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HEPATITIS B (JK LIM, SECTION EDITOR)

The Role of Traditional Chinese Medicines (TCM) and Other Complementary and Alternative Medicines (CAM) in the Management of Chronic Hepatitis B

Guqi Wang[1,2,3] · Peng Liang[4] · Ping Li[4] · Yang Hui Tan[5] · Herbert L. Bonkovsky[1]

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Abstract

Purpose of Review To provide a review and update of complementary and alternative medicine (CAM) approaches to the management of chronic hepatitis B, with particular emphasis upon traditional Chinese medicines (TCM).

Recent Findings The major findings are as follows: (1) TCMs were better than interferons [IFN] in lowering serum HBeAg and normalizing serum ALT, and equivalent to IFN in clearing serum HBV DNA; (2) TCMs were equivalent to lamivudine [LAM] in lowering serum HBeAg, normalizing serum ALT, and clearing serum HBV DNA; (3) TCMs along with IFN or LAM significantly lowered serum HBeAg and improved the clearance of serum HBV DNA and the normalization of serum ALT, compared with IFN or LAM alone; (4) no serious adverse reactions of TCM were reported in all cited clinical trials. Although the composition of traditional medicines in the TCMs varied among RCTs, about 60% of the used herbs were homologous. Our major overarching conclusion was that TCMs seem effective as alternative remedies for patients with CHB. Other CAM approaches also are widely used, especially in east Asian countries, and there is limited evidence of benefit for some.

Summary CHB continues to be a major health problem worldwide. Although nucleosides such as tenofovir and entecavir are highly effective at suppression of HBV replication, they are expensive and often beyond reach of patients, especially in resource-limited nations and regions. Many such patients will continue to rely upon CAM and TCM for management of their chronic hepatitis B infections. Additional carefully done, placebo-controlled prospective randomized trials of CAM and TCM in chronic hepatitis B should be performed.

Keywords Chronic infection · Complementary and alternative medicines · Hepatic cirrhosis · Hepatitis B · Hepatocellular carcinoma · Traditional Chinese medicines

This article is part of the Topical Collection on *Hepatitis B*

✉ Herbert L. Bonkovsky
hbonkovs@wakehealth.edu

Guqi Wang
guqiwang@yahoo.com

Peng Liang
Pengliang8028@163.com

Ping Li
Ip8675@163.com

Yang Hui Tan
sanhy2013@126.com

[1] Section on Gastroenterology & Hepatology, Department of Internal Medicine and Department of Molecular Medicine & Translational Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

[2] Management Committee of Shangrao National Chinese Medicine Health Tourism Demonstration Zone, Shangrao, Jiangxi, China

[3] Whole Pharm Biotechnology, Charlotte, NC, USA

[4] Beijing Key Lab Immune-Mediated Inflammatory Diseases, Institute of Clinical Medical Science, China-Japan Friendship Hospital, Beijing, China

[5] Guangzhou Ren Ai Tianhe Hospital, Guangzhou, Guangdong, China

Introduction

Infection by the hepatitis B virus (HBV) can cause liver inflammation, fibrosis, cirrhosis, and/or hepatocellular carcinoma (HCC). Despite global efforts at vaccination for primary prophylaxis, chronic viral hepatitis B (CHB) continues to be one of the major public health concerns worldwide, with an estimated 257 million people living with chronic HBV infection and more than 600,000 HBV-related deaths in 2015 [1]. Currently, the approved therapies for HBV infection include mainly interferons (IFN), lamivudine (LAM), or other nucleoside analogues (e.g., adefovir dipivoxil, entecavir, telbivudine, tenofovir). However, these antiviral agents may be associated with adverse reactions, and their efficacies are compromised in some patients by development of antiviral resistance after prolonged use [2]. In addition, the newer and more effective nucleosides are expensive and often beyond the reach of persons of limited means and little or no health insurance. Therefore, safe and effective novel anti-HBV drugs and alternative medicines continue to be needed. In this chapter, we review the status of complementary and alternative medicines (CAM), with special emphasis upon traditional Chinese medicines (TCM) for management of CHB, which remains a chronic infection without cure for millions of persons, especially in resource-limited nations.

Traditional Chinese medicines (TCM), as a type of complementary and alternative medicine (CAM), are integral parts of a time-honored, traditional form of healthcare in China. Many TCMs continue to be widely used to treat hepatitis B in China and a number of other countries [3]. Clinical surveys revealed recently that more than 90% of CHB patients in China received TCM therapy [4•]. Over 80% of natural supplements thought useful for management of liver diseases are Chinese herbs and/or herb extracts, and over 80% of articles published in Chinese regarding hepatitis and hepatic fibrosis are TCM-related [5••]. These are much higher proportions than those for western medicines used in China. With respect to the treatment of CHB with TCM, major questions include the following: "Are TCMs effective therapeutic agents for CHB?" If yes, "Why are so many millions of Chinese chronically infected with the hepatitis B virus?" "Does TCM therapy treat the cause (clearing or inhibiting HBV) or mainly treat symptoms and subsequent liver inflammation and fibrogenesis?" There are both medical and cultural dimensions to these questions.

Summary of Effects of CAM and TCM on Chronic Hepatitis B

To better understand the use of TCMs in the treatment of CHB in China, we performed a comprehensive review, summarizing and analyzing information collected from the databases of PubMed and the China National Knowledge Infrastructure (CNKI). The prospective randomized clinical trials (RCTs), non-randomized clinical trials (non-RCTs), and summaries of clinical experience were selected for analysis in the study. The clinical trials included single-blind, double-blind, or not blinded studies in humans that involved TCMs only versus antiviral drugs and TCMs along with antiviral drugs versus antiviral drug alone. We also analyzed the TCM formulations used in the research and clinical trials, and determined the most frequently used herbs in CHB treatment. The results of our study were published in *Hepatology* [6] with the title "Contemporary Clinical Research of Traditional Chinese Medicines for Chronic Hepatitis B in China: An Analytical Review". The major findings were (1) TCMs have a similar therapeutic effect as do IFN/LAM in patients with CHB as evidenced by the loss of serum HBeAg and reduction in HBV DNA; (2) TCMs have a somewhat greater beneficial effect on normalization of serum ALT (Fig. 1); (3) TCMs enhance IFN and LAM antiviral activities and improvements of liver tests of inflammation (Fig. 2); (4) No serious adverse reactions of TCM were reported in the cited clinical trials. Although the composition of traditional medicines in the TCMs varied among RCTs, about 60% of the herbs used were homologous; that is, their purported mechanisms of action were similar according to traditional Chinese medical theories. The results suggested that TCMs appear to be somewhat effective as alternative remedies for CHB patients, especially in PR China, where there is a long tradition of TCM practice and use and where there are millions of persons chronically infected with HBV who are unable to afford or gain access to entecavir or tenofovir. Of course, TCMs for CHB should best be further evaluated in well-designed, adequately powered prospective RCTs.

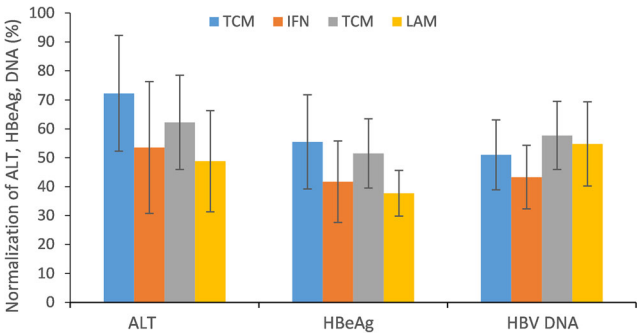

Fig. 1 Summary of key results of 55 RCTs of TCM vs IFN/LAM for CHB in China. The results plot the mean values ± SD for percentage of subjects that showed improvements of serum ALT (TCM vs IFN, OR 2.42, 95% CI 1.51–3.89, $p = 0.0003$; TCM vs LAM, OR 1.96, 95% CI 1.15–3.32, $p = 0.01$), and no differences in reducing serum HBeAg and (TCM vs IFN, OR 1.60, 95% CI 1.00–2.54, $p = 0.07$; TCM vs LAM, OR 1.57, 95% CI 0.60–4.12, $p = 0.36$) no differences in clearing serum HBV DNA (TCM vs IFN, OR 1.31, 95% CI 0.87–1.98, $p = 0.20$; TCM vs LAM, OR 1.20, 95% CI 0.61–2.36, $p = 0.59$). Note that the percentages were higher in those treated with TCM (data are plotted from the results of our recent review [5••])

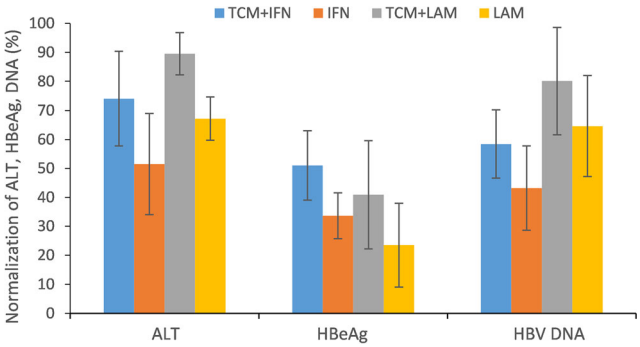

Fig. 2 Summary of 55 RCTs of TCM+IFN/LAM vs IFN/LAM for CHB in China. The results plot the mean values ± SD for percentage of subjects that showed significant improvements of serum ALT (TCM+IFN vs IFN, OR 3.07, 95% CI 2.35–4.00, $p < 0.00001$; TCM+LAM vs LAM, OR 3.40, 95% CI 2.45–4.70, $p < 0.00001$), and significant effects on reducing serum HBeAg and (TCM+IFN vs IFN, OR 2.17, 95% CI 1.74–2.72, $p < 0.00001$; TCM+LAM vs LAM, OR 2.54, 95% CI 1.95–3.32, $p < 0.00001$) significantly improved clearance of serum HBV DNA (TCM+IFN vs IFN, OR 2.05, 95% CI 1.59–2.65, $p < 0.00001$; TCM+LAM vs LAM, OR 3.20, 95% CI 2.09–4.92, $p < 0.00001$). Note that the percentages were higher in those treated with TCM (data are plotted from the results of our recent review [5••])

As we pointed out in the review, the methodological quality of the clinical trials reported in our study was not high. Seventy percent of the RCTs were scored as having mediocre methodological quality. Only 24% of the RCTs had included attempts at long-term follow-up studies. The funnel plots in our study did not reveal evidence of major publication bias; however, other concerns remain. The claimed effectiveness of TCM formulations for CHB treatment could be overstated if only positive results were reported in the publications. Many TCM formulations or individual herbs were used in these RCTs, and what the common standards or criteria to select the formula of herbs for the RCTs were not revealed. Whether Chinese western medicine practitioners also use TCMs commonly in their clinical practices for CHB remains unclear. The quality assurance and quality control of the TCM formulations used in all these clinical trials were not stated. No safety data of the TCM formulations used in these RCTs were presented. These concerns, in addition to the low methodological quality of the RCTs, make it problematical to firmly place the usefulness of TCMs for CHB and/or to recommend the therapies to clinicians.

Our study also revealed that herbs usually used for HBV treatment in different formulations of TCMs are very similar. In 235 hepatitis B clinical trials, 235 TCM formulas were used, which included 203 herbal preparations. The most commonly used herbs were Huang Qi, Dan Shen, Hu Zhang, and Bai Hua She She Cao. Noteworthy is that milk thistle (Shui Fei Je), the widely used herb for viral hepatitis and other liver diseases in Europe and North America, was not ranked among the mostly used herbs in China (Table 1). Nonetheless, similar to TCMs, milk thistle and silymarin (thought to be its main active ingredient) have time-honored history for medicinal purposes, and their touted liver-health properties continue to attract attention. Although some studies reported successful treatment of HBV-infected patients with milk thistle, these findings have not been repeated in high-quality clinical trials

Table 1 The 17 most used herbs in HBV clinical trials in China

Herb (Chinese Pinyin)	Times used in the formulas	Number of patients studied
Mongolian milkvetch root (Huang Qi)	143	12674
Salvia miltiorrhiza (Dan Shen)	135	10784
Large head atractylodes rhizome (Bai Shu)	113	8304
Radix bupleuri (Chai Hu)	108	9888
Polygonum cuspidatum (Hu Zhang)	102	8700
Oldenlandia diffusa (Bai Hua She She Cao)	92	9198
Radix glycyrrhizae (Gan Cao)	85	7219
Herba artemisiae capillaries (Yin Chen)	79	7545
Radix paeoniae rubra (Chi Shao)	71	5580
Radix cureumae wenyujin (Yu Jin)	64	6323
Poria (Fuling)	60	4528
Radix paeoniae alba (Bai Shao)	60	4040
Radix angelicate sinensis (Dang Gui)	56	4391
Radix codonopsis (Dang Shen)	46	3308
Radix et rhizoma rhei (Da Huang)	38	3719
Radix isatidis (Ban Lan Gen)	35	2554
Fructus schisandrae chinensis (Wu Wei Zi)	33	3096

Results extracted from our extensive review of Chinese literature

[7••]. Nevertheless, studies in animal models have shown that milk thistle can benefit the liver by protecting and promoting the growth of hepatocytes, by exerting antioxidant effect, and by inhibiting inflammation [8].

Curcumin from turmeric was also not listed in Table 1, although it has long been used in Ayurvedic and Chinese traditional medicines and practices for liver diseases, including hepatitis and jaundice, and other GI symptoms. It has been reported that curcumin inhibits hepatitis B virus (HBV) replication and expression [9•], and has hepatoprotective effects to inhibit several factors like nuclear factor-kappa B, which modulates several pro-inflammatory and profibrotic cytokines, as well as curcumin's well-known antioxidant properties [10, 11]. These evidences provide some rationale to use curcumin in hepatic disorders.

In recent years, additional clinical trials have been conducted to assess the therapeutic value of TCM for hepatitis B infection. The effects of TCM alone and TCM in combination with western medicine on CHB have been assessed. For example, a population-based case-control study in Taiwan showed that the use of TCMs was associated with a significantly reduced risk of acute exacerbation of hepatitis and subsequent development of cirrhosis and hepatocellular carcinoma (HCC) in patients with HBV [12••] in comparison with the effects of conventional western medicine therapy. Moreover, a recent multi-center double-blind RCT study of 596 patients with CHB showed that Tiaogan-Yipi Granules or Tiaogan-Jianpi-Jiedu Granules plus entecavir (ETV) were superior to ETV monotherapy in enhancing HBeAg loss rate [13•]. Another RCT conducted among 148 individuals with CHB compared the effectiveness of combining conventional western medicine and the TCM Diwu Yanggan capsules, and reported that integrating TCM and western medicine significantly improved liver histology [14•]. Additionally, in a randomized placebo-controlled study, Zhang et al. found that the use of Wenshen formula was associated with a significantly reduced risk of HCC in patients with CHB [15••]. A 15-year follow-up study reported that CHB patients who received TCM had significantly lower HCC risk compared with non-TCM users [16], which suggests that the integration of TCM into clinical practice may be associated with a more favorable prognosis. There were no updated data of TCM clinical trials that directly compared TCM with antivirals or interferon on the clearance of serum HBeAg and HBV DNA; however, an overreview of Chinese Herbal Medicine Formula Granules demonstrated that TCM formula granules were superior to placebo for the clearance of serum HBV DNA and HBeAg in chronic HBV carriers [17].

Other CAM have also been extensively studied for CHB treatment. A combined therapy of Korean Red Ginseng with nucleosidic antiviral drugs (lamivudine, adefovir dipivoxil, entecavir, or tenofovir) for CHB treatment for 56 weeks provided more significant downregulation of the expression of serum markers of fibrosis, such as TGF-beta and hyaluronic acid [18•] than the nucleosides alone. The use of mushroom (*Agaricus blazei Murill*) extracts in patients with chronic hepatitis B benefited to normalize liver tests [19]. An aqueous extract of the Korean herbal formulation KYH-1 demonstrated antiviral activity for HBV infections [20].

In a drug repurposing screening study, including 1018 Food and Drug Administration (FDA)-approved compounds, tazarotene, as well as other members in the family of retinoic acid receptor agonists, were identified to inhibit HBV and to exert a synergistic effect with entecavir on repressing HBV DNA [21•]. Therefore, tazarotene and other derivatives of vitamin A may be potential novel anti-HBV agents. These findings suggest that the integration of TCMs and other CAMs into allopathic clinical practice or complementary therapy may contribute to more favorable outcomes.

The art of traditional Chinese medicine emphasizes holistic medicine: It emphasizes the whole human body as a unit, and then uses several herbal formulations, which are selected according to the individual characteristics of herbs and their claimed complementary ability to treat diseases. Hundreds of herbal medicines have been used in scores of different traditional Chinese medicine formulations for the treatment of hepatitis B. The purported health benefits of TCMs are believed to result from an intricate combining and interaction of these ingredients (Table 2). However, from a western reductionist viewpoint of clinical analysis or research design, the traditional Chinese medicine approach of combining many herbs with purported diverse effects complicates attempts to determine which ingredients are responsible for particular physiological effects. Several TCMs (e.g., *Phyllanthus*, *Salvia miltiorrhiza*, *Rheum palmatum*, *Radix Astragali*) have recently been identified to be potential antivirals against HBV

Table 2 Purported mechanisms of action of the 4 most used herbs in CHB clinical trials in China

Herbs	Purported properties of the TCM
Huang Qi	Improve immune activities and replenish Qi
Dan Shen	Promote blood flow, remove blood stasis, and anti-fibrosis
Hu Zhang	Remove heat, dampness, and toxic substances from the body; promote blood circulation; and anti-virus
Bai Hua She She Cao	Antipyretic, detoxicant, diuretic, and anticancer agent

Results summarized from our extensive study and knowledge of TCM

[22], and multiple active compounds have been extracted (e.g., wogonin, artesunate) [23]. Bioactive compounds extracted from natural products have characteristics similar to chemically synthesized medications, and can be obtained from various organisms without the need for laborious or industrial chemosynthesis. Thus, TCMs could be good candidates for new antiviral development.

Prevalence of CAM or TCM use is commonly correlated with the presence of chronic diseases or recurrent or incurable conditions. CAM use among CHB patients is extensive, especially the use of vitamin and mineral preparations, and frequency of their use appears to be directly correlated with socio-economic status, rather than with ethnicity or liver disease severity [24•]. As summarized above, many reviews provide evidence of CAM use among adults with CHB; however, data on CAM administration to children with this chronic infection are sparse. Recently, it was reported that the use of CAM in Turkish children was common, and independently associated with the current or previous use of antiviral medications for viral hepatitis, but that there is infrequent dialog among patients, their parents, and pediatric health care providers regarding the use of CAM [25]. This further emphasizes that the use of CAM among patients and, in pediatrics especially, among children given CAM by their parents should be actively inquired and should be a routine part of medical history. Medical practitioners should be knowledgeable about CAM therapies and cognizant of their patients' potential use of CAM, which most will not report unless specifically queried.

Although it is true that natural remedies have not been proven to cure HBV in adequately powered well-designed trials, there are many complementary therapies that may improve symptoms and subsequent events associated with CHB. The advantages of TCM, such as their long history of use, ready availability, multi-objective, integrated medical treatment (sometimes integrated with Western medicine), and affordable costs make them worthy of further rigorous scientific research, especially in China, which is the country with both the largest population and the most CHB patients.

The potential toxicity and side effects of TCMs have not been considered with sufficient care heretofore. A recent nationwide, retrospective study in mainland China found that TCM and herbal dietary supplements were the leading causes of drug-induced liver injury [26••], especially in the treatment of patients with pre-existing liver diseases. Moreover, several studies have reported that some TCMs may cause obvious adverse reactions. A recent review indicated that the major adverse reactions to TCMs are gastrointestinal symptoms, including abdominal bloating or pain, epigastric discomfort, and "stomach disorders," followed by diarrhea, headaches, nausea, breast distension or pain, abnormal vaginal bleeding, and dizziness [27]. On the whole, concerns about adverse reactions and toxicity of TCM or other CAM in management of CHB (or other chronic liver disorders) remain insufficient. Among the obstacles to evaluate adverse reactions are the following: (1) experimental data are usually limited to pharmacokinetics; (2) few studies focusing on organ toxicity are documented; and (3) evidence is not sufficient to elucidate the biochemical mechanisms responsible for biological activities of TCMs. Thus, further studies are needed to characterize the pharmacokinetics, pharmacodynamics, and features of TCMs and their active compounds, and more nearly comprehensive and better validated data should be collected through clinical trials. Furthermore, mechanisms causing adverse reactions to TCMs need to be explored in greater depth.

Conclusion

The current clinical research shows that TCM and CAM have limited effects on HBV clearance; however, some may improve symptoms and decrease the rate of progression of chronic liver disease and development of hepatocellular carcinoma associated with CHB. Medical practitioners should be knowledgeable about CAM therapies and be aware of their patients' potential use of CAM and TCM.

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Compliance with Ethical Standards

Conflict of Interest Drs. Liang, Li, Tan, Wang, and Bonkovsky declare no conflicts of interest relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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