, Rouansanjie Decoction, Rhubarb Zhejiao Capsule, Ganshuang Granules, Fuzheng Huayu Tablet, Heluo Shugan Tablet, Peituhua Disease Decoction, Qi Qi Fuzheng Huayu formula, Qingganhua ji formula, Anluo Huayuan Wan, Shugan Jianpeng formula, Shugan Jianpi Decoction, Rouanhua Huayu Soup. The basic information of the included literature is shown in Table 1.

Table 1 Basic information of the included research literature

Serial number	Included literature	Mean age		Intervention measure		Course of treatment	Outcome index
		Control group	Experimental group	Control group	Experimental group		
1	Gao Yuhua [4]	40.54±4.88	40.74±4.63	ETV0.5mg	Dan Ji Huoxue Soup	6 months	①②③④

Serial number	Included literature	Mean age		Intervention measure		Course of treatment	Outcome index
		Control group	Experimental group	Control group	Experimental group		
2	Zhang Shaojun [5]	43.02 ± 4.13	42.76 ± 3.68	ETV0.5mg	compound Biejia soft liver tablet	6 months	①②
3	Yang Huili [6]	42.62 ± 3.31	42.84 ± 3.26	ETV0.5mg	compound Biejia soft liver tablet	6 months	①
4	Zhang Furong [7]	41.29 ± 15.42	41.78 ± 15.16	ETV0.5mg	Qi Shen Ruangan Capsule	6 months	①
5	Song Chunxia [8]	45.6	48.4	ETV0.5mg	Soft liver Sanjie Soup	6 months	①④
6	Yao Zhongcai [9]	49.41 ± 3.56	51.46 ± 5.29	ETV0.5mg	Rhubarb insect capsules	6 months	①②③
7	Bai Li [10]	49.82 ± 4.05	49.89 ± 4.14	ETV0.5mg	Ganshuang granules	6 months	①③④
8	Wang Jufeng [11]	49.91 ± 6.44	49.63 ± 6.12	ETV0.5mg	Fuzheng Huayu tablets	6 months	①③
9	Xue Hongli [12]	55.3 ± 11.6	56.9 ± 13.2	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①④
10	Guo Jingyun [13]	43.16 ± 3.80	43.09 ± 3.71	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①②
11	Chen Liying [14]	\	\	ETV0.5mg	Ganshuang granules	6 months	①②③
12	Somingo [15]	50.46 ± 12.17	50.66 ± 12.31	ETV0.5mg	Ganshuang granules	6 months	①④
13	Feng Haiqun [16]	58.59 ± 10.61	59.31 ± 11.23	ETV0.5mg	Heluo Shugan tablet	6 months	①②④
14	Li Chengcheng [17]	43.5 ± 10.7	43.7 ± 10.5	ETV0.5mg	Soil cultivation disease decoction	6 months	①②③④
15	Duan Hongguang [18]	57.67 ± 3.56	57.74 ± 3.35	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①②
16	Hong Hailong [19]	51.21 ± 6.24	51.26 ± 6.26	ETV0.5mg	Rhubarb insect capsules	6 months	①②③
17	Xie Hongxia [20]	56.31 ± 4.24	56.27 ± 4.13	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①②③
18	Cheng Juan [21]	57.25 ± 8.59	54.67 ± 8.11	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①
19	Fang Rong [22]	45.0 ± 5.0	45.5 ± 5.5	ETV0.5mg	Ganshuang granules	6 months	①②③
20	Yin Yantao [23]	54.24 ± 6.43	53.42 ± 7.91	ETV0.5mg	Soothing the liver and strengthening the spleen decoction	6 months	①②③④
21	Cai Xiaoqi [24]	44.97 ± 6.57	44.85 ± 6.62	ETV0.5mg	Replenishing qi and detoxifying collaterals	6 months	①②③
22	Huang Fengliu [25]	43.42 ± 10.89	42.52 ± 11.31	ETV0.5mg	Shenqi Fuzheng Huayu Formula	6 months	①②③
23	Wu Dan [26]	54.23 ± 9.32	51.25 ± 7.02	ETV0.5mg	Qingganhua accumulation formula	6 months	①②③
24	Li Caihong [27]	65.93 ± 6.10	66.31 ± 6.14	ETV0.5mg	Anluo chemical fiber pills	6 months	①②③
25	Liu Xuan [28]	44.52 ± 10.23	42.81 ± 11.65	ETV0.5mg	Rhubarb insect capsules	6 months	①③
26	Zhang Ruilin [29]	41.69 ± 3.31	41.72 ± 3.16	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①③
27	Xiao Qinwen [30]	\	\	ETV0.5mg	Soft liver Sanjie Soup	6 months	①③
28	Shi Xiaoling [31]	42.53 ± 3.71	42.69 ± 3.68	ETV0.5mg	Compound Biejia soft liver tablet	6 months	①③
29	Di Shujie [32]	66.48 ± 6.74	65.83 ± 6.67	ETV0.5mg	Heluo Shugan tablet	6 months	①②③
30	Chen Liming [33]	\	\	ETV0.5mg	Soothing the liver and invigorating the spleen and activating the blood	6 months	①②
31	Guo Wenqiang [34]	50.25 ± 3.47	51.33 ± 4.36	ETV0.5mg	Soothing the liver and strengthening the spleen decoction	6 months	①③④
32	Wang Hong [35]	51.4 ± 7.2	54.7 ± 6.7	ETV0.5mg	Soft liver Huayu Decoction	6 months	①
33	Hou Shuya [36]	47.9 ± 2.1	46.3 ± 1.6	ETV0.5mg	Soft liver Sanjie Soup	6 months	①②③
34	Liu Zhiyuan [37]	41.5 ± 3.7	40.7 ± 3.4	ETV0.5mg	Soft liver Sanjie Soup	6 months	①②

Note: Outcome index ① liver function index ALT; ② liver fibrosis index HA; ③ therapeutic effect (total effective rate); ④ adverse reactions.

Inclusion study evaluation

Random allocation method, the study for low risk, using the random number table method [5, 7, 9, 15–17, 19, 23–25, 27–29, 31, 32, 34, 35] were randomly assigned; Four studies were high-risk, using lottery [10, 14] or admission sequence [18, 22]; The rest of the 13 studies [4, 6, 8, 11–13, 20, 21, 26, 30, 33, 36, 37] only mention random, did not give specific random allocation methods. Random-assigned hiding and blinding are not mentioned in any of the studies. Overall data integrity is good and there is no selective reporting. Other sources of bias are unclear. See Figure 2 for the specific risk assessment of bias arising from inclusion studies.

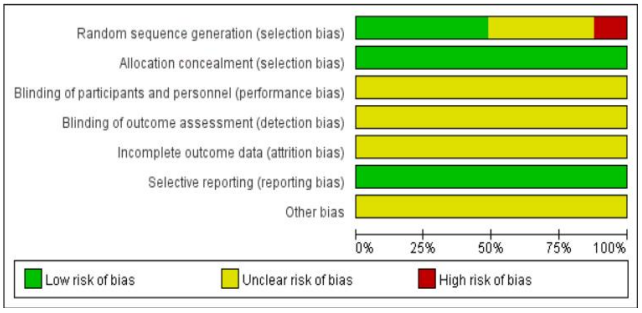

Figure 2 Proportion of included projects with a risk of bias

Liver function ALT index

Evidence network diagram

Liver function indicators (ALT) have been reported in 30 studies [4–7, 9, 10, 12–34, 36, 37].14 TCM compound prescriptions were involved, 14 were directly compared, and no closed ring was formed. The thickness of the lines in the figure represents the number of studies, and the size of the dots represents the size of the sample. The results showed that there were the most experiments (8 in total) and the largest sample size (732 cases in total) in the comparison of compound Biejiruangan Tablets combined with Entecavir and Entecavir alone. The evidence network of liver function ALT index is shown in Figure 3.

Publication bias

The comparation-correction funnel plot results showed that the study was roughly distributed on both sides of the X = 0 vertical line, suggesting that publication bias and small sample effect were less likely. (Figure 4)

Network meta-analysis

A network meta-analysis was performed on 14 TCM compounds, and 87 pairs were compared. Of these, 29 were statistically significant. Compared to treatment with entecavir alone, Entecavir combined with Danji Huoxuet Decoction (MD = -16.68, 95%CI [-30.07, -3.30]), combined with Compound Bijiaruganan Tablet (MD = -12.93, 95%CI [-18.22, -7.64]), Qishenrugancapsule (MD = -19.40, 95%CI [35.79, 3.00]), liver fights soup (MD = 10.53, 95%CI [19.09, 1.98]), liver bright particles (MD = 15.98, 95%CI [23.44, 8.53]), and winding the liver slices (MD = 30.89, 95%CI[-41.15, -20.63]), Shenqi Fuzheng Huayu Prescription (MD = -36.61, 95%CI [-51.01 ,-22.22]), Anluo Huaxian Wan (MD = -18.94, 95%CI [-33.37, -4.52]), Shugan invigorating Spleen and Huoxui prescription (MD = -28.50, 95%CI [-42.87, -14.13]) in the treatment of hepatitis B cirrhosis, ALT index decreased significantly better than Entecavir alone. Compared with Entecavir combined compound Bieijia Ruganan Tablets, Entecavir combined with Luo Shugan tablets (MD = 17.96, 95%CI [6.42, 29.50]) and qi supplementing and detoxifying Tongluo methods (MD = 23.69, 95%CI [8.35, 39.02]) were better. Compared with Entecavir combined with Ruogan Sanjie Decoction, Entecavir combined with Heluoshugan Tablets (MD = 20.36, 95%CI [7.00, 33.72]), Supplementing Qi and detoxifying Tongluo method (MD = 26.08, 95%CI [9.33, 42.83]), Anluo Huaxian Wan (MD = 17.97, 95%CI [1.24, 34.69]) better; Compared to Entecavir combined with rhubarb Insect capsules,Entecavir combined with Heluoshugan Tablets (MD = 24.41, 95%CI [11.17, 37.65]), Supplementing Qi and detoxifying Tongluo method (MD = 30.14, 95%CI [13.49, 46.79]), Anluo Huaxian Wan (MD = 22.02, 95%CI [5.39, 38.65]) better;Compared with Entecavir combined Ganshuanggranules, Entecavir combined with Luoshugan Tablets (MD = 14.91, 95%CI [2.22, 27.59]) and supplementing qi and detoxifying and Tongluo methods (MD = 20.63, 95%CI [4.42, 36.85]) were better. Compared to Entecavir combination and Luoshugan Tablet,Entecavel combined with Peituhuazhi Decoction (MD = -23.21, 95%CI [-40.93, -5.49]), Shenqi Fuzheng Huayu prescription (MD = -22.18, 95%CI [-40.78, -3.58]), Shugan Jianpi Huoxui prescription (MD = -24.26,95%CI [42.25, 6.27]), liver, spleen decoction (MD = 21.69, 95%CI [36.18, 7.20]) better; Compared with Entecavir combined with Tutuhua Syndrome Decoction, Entecavir combined with supplementing qi and detoxifying and regulating collaterals (MD = 28.94, 95%CI [8.54, 49.34]) was better. Compared with Entecavir combined with supplementing qi and detoxifying and regulating collaterals, Entecavel combined with Shenqi Fuzheng Huayu Formula (MD = -27.91, 95%CI [-49.07, -6.74]), Shugan Jianpi Huoxui formula (MD = -29.98, 95%CI [-50.61, -9.35]), Shugan Jianpi Decoction (MD = -27.42, 95%CI [-45.08, -9.75]) better; Compared to Entecavir combined with Anluo chemical fiber pills, Entecavir combined with Shugan Jianpi Huoxui prescription (MD = -21.87) and Shugan Jianpi Decoction (MD = -19.30, 95%CI [-36.94, -1.66]) were better. (Table 2)

Ranking of mesh meta-analysis results

According to the results of mesh meta-analysis, The probability ranking of ALT index of 14 TCM compounds combined with Entecavir in the treatment of liver function in the compensatory stage of hepatitis B cirrhosis was in the order of Entecavir combined with Yiqi Jiedu Tongluo Method > Heluo Shugan Tablet > Anluo Huayuan Wan > Qishenrugan Capsule > Qingganhuaji Decoction > Ganshuang Granule > Compound Biejia Rugan Tablet > Rugan Sanjie Decoction > Shugan Jianpi Decoction > Shenqi Fuzheng Huayu Prescription > Petuhua diseaseDecoction > Spleen-invigorating and blood-activating prescription > Rhubarb insect capsules. Table 3 shows the results and ranking of ALT index SUCRA of 14 TCM compounds combined with Entecavir in the treatment of hepatitis B cirrhosis during the compensatory period.

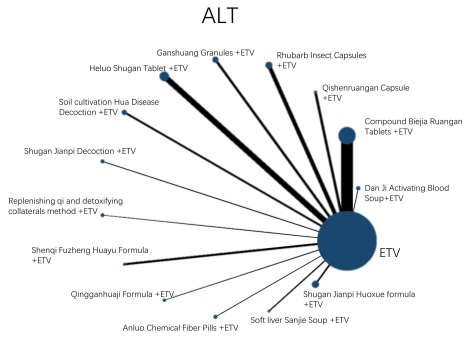

Figure 3 Evidence network of liver function ALT index

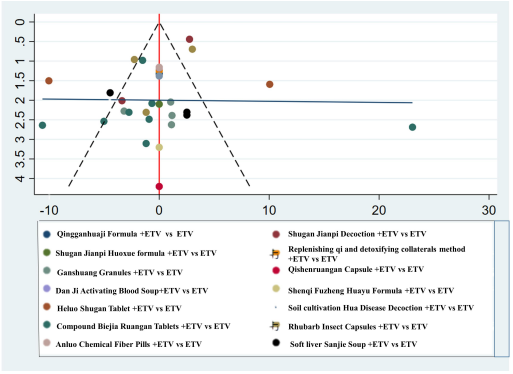

Figure 4 Funnel plot of ALT index correction comparison

Table 2 Mesh meta-analysis of liver function ALT index

Intervention measure	Dan Ji Huoxue Soup + ETV	Compound Biejia Ruangan Tablets + ETV	Qishenruangan Capsule + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang Granules + ETV	Heluo Shugan Tablet + ETV
Dan Ji Huoxue Soup + ETV	0						
Compound Biejia Ruangan Tablets + ETV	-3.76 (-18.11,10.60)	0					
Qishenruangan Capsule + ETV	2.71 (-18.41,23.84)	6.47 (-10.76,23.70)	0				
Soft liver Sanjie	-6.15	-2.40	-8.87	0			

Intervention measure	Dan Ji Huoxue Soup + ETV	Compound Biejia Ruangan Tablets + ETV	Qishenruangan Capsule + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang Granules + ETV	Heluo Shugan Tablet + ETV
Soup + ETV	(-22.00,9.70)	(-12.45,7.66)	(-27.36,9.63)				
Rhubarb Insect Capsules + ETV	-10.21 (-25.96,5.54)	-6.45 (-16.34,3.44)	-12.92 (-31.32,5.48)	-4.05 (-16.01,7.91)	0		
Ganshuang Granules + ETV	-0.70 (-15.99,14.58)	3.05 (-6.08,12.19)	-3.41 (-21.43,14.60)	5.45 (-5.89,16.80)	9.51 (-1.70,20.71)	0	
Heluo Shugan Tablet + ETV	14.20 (-2.63,31.04)	17.96 (6.42,29.50)	11.49 (-7.85,30.83)	20.36 (7.00,33.72)	24.41 (11.17,37.65)	14.91 (2.22,27.59)	0
Soil cultivation Hua Disease Decoction + ETV	-9.01 (-28.68,10.66)	-5.25 (-20.64,10.13)	-11.72 (-33.58,10.13)	-2.86 (-19.65,13.93)	1.20 (-15.49,17.89)	-8.31 (-24.57,7.95)	-23.21 (-40.93,-5.49)
Replenishing qi and detoxifying collaterals method + ETV	19.93 (0.30,39.56)	23.69 (8.35,39.02)	17.22 (-4.60,39.04)	26.08 (9.33,42.83)	30.14 (13.49,46.79)	20.63 (4.42,36.85)	5.73 (-11.96,23.41)
Shenqi Fuzheng Huayu Formula + ETV	-7.98 (-28.43,12.48)	-4.22 (-20.61,12.17)	-10.69 (-33.26,11.88)	-1.82 (-19.54,15.89)	2.23 (-15.39,19.85)	-7.27 (-24.48,9.93)	-22.18 (-40.78,-3.58)
Qingganhuaji Formula + ETV	2.26 (-17.39,21.91)	6.01 (-9.35,21.38)	-0.45 (-22.29,21.38)	8.41 (-8.36,25.18)	12.47 (-4.21,29.14)	2.96 (-13.28,19.20)	-11.95 (-29.65,5.76)
Anluo Chemical Fiber Pills + ETV	11.81 (-7.80,31.43)	15.57 (0.26,30.88)	9.10 (-12.70,30.90)	17.97 (1.24,34.69)	22.02 (5.39,38.65)	12.51 (-3.68,28.70)	-2.39 (-20.05,15.27)
Shugan Jianpi Huoxue formula + ETV	-10.05 (-29.96,9.86)	-6.30 (-21.99,9.39)	-12.77 (-34.84,9.30)	-3.90 (-20.97,13.17)	0.15 (-16.82,17.13)	-9.35 (-25.90,7.20)	-24.26 (-42.25,-6.27)
Shugan Jianpi Decoction + ETV	-7.48 (-24.30,9.33)	-3.73 (-15.24,7.79)	-10.20 (-29.52,9.13)	-1.33 (-14.67,12.00)	2.72 (-10.49,15.93)	-6.78 (-19.44,5.87)	-21.69 (-36.18,-7.20)
ETV	-16.68 (-30.07,-3.30)	-12.93 (-18.22,-7.64)	-19.40 (-35.79,-3.00)	-10.53 (-19.09,-1.98)	-6.48 (-14.84,1.88)	-15.98 (-23.44,-8.53)	-30.89 (-41.15,-20.63)

Intervention measure	Replenishing qi and detoxifying collaterals method + ETV	Shenqi Fuzheng Huayu Formula + ETV	Qingganhuaji Formula + ETV	Anluo Chemical Fiber Pills + ETV	Shugan Jianpi Huoxue formula + ETV	Shugan Jianpi Decoction + ETV	ETV
Dan Ji Huoxue Soup + ETV							
Compound Biejia Ruangan Tablets + ETV							
Qishenruangan Capsule + ETV							
Soft liver Sanjie Soup + ETV							
Rhubarb Insect Capsules + ETV							
Ganshuang Granules + ETV							
Heluo Shugan Tablet + ETV							
Soil cultivation Hua Disease Decoction + ETV							
Replenishing qi and detoxifying collaterals method + ETV	0						
Shenqi Fuzheng Huayu Formula + ETV	-27.91 (-49.07,-6.74)	0					
Qingganhuaji Formula + ETV	-17.67 (-38.05,2.71)	10.23 (-10.95,31.42)	0				
Anluo Chemical Fiber Pills + ETV	-8.12 (-28.46,12.23)	19.79 (-1.36,40.93)	9.55 (-10.81,29.92)	0			
Shugan Jianpi Huoxue formula + ETV	-29.98 (-50.61,-9.35)	-2.08 (-23.50,19.34)	-12.31 (-32.96,8.34)	-21.87 (-42.48,-1.26)	0		
Shugan Jianpi	-27.42	0.49	-9.74	-19.30	2.57	0	

Decoction + ETV	(-45.08,-9.75)	(-18.09,19.07)	(-27.43,7.94)	(-36.94,-1.66)	(-15.40,20.54)		
ETV	-36.61 (-51.01,-22.22)	-8.71 (-24.22,6.80)	-18.94 (-33.37,-4.52)	-28.50 (-42.87,-14.13)	-6.63 (-21.40,8.14)	-9.20 (-19.43,1.03)	0

Table 3 SUCRA ranking of liver function ALT index

Intervention measure	SUCRA/%/	ranking
Entecavir + Dan Ji Activating Blood Soup	58.4	6
Entecavir + Compound Biejia Soft liver Tablets	46.7	8
Entecavir + Qishenrugan Capsule	64.5	4
Entecavir + Rhubarb Insect Capsules	23.5	14
Entecavir + Ganshuang Granules	58.0	7
Entecavir + Heloshugan tablets	89.7	2
Entecavir + soil cultivation syndrome decoction	29.5	12
Entecavir + Soothing liver and strengthening Spleen Decoction	33.2	10
Entecavir + Soothing liver and strengthening Spleen Decoction	95.6	1
Entecavir + Shenqi Fuzheng Huayu prescription	32.4	11
Entecavir + Qingganhuaji prescription	64.4	5
Entecavir + Amro chemical fiber pills	85.2	3
Entecavir + Ruogan Sanjie Soup	38.0	9
Entecavir + soothing the liver and strengthening the spleen and promoting blood circulation prescription	26.6	13

HA index of hepatic fibrosis

Evidence network

25 studies reported on liver fibrosis index HA [4, 5, 8–14, 16–18, 20, 22–27, 29, 32, 33, 35–37]. It involves 15 kinds of TCM compound treatment schemes. The dot size indicates the sample size using the intervention, and the line thickness indicates the number of RCTS using the intervention. The study of 15 TCM compounds was direct comparison without closed-loop formation. The number of studies comparing the treatment of compound Biejiaruangan Tablet combined with Entecavir and Entecavir alone was the largest (6 in total), and the sample size included was the largest (518 cases in total). The evidence network of HA index in hepatic fibrosis is shown in Figure 5.

Publication bias

The funnel plot of HA index suggests that there may be a high degree of publication bias and small sample effect. Comparison of 15 Chinese herbal compounds combined with Entecavir versus Entecavir alone in the treatment of hepatic fibrosis HA index in patients with hepatitis B cirrhosis in compensatory stage the funnel plot is as follows. (Figure 6)

Network meta-analysis

A network meta-analysis of 15 TCM compounds produced 105 pair-to-pair comparisons, among which 12 had statistically significant differences. Compared to treatment with entecavir alone, Entecavel combined with Danji Huoxuet Decoction (MD = -40.75, 95%CI [-75.46, -6.05]), combined with Compound Bijiaruganan Tablet (MD = -16.68, 95%CI [-30.07, -3.30]), combined with Rugansanjie Decoction (MD = -51.23, 95%CI [-85.65, -16.81]), combined with Ganshuang Granules (MD = -48.26, 95%CI [-82.70, -13.83]), Lianhe Luoshugan Pian (MD = -113.63, 95%CI [-155.45, -71.81]), combined with Anluo Huaxian Wan (MD = -16.68, 95%CI [-30.07, -3.30]) is better; Compared to Entecavir combination and Luoshugan Tablet,Entecavir combined with Peituhuazhi Decoction (MD = -95.40, 95%CI [-167.62, -23.18]), Supplementing Qi and detoxifying Tongluo method (MD = -77.52, 95%CI [-150.07, -4.97]), and Shengqi Fuzheng Huayu Formula (MD = -103.80, 95%CI [-176.06, -31.53]), QingganHuaji Fang (MD = -100.02, 95%CI [-173.41, -26.64]), Shugan Jianpi Decoction (MD = -87.88, 95%CI [-161.56, -14.19]), Rugan Huayu Decoction (MD = -90.67, 95%CI [-162.95, -18.39]) is better. (Table 4)

Ranking of network meta-analysis results

According to the results of mesh meta-analysis, The probability ranking of the HA index of 15 TCM compounds combined with Entecavir in the treatment of liver fibrosis in the compensatory stage of hepatitis B cirrhosis was in the order of Entecavir combination and Luoshugan Tablet > Shugan Jianpi Huoxui Prescription > Anluo Huaqian Wan > Compound Biejia Ruangan Tablet > Rugan Sanjie Decoction > Ganshuang Granules > Danji Huoxui Decoction > Qi and detoxification and collateralization method > Rhubarb Zhezhe Capsule > Fuzheng Huayu Tablet > Shugan Jianpi Decoction > Ruogan and Huayu DecoctionDecoction > Peiluhua disease decoction > Qingganhua prescription > Shenqi Fuzheng Huayu prescription. Table 5 shows the HA index SUCRA of 15 Chinese herbal compounds combined with Entecavir in the treatment of liver fibrosis in compensatory stage of hepatitis B cirrhosis.

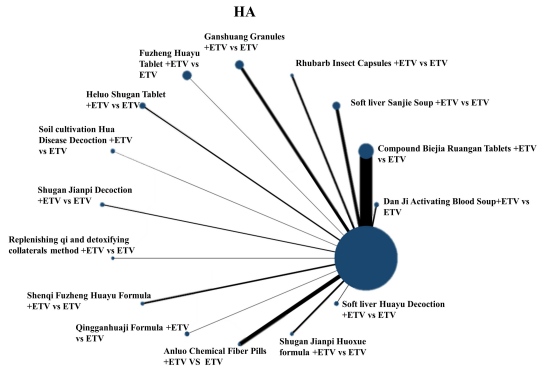

Figure 5 Evidence network of HA indicators

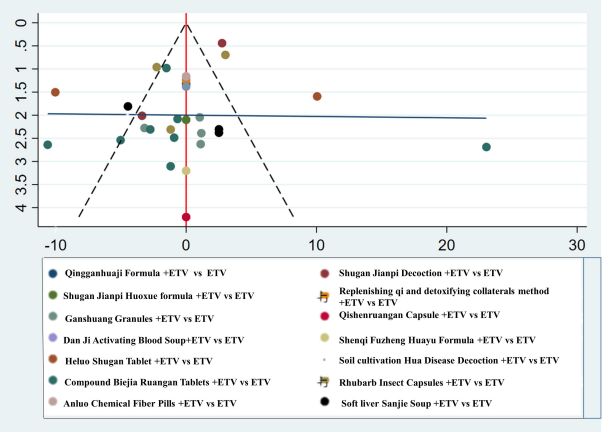

Figure 6 Funnel plot of HA index correction comparison

Table 4 Mesh meta-analysis of HA indexes in liver fibrosis

Intervention measure	Dan Ji Activating Blood Soup + ETV	Compound Biejia Ruangan Tablets + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang Granules + ETV	Fuzheng Huayu Tablet + ETV	Heluo Shugan Tablet + ETV	Soil cultivation Hua Disease Decoction + ETV
Dan Ji Activating Blood Soup + ETV	0							

Intervention measure	Dan Ji Activating Blood Soup + ETV	Compound Biejia Ruangan Tablets + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang Granules + ETV	Fuzheng Huayu Tablet + ETV	Heluo Shugan Tablet + ETV	Soil cultivation Hua Disease Decoction + ETV
Compound Biejia Ruangan Tablets + ETV	10.36 (-31.36,52.07)	0						
Soft liver Sanjie Soup + ETV	10.48 (-37.29,58.25)	0.12 (-42.71,42.95)	0					
Rhubarb Insect Capsules + ETV	-5.27 (-74.93,64.40)	-15.63 (-82.10,50.85)	-15.74 (-86.09,54.60)	0				
Ganshuang granules + ETV	7.51 (-40.25,55.26)	-2.85 (-45.70,40.00)	-2.97 (-51.60,45.67)	12.78 (-57.58,83.13)	0			
Fuzheng Huayu Tablet + ETV	-10.24 (-77.82,57.33)	-20.60 (-84.76,43.56)	-20.72 (-88.88,47.44)	-4.97 (-90.01,80.06)	-17.75 (-85.92,50.42)	0		
Heluo Shugan Tablet + ETV	72.88 (19.34,126.41)	62.52 (13.59,111.44)	62.40 (8.27,116.53)	78.14 (3.88,152.41)	65.37 (11.21,119.52)	83.12 (10.92,155.32)	0	
Soil cultivation Hua Disease Decoction + ETV	-22.53 (-90.10,45.04)	-32.89 (-97.06,31.29)	-33.00 (-101.17,35.16)	-17.26 (-102.30,67.78)	-30.04 (-98.21,38.14)	-12.29 (-95.52,70.95)	-95.40 (-167.62,-23.18)	0
Replenishing qi and detoxifying collaterals method + ETV	-4.64 (-72.58,63.30)	-15.00 (-79.55,49.55)	-15.12 (-83.65,53.42)	0.63 (-84.71,85.96)	-12.15 (-80.69,56.39)	5.60 (-77.94,89.14)	-77.52 (-150.07,-4.97)	17.89 (-65.66,101.43)
Shenqi Fuzheng Huayu Formula + ETV	-30.92 (-98.52,36.67)	-41.28 (-105.50,22.94)	-41.40 (-109.61,26.81)	-25.66 (-110.72,59.41)	-38.43 (-106.64,29.78)	-20.68 (-103.95,62.59)	-103.80 (-176.06,-31.53)	-8.39 (-91.67,74.88)
Qingganhuaji Formula + ETV	-27.15 (-95.88,41.58)	-37.51 (-102.99,27.98)	-37.63 (-107.02,31.77)	-21.88 (-107.91,64.15)	-34.66 (-104.06,34.74)	-16.91 (-101.15,67.34)	-100.02 (-173.41,-26.64)	-4.62 (-88.87,79.63)
Anluo Chemical Fiber Pills + ETV	20.39 (-47.24,88.03)	10.04 (-54.12,74.19)	9.92 (-58.25,78.09)	25.66 (-59.38,110.70)	12.89 (-55.30,81.07)	30.64 (-52.61,113.88)	-52.48 (-124.66,19.70)	42.92 (-40.33,126.18)
Shugan Jianpi Huoxue formula + ETV	23.38 (-52.63,99.38)	13.02 (-60.40,86.44)	12.90 (-64.06,89.86)	28.64 (-63.59,120.88)	15.87 (-61.10,92.83)	33.62 (-56.96,124.20)	-49.50 (-130.03,31.03)	45.90 (-44.68,136.49)
Shugan Jianpi Decoction + ETV	-15.00 (-84.06,54.06)	-25.36 (-91.18,40.46)	-25.48 (-95.21,44.25)	-9.74 (-96.03,76.56)	-22.51 (-92.24,47.22)	-4.76 (-89.28,79.76)	-87.88 (-161.56,-14.19)	7.53 (-77.00,92.05)
Soft liver Huayu Decoction + ETV	-17.79 (-85.43,49.85)	-28.15 (-92.40,36.10)	-28.27 (-96.51,39.97)	-12.53 (-97.62,72.57)	-25.30 (-93.54,42.94)	-7.55 (-90.85,75.74)	-90.67 (-162.95,-18.39)	4.74 (-78.56,88.03)
ETV	-40.75 (-75.46,-6.05)	-51.11 (-76.70,-25.52)	-51.23 (-85.65,-16.81)	-35.49 (-96.88,25.91)	-48.26 (-82.70,-13.83)	-30.51 (-89.39,28.36)	-113.63 (-155.45,-71.81)	-18.23 (-77.11,40.66)

Intervention measure	Replenishing qi and detoxifying collaterals method + ETV	Shenqi Fuzheng Huayu Formula + ETV	Qingganhuaji Formula + ETV	Anluo Chemical Fiber Pills + ETV	Shugan Jianpi Huoxue formula + ETV	Shugan Jianpi Decoction + ETV	Soft liver Huayu Decoction + ETV	ETV
Dan Ji Activating Blood Soup + ETV Compound Biejia Ruangan Tablets + ETV Soft liver Sanjie Soup + ETV Rhubarb Insect Capsules + ETV Ganshuang Granules + ETV Fuzheng Huayu Tablet + ETV Heluo Shugan Tablet + ETV Soil cultivation Hua Disease Decoction + ETV								
Replenishing qi and detoxifying collaterals method + ETV	0							
Shenqi Fuzheng Huayu Formula + ETV	-26.28 (-109.86,57.30)	0						
Qingganhuaji Formula + ETV	-22.51 (-107.06,62.04)	3.77 (-80.50,88.05)	0					
Anluo Chemical Fiber Pills + ETV	25.04 (-58.51,108.59)	51.32 (-31.97,134.61)	47.54 (-36.72,131.81)	0				
Shugan Jianpi Huoxue formula + ETV	28.02 (-62.84,118.88)	54.30 (-36.32,144.92)	50.53 (-40.99,142.04)	2.98 (-87.60,93.56)	0			
Shugan Jianpi Decoction + ETV	-10.36 (-95.18,74.46)	15.92 (-68.63,100.47)	12.15 (-73.37,97.66)	-35.40 (-119.93,49.14)	-38.38 (-130.14,53.38)	0		
Soft liver Huayu Decoction + ETV	-13.15 (-96.75,70.45)	13.13 (-70.20,96.46)	9.36 (-74.95,93.66)	-38.19 (-121.50,45.12)	-41.17 (-131.81,49.47)	-2.79 (-87.37,81.79)	0	
ETV	-36.11 (-95.42,23.19)	-9.83 (-68.76,49.10)	-13.60 (-73.91,46.70)	-61.15 (-120.03,-2.26)	-64.13 (-133.02,4.76)	-25.75 (-86.44,34.93)	-22.96 (-81.93,36.00)	0

Table 5 SUCRA ranking of HA index in hepatic fibrosis

Intervention measure	SUCRA/%/	ranking
Entecavir + Dan Ji Activating Blood Soup	53.8	7
Entecavir + Compound Biejia Soft liver Tablets	65.1	4
Entecavir + Ruogan Sanjie Soup	64.5	5
Entecavir + Rhubarb Insect Capsules	48.3	9

Entecavir + Ganshuang Granules	61.2	6
Entecavir + Fuzheng Huayu tablets	43.5	10
Entecavir + Heloshugan tablets	98.1	1
Entecavir + soil cultivation syndrome decoction	32.7	13
Entecavir + Qi qi detoxification and collateral-clearing method	48.4	8
Entecavir + Shenqi Fuzheng Huayu prescription	26.2	15
Entecavir + Qingganhuaji prescription	28.8	14
Entecavir + Amro chemical fiber pills	70.1	3
Entecavir + soothing the liver and strengthening the spleen and promoting blood circulation prescription	71.1	2
Entecavir + Soothing liver and strengthening Spleen Decoction	39.2	11
Entecavir + Soothing Liver Huayu Decoction	36.7	12

Adverse reaction

Evidence network diagram

Eight studies [7, 10, 12, 16, 21, 23, 24] reported the incidence of adverse reactions involving six TCM compounds, six of which were directly compared without closed-loop formation. The results showed that Qishenrugan Capsule and Shuganjianpi Decoction combined with Entecavir had the largest number of studies (2 RCTs for both), and Shuganjianpi Decoction combined with Entecavir had the largest sample size (262 cases). (Figure 7)

Publication bias

The results of comparation-correction funnel plot showed that the research was basically distributed on both sides of the stack of X = 0 vertical line, which suggested that there was a small possibility of publication bias and small sample effect (Figure 8)

Network meta-analysis

Network meta-analysis was conducted on 6 TCM compounds, and a total of 21 pairwise comparisons were made, among which only 1 comparison difference was statistically significant. Compared with Entecavir alone, Entecavir combined with Shuganjianpi Decoction (MD = -1.60, 95%CI [-2.99, -0.21]) was better. The pairwise comparison of other intervention measures showed no statistical significance. (Table 6)

Ranking of network meta-analysis results

Adverse reaction index was evaluated by ranking probability table, from the best to the worst: Shuganjianpi Decoction, Qishenrugan capsule, Ganshuang granules, Peituhuazhi Decoction, compound Biejirugan Tablet, and Luoshugan tablet combined with Entecavir, respectively. (Table 7)

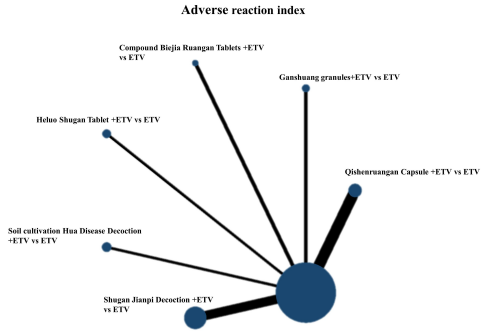

Figure 7 Evidence network diagram of adverse reaction index

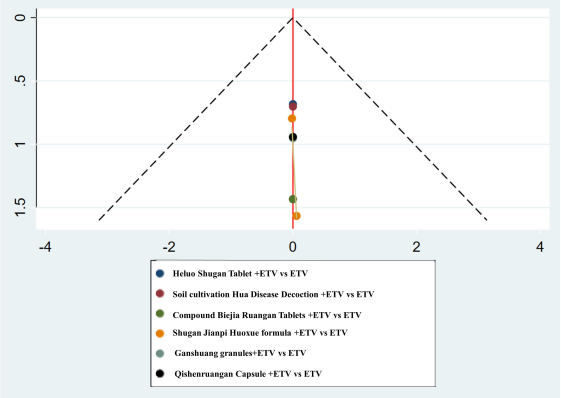

Figure 8 Funnel plot for comparison of adverse reactions

Table 6 Mesh meta-analysis of adverse reaction indicators

Intervention measure	Compound Biejia Ruangan Tablets + ETV	Qishenruangan Capsule + ETV	Ganshuang Granules + ETV	Heluo Shugan Tablet + ETV	Soil cultivation Hua Disease Decoction + ETV	Shugan Jianpi Decoction + ETV	ETV
Compound Biejia Ruangan Tablets + ETV	0						
Qishenruangan Capsule + ETV	0.43 (-2.28,3.14)	0					
Ganshuang Granules + ETV	0.44 (-2.28,3.17)	0.01 (-2.61,2.63)	0				
Heluo Shugan Tablet + ETV	-0.46 (-2.85,1.94)	-0.89 (-3.17,1.39)	-0.90 (-3.19,1.40)	0			
Soil cultivation Hua Disease Decoction + ETV	0.24 (-2.17,2.66)	-0.19 (-2.49,2.11)	-0.20 (-2.52,2.12)	0.70 (-1.22,2.62)	0		
Shugan Jianpi Decoction + ETV	1.60 (-0.82,4.03)	1.17 (-1.14,3.48)	1.16 (-1.17,3.49)	2.06 (0.13,3.99)	1.36 (-0.60,3.31)	0	
ETV	-0.00 (-1.99,1.99)	-0.43 (-2.28,1.41)	-0.44 (-2.31,1.42)	0.46 (-0.88,1.79)	-0.24 (-1.62,1.13)	-1.60 (-2.99,-0.21)	0

Table 7 SUCRA ranking of adverse reaction indicators

Intervention measure	SUCRA/%	Ranking
Compound Biejia Ruangan Tablets + ETV	40.7	5
Qishenruangan Capsule + ETV	54.5	2
Ganshuang granules + ETV	55.2	3
Heluo Shugan tablet + ETV	21.7	7
Soil cultivation disease decoction + ETV	48.9	4
Soothing the liver and strengthening the spleen decoction + ETV	90.9	1
ETV	38.1	6

Therapeutic effective rate

Evidence network diagram

21 study reported the treatment efficient [9–11, 14, 15, 17, 19, 20, 22–32, 34, 36], involving 12 kinds of Chinese medicine compound, 12 direct comparisons,No closed ring is formed. The thickness of the lines in the figure represents the number of studies, and the size of the dots represents the size of the sample.The results showed that Ganshuang Granules combined with Entecavir had the largest number of studies (4 in total), with a sample size of 366 cases. (Figure 9)

Publication bias

The results of comparation-correction funnel plot showed that the study was asymmetrically distributed on both sides of the vertical line (X = 0), indicating that there was a high possibility of publication bias and small sample effect in the study results of treatment effectiveness. (Figure 10)

Network meta-analysis

A total of 78 pairwise comparisons were generated in the mesh meta-analysis, of which 4 were statistically significant.Compared with Entecavir combined Ganshuang Granules, Entecavir combined Rugansanjie Decoction (MD = -0.36, 95%CI [-1.54, 0.82]) and Rhubarb Zhezhan Capsule (MD = -0.42, 95%CI [-1.55, 0.70]) were better. Compared with Entecavir combined with Shuganjianpi Decoction, Entecavir combined with Peituhuazhi Decoction (MD = -0.20, 95%CI [-1.31, 0,91]) and Shenqi Fuzhenghuayu prescription (MD = -0.65, 95%CI [-2.17, 0.86]) were better. Other comparative differences were not statistically significant. (Table 8)

Ranking of network meta-analysis results

According to the results of mesh meta-analysis,The probability of effective rate of 12 TCM compounds in the treatment of hepatitis B cirrhosis in the compensatory period was in the order of Entecavir combined with Ganshuang Granules > Compound Biejia Ruangan Tablets > HeLuoshugan Tablets > Rougansanjie Decoction > Rhubarb Zhezhe Capsules > Yiqi detoxifying Tongluo Method > Qingganhuaji prescription > Anluo Huaxin Wan > Shugan Jianpi Decoction > Fuzheng Huayu Tablets > Peituhuazhi Decoction > Shenqi Fuzheng Huayu Prescription > ETV. The results and ranking of effective SUCRA of Entecavir combined with 12 Chinese herbal compounds in the compensatory period of hepatitis B cirrhosis are shown in Table 9.

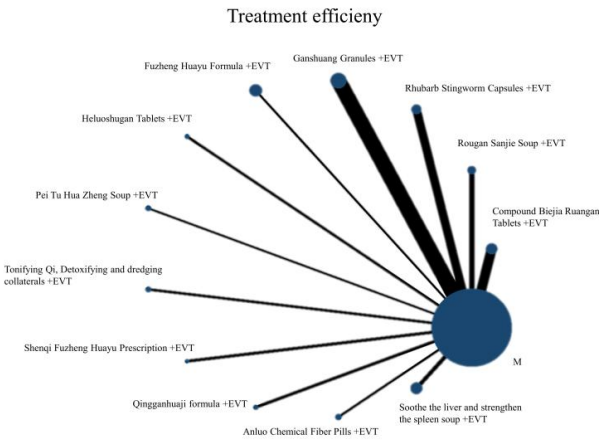

Figure 9 Evidence network diagram of treatment effectiveness

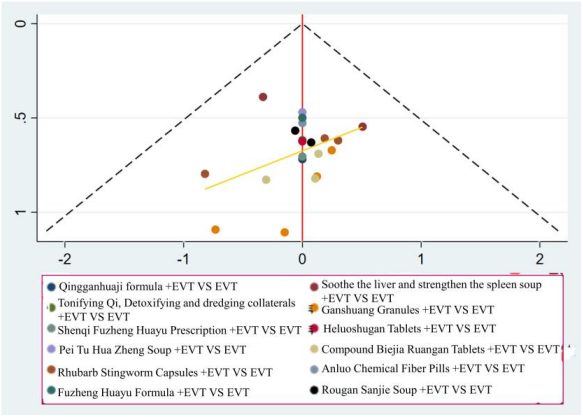

Figure 10 Adjusted comparison funnel plot of treatment response rate

Table 8 Mesh meta-analysis of treatment effectiveness

Intervention measure	Compound Biejia Ruangan Tablets + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang granules + ETV	Fuzheng Huayu tablets + ETV	Heluo Shugan tablet + ETV
Compound Biejia soft liver tablet + ETV	0					
Soft liver Sanjie Soup + ETV	0.22 (-0.99,1.42)	0				
Rhubarb insect capsules + ETV	0.28 (-0.87,1.43)	0.06 (-1.05,1.17)	0			
Ganshuang granules + ETV	-0.15 (-1.36,1.07)	-0.36 (-1.54,0.82)	-0.42 (-1.55,0.70)	0		
Fuzheng Huayu tablets + ETV	0.65 (-0.66,1.96)	0.44 (-0.84,1.72)	0.38 (-0.85,1.61)	0.80 (-0.49,2.09)	0	
Heluo Shugan tablet + ETV	0.18 (-1.32,1.69)	-0.03 (-1.51,1.44)	-0.09 (-1.53,1.34)	0.33 (-1.16,1.82)	-0.47 (-2.04,1.10)	0
Soil cultivation disease decoction + ETV	0.71 (-0.56,1.98)	0.49 (-0.75,1.73)	0.43 (-0.76,1.62)	0.85 (-0.40,2.10)	0.05 (-1.29,1.40)	0.52 (-1.01,2.05)
Replenishing qi and detoxifying collaterals + ETV	0.35 (-1.14,1.84)	0.13 (-1.33,1.60)	0.07 (-1.35,1.50)	0.50 (-0.98,1.97)	-0.30 (-1.86,1.25)	0.17 (-1.55,1.89)
Shenqi Fuzheng Huayu Formula + ETV	1.16 (-0.48,2.79)	0.94 (-0.67,2.55)	0.88 (-0.69,2.45)	1.30 (-0.32,2.92)	0.50 (-1.19,2.19)	0.97 (-0.87,2.82)
Qingganhua accumulation formula + ETV	0.51 (-1.14,2.17)	0.30 (-1.33,1.93)	0.24 (-1.36,1.83)	0.66 (-0.98,2.30)	-0.14 (-1.85,1.58)	0.33 (-1.53,2.20)
Anluo chemical fiber pills + ETV	0.53 (-0.83,1.88)	0.31 (-1.01,1.63)	0.25 (-1.03,1.52)	0.67 (-0.66,2.01)	-0.13 (-1.55,1.29)	0.34 (-1.26,1.94)
Soothing the liver and strengthening the spleen decoction + ETV	0.50 (-0.57,1.57)	0.29 (-0.75,1.32)	0.23 (-0.75,1.20)	0.65 (-0.40,1.70)	-0.15 (-1.31,1.01)	0.32 (-1.05,1.69)
ETV	1.64 (0.77,2.51)	1.42	1.36 (0.62,2.11)	1.79 (0.94,2.63)	0.99 (0.01,1.96)	1.46

Intervention measure	Compound Biejia Ruangan Tablets + ETV	Soft liver Sanjie Soup + ETV	Rhubarb Insect Capsules + ETV	Ganshuang granules + ETV	Fuzheng Huayu tablets + ETV	Heluo Shugan tablet + ETV
		(0.60,2.25)				(0.23,2.68)

Intervention measure	Soil cultivation disease decoction + ETV	Replenishing qi and detoxifying collaterals + ETV	Shenqi Fuzheng Huayu Formula + ETV	Qingganhua accumulation formula + ETV	Anluo chemical fiber pills + ETV	Soothing the liver and strengthening the spleen decoction + ETV	ETV
Compound Biejia Ruangan Tablets + ETV							
Soft liver Sanjie Soup + ETV							
Rhubarb Insect Capsules + ETV							
Ganshuang Granules + ETV							
Fuzheng Huayu Tablet + ETV							
Heluo Shugan Tablet + ETV							
Soil cultivation Hua Disease Decoction + ETV	0						
Replenishing qi and detoxifying collaterals method + ETV	-0.36 (-1.88,1.17)	0					
Shenqi Fuzheng Huayu Formula + ETV	0.45 (-1.21,2.11)	0.80 (-1.03,2.64)	0				
Qingganhuaji Formula + ETV	-0.19 (-1.87,1.49)	0.16 (-1.69,2.02)	-0.64 (-2.61,1.33)	0			
Anluo Chemical Fiber Pills + ETV	-0.18 (-1.56,1.20)	0.17 (-1.42,1.77)	-0.63 (-2.35,1.10)	0.01 (-1.74,1.76)	0		
Shugan Jianpi Decoction + ETV	-0.20 (-1.31,0.91)	0.15 (-1.21,1.51)	-0.65 (-2.17,0.86)	-0.01 (-1.55,1.53)	-0.02 (-1.23,1.18)	0	
ETV	0.93 (0.01,1.86)	1.29 (0.08,2.50)	0.49 (-0.90,1.87)	1.13 (-0.28,2.53)	1.11 (0.08,2.15)	1.14 (0.52,1.76)	0

Table 9 SUCRA results and ranking of treatment effectiveness

Intervention measure	SUCRA/%	ranking
Compound Biejia soft liver tablet + ETV	74.4	2
Soft liver Sanjie Soup + ETV	63.8	4
Rhubarb insect capsules + ETV	60.8	5
Ganshuang granules + ETV	81.5	1
Fuzheng Huayu tablets + ETV	41.3	10
Heluo Shugan tablet + ETV	64	3
Soil cultivation disease decoction + ETV	38.1	11
Replenishing qi and detoxifying collaterals + ETV	56.1	6
Shenqi Fuzheng Huayu Formula + ETV	23.1	12
Qingganhua accumulation formula + ETV	48.5	7
Anluo chemical fiber pills + ETV	47.6	8
Soothing the liver and strengthening the Spleen Decoction + ETV	47.5	9
ETV	3.3	13

Discussion

Cirrhosis is a common chronic progressive liver disease in clinic, and the common causes are hepatitis B, alcoholic liver disease, autoimmune liver disease, HBV infection, hepatitis C, etc. [38]. Histopathology showed extensive hepatocyte necrosis, nodular regeneration of residual hepatocytes, connective tissue hyperplasia and fibrous septum formation, leading to the destruction of hepatic lobule structure and the formation of pseudlobule. The liver was gradually deformed and hardened and developed into cirrhosis. The development of cirrhosis can affect gastrointestinal function as well as liver function. The liver plays an important role in regulating gastrointestinal hormone metabolism and affecting gastrointestinal motility. Cirrhosis impairs liver function and leads to abnormal metabolism of gastrointestinal hormones, which is further manifested as abnormal gastrointestinal motility in patients with cirrhosis [39]. At the same time, impaired liver function leads to reduced production of hematopoietic growth factor TPO, and decreased plasma TPO content further aggravates the degree of thrombocytopenia [40]. In traditional Chinese medicine, cirrhosis is called accumulation or distention, and the core pathogenesis of early cirrhosis of hepatitis B is summed up as fire, dampness, deficiency, phlegm and blood stasis. Its pathological basis is phlegm turbidified blood stasis mixed, and the

pathogenic nature of dampness-heat evil HBV is the lack of positive qi in the body, and the weakness of anti-evil causes the evil qi to be depressed for a long time and difficult to remove itself, eventually leading to HBV infection [41]. Entecavir is the first choice of antiviral therapy for patients with chronic hepatitis B. Currently, it is mainly used for antiviral therapy of hepatitis B. It has the characteristics of quick effect, strong resistance to hepatitis B virus and low drug resistance. Studies have shown that Entecavir, a guanine nucleoside analogue, can effectively inhibit the body's polymerase and other substances, so as to reduce liver fibrosis and improve liver function [42]. Modern scholars have found that Entecavir combined with Chinese herbal compound in the treatment of hepatitis B cirrhosis can improve the treatment rate of the compensatory period, but there is no comparison of the efficacy and safety of different Chinese herbal compound in the treatment of hepatitis B cirrhosis. In this study, network meta-analysis was used and Entecavir treatment was used as a co-intervention to compare the efficacy and safety of different Chinese herbal compounds in the treatment of hepatitis B cirrhosis during the compensatory period, so as to provide reference for the clinical treatment of hepatitis B cirrhosis during the compensatory period

A total of 34 RCTs, 16 TCM compounds and 16 interventions were included in this study. The results showed thatLiver function ALT index ranking from the best to the worst was Yiqi Jiedu Tongluo method, Heluo Shugan tablet, Anluo Huaxian pill, Qishenrugan Capsule, Qingganhuaji Decoction, Danji Huoxue decoction, Ganshuang Granule, Compound Biejia Ruangan tablet, Ruigansanjie Decoction, Shugan Jianpi Decoction, Shenqi Fuzheng Huayu prescription, Peituhua decoction, Shugan Jianpi Huoxue prescription, rhubarb Zhezhan capsule combined with Entecavir treatment respectively; The results showed thatLiver function ALT index ranking from the best to the worst was Yiqi Jiedu Tongluo method, Heluo Shugan tablet, Anluo Huaxian pill, Qishenrugan Capsule, Qingganhuaji Decoction, Danji Huoxue decoction, Ganshuang Granule, Compound Biejia Ruangan tablet, Ruigansanjie Decoction, Shugan Jianpi Decoction, Shenqi Fuzheng Huayu prescription, Peituhua decoction, Shugan Jianpi Huoxue prescription, rhubarb Zhezhan capsule combined with Entecavir treatment respectively; The adverse reactions ranked from best to worst as Shuganjianpi Decoction, Qishenrugan Capsule, Ganshuang Granules, Peituhuazhi Decoction, compound Biejirugan tablet, Heluoxugan tablet combined with Entecavir; The effective rate of treatment was Ganshuang Granules, compound Biejia Ruangan Tablets, Heluo Shugan tablets, Rougan Sanjie Decoction, Rhubarb Zhezhe capsule, Yiqi Jiedu Tongluo method, Qingganhuaji prescription, Anluo Huaxiwan, Shugan Jianpi Decoction, Fuzheng Huayu tablets, Peituhua Decoction, Shenqi Fuzheng Huayu prescription combined with Entecavir, respectively. The method of supplementing Qi and detoxifying collaterals is a compound preparation of traditional Chinese medicine made of raw astragalus, poria cocos, Tangerine peel, Radix sophora, poria cocos, Sanling, Curcuma zedoary, panax notoginseng, turtle shell and so on. It has the effects of nourishing qi and replenishing deficiency, promoting blood circulation and removing blood stasis, clearing heat and detoxifying and dispelling dampness. Studies have shown that the mechanism of the treatment of hepatitis B cirrhosis by supplementing qi and detoxifying and dreading channels may be through promoting the increase of PDGF-AB and PDGF-BB concentrations, so as to control the degree of normal functional vascular regeneration and thus delay the progression of cirrhosis [43]. Heluo Shugan Tablet is a pure Chinese medicine compound composed of 27 traditional Chinese medicines such as white Rhizoma, white peony, Sanling, Xiangfu, Zedoary, Angelica, papaya, etc. It has the effect of soothing the liver and regulating qi, clearing away dampness and heat, promoting blood circulation and removing blood stasis, and nourishing the liver and kidney. Studies have shown that the main components of Heluosugan tablets can inhibit the replication of hepatitis B virus and prevent liver cell damage; meanwhile, it can improve the phagocytosis function of reticuloendothelial system and immune function of the body, and can rapidly reduce the index of transaminase and bilirubin, thus improving liver function [44]. Shugan Jianpi Decoction is composed of Chinese herbs such as angelica sinensis, Radix aconite, bupleurum radix, trichosanthin powder, peony bark, sour jujube seeds, night cross rattan and so on. It has the effect of soothing liver and relieving depression, nourishing blood and invigorating spleen. Radix bupleurum, atractylodes and other drugs used in the prescription can reduce the toxin level in the body of patients, reduce the activation of inflammatory cells in the body, improve the body's microcirculation and tissue irrigation ability, and promote the body's metabolism [45]. The main components of Ganshuang granules are bupleurum, codonopsis, Paeoniae Radix, angelica sinensis, poria cocos, Atractylote, turtle shell, dandelion, Polygonum prunus, prunus prunus, salvia miltiorrhiza and peach kernel, which have the functions of soothing the liver and strengthening the spleen, clearing heat and dispersing blood stasis, protecting the liver and protecting the liver, soft and strong dispersing the tie. Modern pharmacological studies have shown that Ganshuang granules can inhibit the synthesis of type I and type III collagen, thus weakening the inhibitory effect of TIMP1 on matrix metalloproteinase, and also enhance the autophagy ability of cells and play an anti-apoptosis role in fiber cells [46].

Conclusions

The results of this study showed that Entecavir combined with supplementing qi and detoxifying collagal-regulating method had the best effect on ALT index recovery during the compensation period in the treatment of hepatitis B cirrhosis. Entecavir combination and Luoshugan tablet were the best treatment for HA index of hepatic fibrosis. Entecavir combined with Shuganjianpi Decoction was the best treatment for adverse reactions. The best treatment efficiency was Entecavir combined with Ganshuang granules. In this study, mesh meta-analysis was used to compare the efficacy and safety of different Chinese herbal compounds combined with Entecavir in the treatment of hepatitis B cirrhosis during the compensatory period, providing certain scientific guidance and opinions for future scholars to study the treatment of hepatitis B cirrhosis.

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