Efficacy and safety of YinQiSanHuang-antiviral decoction on chronic hepatitis B: study protocol for a randomized, placebo-controlled, double-blinded trial

CURRENT STATUS: UNDER REVISION

qing-juan wu
China Academy of Chinese Medical Sciences Guanganmen Hospital

Wen-Liang Lv
wenlianglv@126.com Corresponding Author
ORCiD: https://orcid.org/0000-0002-4552-919X

Juan-Mei Li
guang'anmen hospital of china academy of Chinese medical sciences.

Ting-Ting Zhang
Guang'anmen Hospital of China Academy of Chinese Medical Sciences.

Wen-hui Zhou
Guang'anmen Hospital of China Academy of Chinese Medical Sciences.

Qiang Zhang
guang'anmen hospital of china academy of Chinese medical sciences.

Jiu-Chong Wang
guang'anmen hospital of china academy of Chinese medical sciences.

Qing-Nan Wang
guang'anmen hospital of china academy of Chinese medical sciences.

Ruo-Xuan Zhang
guang'anmen hospital of china academy of Chinese medical sciences.

Xin Zhao
guang'anmen hospital of china academy of Chinese medical sciences.

Si-Tong Chen
guang'anmen hospital of china academy of Chinese medical sciences.
| Name            | Hospital                                      |
|-----------------|-----------------------------------------------|
| Shuang Liu      | guang'anmen hospital of china academy of Chinese medical sciences. |
| Gao-Hui Li      | guang'anmen hospital of china academy of Chinese medical sciences. |
| Zheng-Min Cao   | guang'anmen hospital of china academy of Chinese medical sciences. |
| Lei Xu          | guang'anmen hospital of china academy of Chinese medical sciences. |
| Jing Chen       | guang'anmen hospital of china academy of Chinese medical sciences. |

**DOI:** 10.21203/rs.2.20189/v1

**SUBJECT AREAS**
- Integrative & Complementary Medicine
- Internal Medicine

**KEYWORDS**
- chronic hepatitis B, cirrhosis, traditional Chinese medicine, clinical trial, efficacy
Abstract

Background: Chronic hepatitis B (CHB) is a global public health problem. Antiviral therapy is the primary treatment. Studies have shown that combined therapy of traditional Chinese medicine (TCM) and conventional antiviral drugs has better clinical efficacy than conventional antiviral for treatment of CHB. YinQiSanHuang-antiviral decoction (YQSH) is a TCM compound preparation used for over thirty years, and has shown its effect on anti-hepatitis B virus and slowing progression of hepatitis B-related liver diseases in a small-scale clinical observation. Until now there is no convincing evidence demonstrating the clinical effectiveness of YQSH in anti-liver cirrhosis and anti-liver cancer. To evaluate the efficacy and safety of YQSH and its preventive effect on hepatitis B cirrhosis, a rigorously designed randomized, double-blind, placebo-controlled clinical trial is needed.

Methods: This is a multicenter, randomized, placebo-controlled, double-blinded trial, 5 hospitals involved in. Totally 802 patients are randomly allocated to two groups: the YQSH group (n=401) or the placebo group (n=401). The YQSH group receives YQSH with Entecavir, the placebo group receives granule of placebo with Entecavir. Patients receive treatment for 52 weeks, and then are followed up for 52±2 weeks. The primary outcome measure is the annual incidence of cirrhosis. The secondary outcome measures are HBV-DNA negative rate, HBsAg negative rate, HBeAg seroconversion rate, liver function (Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), serum albumin (ALB) and total bilirubin (TBIL)), spleen thickness, evaluation scores of patients’ clinical symptoms and safety assessment. Outcomes will be assessed at baseline and after treatment.

Discussion: Combination therapy could become a trendy of treatment of CHB, this trial expecting to provide credible clinical evidence for the future combination of TCM and conventional antiviral drugs for the treatment of CHB.

Trial registration: ChiCTR1900021521, this protocol was registered in the Chinese Clinical Trial Registry (URL: http://www.chictr.org.cn) on February 25th, 2019. Keywords: chronic hepatitis B, cirrhosis, traditional Chinese medicine, clinical trial, efficacy
Chronic hepatitis B (CHB) is a chronic viral infection caused by Hepatitis B virus (HBV) and characterized by the persistence of HBsAg for at least 6 months (with or without concurrent HBeAg). As a global health problem, more than 257 million people worldwide suffer from chronic HBV infection[1−2]. In 2015, an estimated 887 000 deaths resulted from hepatitis B are mostly from cirrhosis and hepatocellular carcinoma (i.e. primary liver cancer),[3] among which CHB is responsible for 30% of all deaths from cirrhosis and 40% from hepatocellular carcinoma (HCC).[4−6] China is one of the highest prevalence country with about 20 million CHB cases, accounted for 21.5% among 93 million cases of HBV infection. Without timely testing and treatment, most CHB will develop into cirrhosis, HCC or finally lead to death. [7−8]It is estimated that in China there are 20–30 million people with CHB, 1 million with liver cirrhosis and 0.3 million with HCC caused by hepatitis B. [9] Deaths due to HBV-related liver diseases in China (0.308 million deaths per year) account for more than 30% of the global mortality from HBV (0.887 million deaths per year). [10] The antiviral therapy is the primary link to slow the conversion of CHB into cirrhosis, which can effectively restore liver function and improve survival rate in patients with CHB. [11−12] Currently, the US Food and Drug Administration (FDA) has approved two types of anti-hepatitis B virus drugs: interferon (IFN) and nucleos(t)ide analogues (NAs), however they showed limitations in clinical applications. [13−14] Chinese herbal medicine (CHM), as one of the most popular complementary and alternative therapies of CHB, a large number of studies have reported its anti-hepatitis B virus effect. CHMs have two major characteristics: a) it is flexible and variable in various kinds of herbal medicines, it has complex compositions which means not easy causing drug resistance. b) Chinese herbal medicines are taken from the natural environment, with a rich source and easy to obtain, and it induce less adverse reactions. CHMs are generally well tolerated for long-term treatment, which shows good therapeutic effect on the prevention and treatment of CHB. A cohort study showed that the use of CHM is associated with a significantly reversed cirrhosis and reduced HCC risk in patients with CHB. [15] Lots of researches identified the active ingredients in single herb or in herbal formula has therapeutic
effect on CHB, the mechanisms related in anti-HBV, anti-fibrosis, liver protection, anti-tumour, antibacterial, antioxidant, anti-acute liver injury and anti-hepatocellular carcinoma. The ideal anti-hepatitis B virus drugs should have good safety, good drug resistance, long-lasting effects and no withdraw rebound, which can stimulate the host immune responses, and effectively inhibit virus replication or even eliminate the virus. Study identified that CHM not only has antiviral effect, but also can enhance the body's immunity to improve the antiviral ability. YinQiSanHuang-antiviral decoction (YQSH) is a CHM formula used over thirty years for CHB treatment, which has showed effects on anti-HBV-DNA and increasing the level of alanine aminotransferase (ALT) in a small-scale clinical study. Research results suggested that YQSH not only Enhances the antiviral effect of entecavir, but also has a significant prevention effect on CHB related cirrhosis. However, there is still lacking of multicenter large-scale randomized controlled double-blind trial, to provide a credible evidence for the efficacy and safety of YQSH.

Methods/design
Trial organization
An independent third-party organization, the Medical Statistics Center of Tianjin University of Traditional Chinese Medicine, will monitor the conduct and safety of the trial. Before the start of clinical trials, uniform training should be conducted for all the participators in clinical trials, which including Good Clinical Practice (GCP), research protocols, Electronic Data Capture System (EDC), central stochastic systems, and the use of scales. All medicines should be managed by designated person, including the process of receiving, issuing, counting, recycling, and confirming the storage conditions.

Study population
A total 802 patients will be recruited from 5 centers: the main responsible unit XiXi Hospital of HangZhou will recruit 162 cases, Beijing ShunYi Traditional Chinese Medicine Hospital will recruit 160 cases, the Sixth People’s Hospital of ShenYang will recruit 160 cases, Beijing DiTan Hospital Capital Medical University will recruit 160 cases, ChengDu University of Chinese Medicine Affiliated Hospital recruit 160 will cases.

Recruitment of participants
Outpatients in clinics are the main recruitment objects. Posters and online publicity with a brief introduction to the trial and the contact information of researchers will also be used for recruitment. Before enrollment, each patient is provided with a complete and comprehensive description of the test procedure, purpose, potential adverse events and expected benefits. Subjects are also informed that they may withdraw from the trial. If the patient agrees to participate in the trial, the subject will sign two informed consent forms, one kept by the patients and the other one kept by the researcher.

**Inclusion criteria**

The inclusion criteria are as follows: a) patients have a history of hepatitis B infection or HBsAg positive for more than six months, and the current HBsAg and/or HBV-DNA are still positive. b) patients who cater for antiviral indications in the ‘Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update’ [27], or patients taking Entecavir dispersible tablets are also can be included in. c) between 18 to 65 years old. d) patients show syndromes of liver stagnation and spleen deficiency and dampness in TCM. For the TCM diagnostic criteria, we refer to ‘National Standards for TCM Clinical Diagnosis and Treatment of the People's Republic of China’[28] and the ‘Medical Consensus of diagnosis and treatment of cirrhosis with integrated TCM and Western medicine’,[29] which was published by Digestive System Diseases Committee, Society of Integrated Traditional Chinese and Western Medicine.

**Exclusion criteria**

The exclusion criteria are as follows: a) patients with cirrhosis. b) patients with liver cancer. c) patients in acute and chronic hepatitis with non-HBV infection, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosis cholangitis, inherited metabolic liver disease, drug or toxic hepatitis, alcoholic liver disease. d) pregnant or lactating women or women planning to become pregnant during the study period, e) patients who are allergic to the test drugs. f) patients who have mental disorders that cannot cooperate with the study, or patients with epilepsy in unstable status. g) patients with severe systemic diseases related with heart, brain, lung, kidney, and hematopoiesis. h) patients of alcoholism or with other unsuitable conditions that not suitable for enrollment.

**Handling of withdrawal and data management**
If the following conditions occur, it is defined as the subject falls off: a) poor compliance, irregular taking medicine, failure to revisit or revisit on time. b) some combined diseases or complications, or deterioration during the trial. c) subject self-withdrawal. d) combined other drugs, or not taking test drugs according to research regulations. e) lost contact. f) cannot provide complete information.

Subjects should discontinue the trial when the following conditions occur: a) serious adverse reactions occur. b) the overall disease worsen with obvious adverse reactions. c) hepatitis B develop into cirrhosis during the study. d) the test is suspended due to force majeure reasons. After the data is entered into EDC, a medical review should be evaluated by a trained professional researcher. The primary outcome should submit to the clinical endpoint committee to be evaluated by uniform standard. The principal investigator and authorized researcher should review, electronically sign and date the eCRF. The database will be maintained using Excel software. The data management and statistical analysis are performed by an independent third-party institution. The data analysis is performed by SPSS 19.0 statistical software. The frequency and percentage of variables will be calculated by the descriptive statistics program. Pearson’s χ² test will be performed on categorical variables, and Student’s t-test will be performed on measurement variables.

Interventions
The treatment period is 52 weeks and the follow-up assessment period will last for 52 ± 2 weeks. The test group (YQSH group) receives YQSH 150–200 ml twice a day, combined with Entecavir 0.5 mg once a day. The control group (placebo group) receives YQSH placebo 150–200 ml twice a day, combined with Entecavir 0.5 mg once a day. The Entecavir was produced by ChiaTai TianQing Pharmaceuticals in Jiangsu, China (production batch number: H20100019). The main compositions of YQSH, totally 14 kinds of herb, are shown in Table 1. The test drugs are made into Chinese medicine formula granule. Before taking YQSH, boil the mixed formula granule with 150–200 ml water for 3–5 minutes. YQSH placebo is made of excipients, thinners, coloring agents, flavoring agents and fried malt, which is similar to YQSH in the shape, color, smell and taste. Other antiviral medicines must not be taken during the trial, if the un-antiviral medicines combined, record them in the ‘Case Report Form (CRF)’. If the patient shows abnormal liver function (ALT > 2*ULN) during the trial, the
investigator could add hepatoprotective drugs such as Silibinin and other drugs according to the patient's condition. (Fig. 1)

Randomisation and blinding
Central Randomization System (CRS) is applied for a completely randomized design: Firstly, confirm patients with the inclusion criteria, log into the CRS, input the general information of the subjects, generate the random number and fill in the eCRF. Secondly, drug distributors apply for the drug number from CRS according to the random number. Finally, the drug senders verify the code on the drug package with the number in the system, then the drugs been given to patients. This is a double-blind trial. The blinding method is set up and implemented by the Medical Statistics Center of Tianjin University of TCM. Neither the study researchers nor the subjects know the medication grouping. In the course of the trial, there is a scientific and strict management implementation system and feasible operation methods. All the subjects are under a standardized observation with their clinical symptoms carefully recorded. Adverse reactions are carefully observed, and ‘breaking blinding’ is required for serious adverse reactions. A regular supervision, inspection and return system to ensure the implementation of double-blinding method. Unblinding at the end of the test to perform a statistical analysis of all the data.

Primary outcome
The primary outcome is the annual incidence of cirrhosis (the examination methods include liver instantaneous elastic hardness test, abdominal B-ultrasound test or abdominal MRI/CT imaging). The primary outcome is evaluated before the treatment, at the 52 weeks of treatment, and the 52 ± 2 weeks of follow-up.

Secondary outcomes
The secondary outcomes include HBV-DNA negative rate, HBsAg negative rate, HBeAg seroconversion rate, liver function (ALT, AST, GGT, ALP, ALB and TBIL), spleen thickness, and the evaluation scores of patients’ clinical symptoms.
These indicators are observed before the treatment, at the 26 weeks of treatment, the 52 weeks of treatment, the 26 ± 2 weeks of follow-up period, and the 52 ± 2 weeks of follow-up period.

Safety outcomes
The safety outcomes include: a) basic vital signs: body temperature, blood pressure, respiration and heart rate. b) renal function tests blood urea nitrogen (BUN) and creatinine (Cr). c) electrocardiogram (ECG). d) blood, stool and urine routine tests. These biological indicators are monitored from the grouping of these patients until the end of follow-up. (Fig. 2)

**Adverse events**
Any adverse medical events that occur during treatment and follow-up, regardless of whether or not there is a causal relationship with the test medicines, should be considered as an adverse event (AE) and recorded in the specified CRF adverse event table. When filling out the AE report forms, it is necessary to detailedly record the occurrence, time, severity, duration, measures taken and outcomes of adverse events. If serious adverse events occur during the trial, emergency treatments should be taken immediately and report to the lead researcher of the trial, the ethics committees and the China State Food and Drug Administration Safety Supervision Department within 24 hours. All the adverse events should be tracked until the adverse symptoms disappear or the researchers confirm that further follow-up is no longer needed.

**Sample size**
The aim of this study is to reduce the annual incidence of cirrhosis from 2% ~10-1% in CHB patients. Therefore, according to the sample size estimation formula for comparison of two sample rates, the incidence of target events is less than 0.2 (or 0.3) or greater than 0.8 (or 0.7), estimation formula as follows:

$$n = \frac{(u_\alpha + u_\beta)^2}{2(sin^{-1}\sqrt{p_e} - sin^{-1}\sqrt{p_c})^2}$$

The $p_e$ and $p_c$ represent the incidence rates of test group (YQSH group) and placebo group (control group) respectively, and the degree is measured in radians, $\alpha=0.05$, $\beta=0.10$. In this study, two-sided test was chosen, $u_{0.05}=1.96$, $u_{0.10}=1.282$, $p_e=0.05$, $p_c=0.01$. The calculated sample size of each
group is approximately 334 cases, allowing for 20% attrition, therefore, the total number of patients required for this trial is \(334 \times (1+20\%) \times 2 = 802\) cases, with 401 in each group.

**Discussion**

Hepatitis B is a hidden killer. In the course of viral infection for decades, the virus carrier (patients) may show only mild symptoms, which difficult to detected, but it may develop into liver cancer ultimately.\(^{[30]}\) Currently, the direct-acting antiviral agents (DAAs) includes NAs and IFN can only control hepatitis B virus, but cannot eliminate it completely. Therefore, pre-treatment is the best way to prevent the deterioration of CHB and cirrhosis. In the theory of traditional Chinese medicine, there is a viewpoint ‘preventive treatment of disease’, which means precaution should be paid in advance when the disease has no occurred or already occurred, in case of diseases further development or deterioration. In China, CHM has been used over two thousand years and played an important role in the prevention and treatment of diseases. TCM decoction is generally composed by various of Chinese herbs with a certain proportion, its characterized by a multi-targets effect. YQSH is a TCM decoction based on the theory of ‘preventive treatment of disease’ of TCM, in the early small-scale clinical observation, it has suggested a potential effect on delaying the development of CHB related cirrhosis. At present, long-term HBV-DNA inhibition or HBsAg negative is considered to be the best surrogate endpoint for antiviral therapy in patients with CHB or cirrhosis associated with HBV.\(^{[31−34]}\) Studies reported that combined therapy is superior to conventional antiviral therapies,\(^{[35−37]}\) which not only can enhance the antiviral ability, on the other hand, it also can reduce the accompanying symptoms, improve the quality of life and prolong the life of patients.\(^{[38−39]}\) Thus, the combination therapy could become a trendy of CHB treatment. Looking back on the clinical researches about the combination therapy in CHB in recent years, there are mostly single-center, single-field and small sample study, which makes it conclusion less credible. Therefore, this trial protocol was designed into a multicenter, randomized, double-blind, placebo-controlled clinical trial, follow-up as long as 52 ± 2 weeks, to verify the clinical efficacy and safety of the combination therapy of YQSH + entecavir, expecting to provide credible clinical evidence for the future combination of TCM and Western medicines for the treatment
There are also some limitations to the study that should be considered. Due to restrictions in research project funds and trial period, the follow-up period couldn't be longer, and thus additional randomised controlled trials with long-term follow-up are warranted. For the combination therapy, there are still some problems should be clarified, such as how the drugs are combined, what’s the best time for combination therapy, when to stop the drug, whether it can be repeated after stopping the drug, and how to cope with recurrence after drug withdrawal. It is supposed that more combination therapy will be explored in the future based on different mechanisms.

**Trial Status**

The protocol version number is 1 and was finalized in October 2018. The date recruitment began on 21 October 2019. The approximate date when recruitment will be completed is December 2021.

**List Of Abbreviations**

CHB, chronic hepatitis B; YQSH, YinQiSanHuang-antiviral decoction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; ALB, serum albumin; TBIL, total bilirubin; TCM, traditional Chinese medicine; YQSH, YinQiSanHuang-antiviral decoction; ECG, electrocardiogram; HBV, Hepatitis B virus; DAAs, antiviral agents; AE, adverse event; GCP, Good Clinical Practice; BUN, blood urea nitrogen; FDA, Food and Drug Administration; IFN, interferon; NAs, Nucleos(t)ide aAnalogues; CHM, Chinese Herbal Medicine; CRS, Central Randomization System; CRF, Case Report Form; CRS, Central Randomization System; HCC, Hepatocellular Carcinoma.

**Declarations**

**Ethics approval and consent to participate** The protocol has been approved by the Medical Ethics Committee of Hangzhou Xixi Hospital, China (which is the central ethical approval), and the other centres in the trial will not begin recruiting until local ethical approval has been obtained. All study participants will sign two informed consent forms, one kept by the patients and the other one kept by the researcher. The results of this study will be published in a peer reviewed journal.

**Consent for publication**

According to the terms of the informed consent, unless the subject's consent is obtained, all the
subject's personal information is confidential and will not be disclosed to the public.

**Availability of data and materials**

Not applicable.

**Competing interests** All authors confirm that this article content has no conflict of interest.

**Funding** This project is supported by the National Key R&D Program of China (No. 2018YFC1705700).

**Authors' contributions** L-WL conceptualized the idea and revised it critically for intellectual content, provided professional advices. W-QJ wrote the first draft of this manuscript. All authors read and approved the final manuscript. L-JM, Z-TT, Z-Q, W-JC, W-QN, Z-RX and C-ZM were involved in the conception and design, statistical advice and final approval of the manuscript, we will have ultimate authority over these activities.

**Acknowledgements** We would like to thank professor Zhou Bing for polishing manuscript.

**References**

[1] Revill PA, Penicaud C, Brechot Christian, et al. Meeting the Challenge of Eliminating Chronic Hepatitis B Infection. Genes (Basel). 2019;10:undefined.

[2] Schweitzer A, Horn J, Mikolajczyk R T, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546-1555.

[3] Liu J, Liang WN, Jing WZ, et al. Countdown to 2030: eliminating hepatitis B disease, China. Bull, World Health Organ. 2019;97:230-238.

[4] Vittal A, Ghany M G. WHO Guidelines for Prevention, Care and Treatment of Individuals Infected with HBV: A US Perspective. Clin Liver Dis. 2019;23:417-432.

[5] Stanaway J D, Flaxman A D, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388:1081-1088.

[6] Dandri M, Locarnini S. New insight in the pathobiology of hepatitis B virus infection. Gut. 2012;2:16-17.

[7] World Health Statistics 2018: Monitoring health for the SDGs. WHO. 2018;6 June.

[8] Bhattacharya D, Thio C L, Reviewof. Hepatitis B therapeutics. Clin Infect Dis. 2010;51:1201-1208.
[9] Shan S, Jia J. Advances and challenge in prevention and treatment of hepatitis B in China. Zhongguo Bingdubing Zazhi. 2017;01:5-8.

[10] Subic M, Zoulim F. How to improve access to therapy in hepatitis B patients. Liver Int. 2018;38 Suppl 1:115–121.

[11] Yuen Man F, Gane Edward J, Kim Dong J, et al. Antiviral Activity, Safety, and Pharmacokinetics of Capsid Assembly Modulator NVR 3-778 in Patients with Chronic HBV Infection. Gastroenterology. 2019;156:1392-1403.

[12] Calvaruso V, Craxì A. Regression of fibrosis after HBV antiviral therapy. Is cirrhosis reversible? Liver Int. 2014;85-90.

[13] Sun D J, Zhu L J, Yao D H, et al. Recent progress in potential anti-hepatitis B virus agents: Structural and pharmacological perspectives. Eur J Med Chem. 2018;147:205-217.

[14] Lee S H, Cheon G J, Kim H S, et al. Tenofovir disoproxil fumarate monotherapy is superior to entecavir-adeovir combination therapy in patients with suboptimal response to lamivudine-adeovir therapy for nucleoside-resistant HBV: a 96-week prospective multicenter trial. Antiviral Therapy. 2018;23:219-227.

[15] Tsai T Y, Livneh H, Hung T H, et al. Associations between prescribed Chinese herbal medicine and risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide population-based cohort study. BMJ Open. 2017;7:e014571.

[16] Zhao Y, Geng C A, Ma Y B, et al. UFLC/MS-IT-TOF guided isolation of anti-HBV active chlorogenic acid analogues from Artemisia capillaris as a traditional Chinese herb for the treatment of hepatitis. J Ethnopharmacol. 2014;156:147-154.

[17] Han J M, Kim H G, Choi M K, et al. Artemisia capillaris extract protects against bile duct ligation-induced liver fibrosis in rats. Exp Toxicol Pathol. 2013;65:837-844.

[18] Zhao T T, Tang H L, Xie L, et al. Scutellaria baicalensis Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. J Pharm Pharmacol. 2019;71:1353-1369.

[19] Park H S, Park K I, Hong G E, et al. Korean Scutellaria baicalensis Georgi methanol extracts
inhibits metastasis via the Forkhead Box M1 activity in hepatocellular carcinoma cells. J Ethnopharmacol. 2014;155:847-851.

[20] Hsu Y L, Kuo P L, Tzeng T F, et al. Huang-lian-jie-du-tang, a traditional Chinese medicine prescription, induces cell-cycle arrest and apoptosis in human liver cancer cells in vitro and in vivo. J Gastroenterol Hepatol. 2008;23:e290-299.

[21] Ohta Y, Sasaki E, Nishida K, et al. Preventive effect of oren-gedoku-to (huanglian-jie-du-tang) extract on progression of carbon tetrachloride-induced acute liver injury in rats. Am J Chin Med. 1997;25:57-68.

[22] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Hepatol. 2017;67:370-398.

[23] Terrault N A, Bzowej N H, Chang K M, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-283.

[24] Cheng X X, Wang H F, Yang J L, et al. Arctigenin protects against liver injury from acute hepatitis by suppressing immune cells in mice. Biomed Pharmacother. 2018;102:464-471.

[25] Wang J B, Liu R, Liu B X, et al. Systems Pharmacology-based strategy to screen new adjuvant for hepatitis B vaccine from Traditional Chinese Medicine Ophiocordyceps sinensis. Sci Rep. 2017;7:44788.

[26] Wang D P. Clinical study of Yinzhi Sanhuang Jiedu Decoction combined with entecavir in the treatment of chronic hepatitis B. Beijing University of Chinese Medicine. 2018;63-64.

[27] Liaw Y F, Leung N, Kao J H, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int. 2008;2:263-283.

[28] State Bureau of Technical Supervision. National Standards for TCM Clinical Diagnosis and Treatment in the People's Republic of China: Symptoms Section. Beijing: China Standard Press. 1997;4:55.

[29] Chinese Society of Integrated Traditional and Western Medicine, Digestive System Diseases Committee. Consensus on diagnosis and treatment of cirrhosis with integrated traditional Chinese and Western medicine. Chinese Journal of Integrated Traditional and Western Medicine on Digestion.
[30] Tu T, Sandra B, Bartenschlager R. Chronic viral hepatitis and its association with liver cancer. Biological Chemistry. 2017;398:817-837.

[31] Terrault N A, Bzowej N H, Chang K M, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-283.

[32] Liaw Y F, Kao J H, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatology International. 2012;6:531-561.

[33] Testoni B, Leverero M, Zoulim F. Challenges to a Cure for HBV Infection. Seminars in Liver Disease. 2017;37:231-242.

[34] Lok Anna S, Zoulim Fabien, Dusheiko Geoffrey, et al. Hepatitis B cure: From discovery to regulatory approval. J Hepatol. 2017;67:847-861.

[35] He M, Wu Y, Wang M M, et al. Meta-analysis of the clinical value of oxymatrine on sustained virological response in chronic hepatitis B. Ann Hepatol. 2016;15:482-491.

[36] Zhang L, Schuppan D. Traditional Chinese Medicine (TCM) for fibrotic liver disease: Hope and hype. Journal of Hepatology. 2014;61:166-168.

[37] Kang H, Zhao Y, Li C, et al. Integrating clinical indexes into four-diagnostic information contributes to the Traditional Chinese Medicine (TCM) syndrome diagnosis of chronic hepatitis B. Sci Rep. 2015;5:9395.

[38] Chen J X, Xu Q X, Wang J H, et al. A Case of Recurrent Hepatocellular Carcinoma Acquiring Complete Remission of Target Lesion With Treatment With Traditional Chinese Medicine. Integr Cancer Ther. 2017;16:597-604.

[39] Xiong X, Yang X, Liu Y, et al. Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science. Hypertension Research Official Journal of the Japanese Society of Hypertension. 2013;36:570-579.

Table 1

| Chinese name | Latin name                  | English name    | Pharmacological action | Main active ingredient | The original producing area | Medicinal part | Dosage/(g) |
|--------------|-----------------------------|-----------------|------------------------|------------------------|---------------------------|----------------|------------|
| Huang Qi     | Astragalus propinquus       | Radix Astragali | Promote liver cell growth, Astragaloside (I, V, III), | Neimenggu, China        | Rhizome                  | 12             |
| Name          | Scientific Name | Active Constituents | Actions                                                                                           | Country          | Location/Part                           |
|---------------|-----------------|---------------------|---------------------------------------------------------------------------------------------------|------------------|------------------------------------------|
| Schischkin    | Artemisia capillaris Thunb. | Virgate Wormwood Herb Capillary Wormwood Herb | Lower blood lipids to treat fatty liver, reduce alcoholic liver damage, inhibit the replication of hepatitis B virus DNA | Shanxi, China    | Aboveground part of the plant            |
| Yìn Chen      | Scutellaria baicalensis Georgi | Baical Skullcap Root | Anti-hepatocyte inflammation, anti-hepatocyte apoptosis, anti-hepatocyte mitochondrial lipid peroxidation, regulate immunity | Hebei, China     | Rhizome                                  |
| Huang Qin     | Coptis chinensis Franch. | Coptis Root          | Anti-hepatocyte mitochondrial lipid peroxidation, inhibit hepatoma cell proliferation, prevent liver fibrosis | Sichuan, China   | Tuber root                               |
| Huang Lian    | Platycladus orientalis (Linn.) Franco | Bark of Chinese Corktree | Inhibit immune response, Selective inhibit HBAg, anti-inflammatory | Sichuan, China   | Dry bark                                  |
| Huang Bai     | Curcuma aeruginosa Roxb. [C.zedoariano nRosc.] | Rhizome curcumae | Inhibit hepatoma cell proliferation, induced apoptosis of liver cancer cells, anti-liver fibrosis | Guangxi, China   | Tuber root                               |
| E Zhu         | Trionyx sinensis (Wiegmann) | Turtle Shell         | Anti-liver fibrosis, promote immunity, anti-hepatocyte injury                                      | Hubei, China     | Carapace                                 |
| Jiao Shan Zha | Crataegus pinnatifida Bunge var.major N.E.Br. | Hawthorn Fruit       | Lower cholesterol, anti-bacterial, anti-hypertensive                                              | Shandong, China  | Fruit                                    |
| Bai Shao      | Paeoniae alba | Anti-hepatocyte     | Paenoniflorin, oxy-                                                                               | Anhui, China     | Rhizome                                  |
| Name             | Scientific Name                  | Traditional Name       | Function                                                                 | Chemical Constituents                                                                 | Location          | Part   |
|------------------|----------------------------------|------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------|--------|
| Ling Xiao Hua    | Campsis grandiflora (Thunb.) K.Schum. | Trumpet creeper flower | Anti-injury, anti-liver fibrosis, anti-fatty liver                        | Paoniflorin, benzoylpaoniflorin, albi-florin, paoniflorigenone                          | Jiangsu, China    | Flower | 6      |
| Bai Zhu          | Atractylodes macrocephala Koidz. | Largehead Atractylodes rhizome | Inhibit liver cancer cell metastasis, promote cellular immune function, inhibit the activating of metabolic enzymes | Volatile oil (humulene, 3β- elemol, α-curcumene, 3β-acetoxyatractylene), Sesquiterpene lactone compounds (atractylenolide, 8β-ethoxyatractylenolide-II), Polyacetylene (14-acetyl-12-senecioyl-2E,8Z,10E-atracetylentriol) | Zhejiang, China   | Tuber root | 9      |
| Fu Ling          | Poria cocos (Schw. Wolf.)         | Tuckahoe               | Enhance cellular and humoral immunity, inhibit the DNA synthesis of tumor cell, inhibit hepatocyte necrosis, anti-tumor | Pachymic acid, tumulosic acid, pachymic acid methyl ester, pachymian, Pachymaran,      | Yunnan, China     | Dry sclerotia | 9      |
| Chai Hu          | Bupleurum chinense DC.            | Red Thorowax root      | Anti-liver fibrosis, inhibit acute liver injury, inhibit proliferation of liver cancer cells, promote apoptosis of liver cancer cells, anti-liver injury | Volatile oil (pentanoic acid, hexanoic acid, heptanoic acid, 2-heptenoic acid)       | Hebei, China      | Rhizome | 6      |
| Bai Hua She She Cao | Hedyotis diffusa Willd.         | Spreading Hedyotis herb | Enhance hepatocyte immunogenic to anti-tumor, inhibit proliferation of liver cancer cells, promote apoptosis of liver cancer cells | Asperuloside, asperulosidic acid, deacetylasperulosidic acid, geniposidic acid, scandoside | Guangxi, China | Whole plant | 12     |

**Figures**
Flow chart of the randomized, placebo-controlled, double-blinded trial of YQSH for CHB.

Abbreviations:
- a) CHB, chronic hepatitis B.
- b) YQSH, YinQiSanHuang-antiviral decoction.
- c) ALT, alanine aminotransferase.
- d) AST, aspartate aminotransferase.
- e) GGT, gamma glutamyl transferase.
- f) ALP, alkaline phosphatase.
- g) ALB, serum albumin.
- h) TBIL, total bilirubin.
| TIMEPOINT** | Enrolment | Allocation | Treatment | Follow-up |
|------------|-----------|------------|-----------|-----------|
| -3wks-0d   |           | 0d         | 26wks±14d | 52wks±14d |
|            | ENROLMENT:                   |           |           |           |
|            | Eligibility screen          | X         |           |           |
|            | Informed consent            | X         |           |           |
|            | Allocation                  |           | X         |           |
|            | INTERVENTIONS:              |           |           |           |
|            | Placebo group               |           |           |           |
|            | YQSH group                  |           |           |           |
|            | ASSESSMENTS:                |           |           |           |
|            | Safety outcomes             | X         | X         | X         | X         | X         |
|            | Primary outcome:            |           |           |           |
|            | annual incidence            |           |           |           |
|            | of cirrhosis                |           |           |           |
|            | Secondary outcomes         |           |           |           |

Figure 2

The schedule of enrollment, interventions and assessments demonstrated in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- funding documentation.docx
- SPIRIT_checklist 2019-11-28.docx
- Ethical Approval Documents.pdf