REVIEW

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Chinese herbal medicine for carriers of the hepatitis B virus: an updated systematic review and meta-analysis

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More than a third of the world's population is infected with the hepatitis B virus (HBV) and 5% are thought to be HBV carriers, putting them at risk of developing serious liver diseases. The treatment of liver diseases with Chinese herbal medicines (CHM) dates back 2,500 years and the aim of this analysis was to evaluate the efficacy and safety of CHM for HBV carriers compared to Western medicine (WM) or placebo and to summarize the most commonly used herbs. Several databases, such as Pubmed, Embase and the Chinese database CNKI, were used to evaluate randomized, controlled trials (RCTs) focused on CHM treatment for HBV carriers up to 2013. We performed a systematic review and meta-analysis on the herbs and their effect on hepatitis B viral proteins (HBeAg, HBsAg) and HBV DNA. Subgroups were examined based on the study design and pooled risk ratios (RRs) were estimated with 95% confidence intervals (CIs). For the meta-analysis, we focused on 11 out of 52 RCTs (Jadad ≥ 2) and found that CHM was more effective than placebo for HBeAg seroconversion when combined with WM (RR 4.67, 95% CI 1.36–15.98; $P = 0.01$; $I^2 = 39\%$); *Radix Astragali* was the most commonly used herb. Those that received CHM were more prone to adverse events; however, they were mild and reversible. The risk of bias was assessed with regards to blinding, incomplete outcome data and publication bias. It should be noted that, due to the poor methodological quality of the studies and the small number of RCTs, the results cannot fully support the use of CHM in the treatment of HBV carriers. To conclude, CHM may be used to treat HBV carriers, but rigorously designed RCTs with long-term follow-ups are required to further evaluate the benefits and safety of CHM.

1. Introduction

Chronic Hepatitis B viral (HBV) infection is a major public health burden with approximately 350 million infected carriers (WHO 2002). The phases of chronic HBV infection can be differentiated as the "immune tolerant", "immune reactive hepatitis B e antigen (HBeAg)-positive", "inactive HBV carrier", "HBeAg-negative" and "hepatitis B surface antigen (HBsAg)-negative" phases (EASL 2012). The majority of chronically infected individuals are "immune tolerant" carriers, characterized by high levels of HBV replication but normal or low levels of alanine aminotransferase (ALT). Although the majority of this HBV-infected population will not develop chronic hepatitis B, they have an increased risk of developing long-term complications, such as liver cirrhosis and hepatocellular carcinomas (HCCs) (Abdel-Hady and Kelly 2013; Qiu and Chen 2013; Ringelhan et al. 2013), during their lifetime. However, spontaneous HBsAg and HBeAg seroconversion, which is associated with a reduced risk of cirrhosis or HCC and favorable long-term outcomes, rarely occurs in this HBV-infected population. In addition, due to high levels of HBV replication, these carriers are in a highly contagious phase of the virus (EASL 2012). Although antiviral drugs, such as interferon (IFN) or nucleoside analogs, can profoundly inhibit HBV replication and enhance HBsAg and HBeAg clearance rates in HBeAg-positive chronic hepatitis B (CHB) patients, the efficacy of antiviral therapy is poor in "immune tolerant" HBV carriers. Thus, there has been no effective treatment for these chronically infected individuals to date. The use of traditional Chinese medicine (TCM) in the treatment of HBV carriers is widespread in China and has developed over the last 20 years. A previous meta-analysis reported the significant advantage of TCM in improving HBeAg and even HBsAg clearance compared to Western medicine (Liu 2001). However, the number of trials was limited in the analysis and it was conducted more than 10 years ago. Therefore, we aimed to perform an updated meta-analysis to systemically evaluate the efficacy and safety of Chinese herbal medicine (CHM) in treating immune tolerant HBV carriers.

2. Methods

2.1. Search strategy

A systematic literature search was undertaken by two researchers (YY and JHY) to identify and examine TCM treatment in patients with HBV. The TCM approach makes use of Chinese herbs, acupuncture and other medical treatments.
Pubmed, Cochrane and Embase databases were searched from inception to January 2013 using the grouped keywords "hepatitis B virus *or* HBV" and "carrier *or* asymptomatic" and "herb* *or* herbal medicine* *or* traditional Chinese medicine* *or* TCM *or* plant*". The Chinese databases, China National Knowledge Infrastructure (CNKI), Wanfang database, VIP information and Chinese Biological Abstracts (CBA), from inception to November 2012 were searched using the grouped medical search terms "HBV carriers" *and* "Zhong Yao *or* Zhong Yi Yao *or* Zhong Xi Yi Jie He". The reference lists of all review articles or relevant sections of other articles were further searched for relevant studies. Experts were contacted as required. There was no restriction by country or publication state or language. The search was also not restricted by study design, treatment duration or outcome measure, and so on. Additionally, if two or more studies were derived from overlapping populations, only the larger study was included. The inclusion criteria were determined by two of the authors (YY and JHY). For CHM analysis for the treatment of HBV carriers, the criteria were as follows: 1) the patients were HBV carriers with positive serum HBsAg and normal ALT; 2) the types of treatment design were as follows: a) the treatment group was administered an individual herb or formulation or CHM combined with WM; b) the control group was administered WM, placebo, received no treatment or conventional treatment for liver disorders with no specification with regards to the group numbers; c) the CHM was taken predominantly as an individual herb or a formulation, and herbal injections or preparations composed of chemical compounds extracted from the herb were excluded; d) In addition, acupuncture and its variants were excluded. For randomized, controlled trials (RCTs), the study quality was assessed by the Jadad scale. For the meta-analysis of CHM efficacy of the included RCTs, the additional two criteria were included: 1) the Jadad score was greater than or equal to two; 2) the control groups were treated either with WM or placebo and the WM treatment was IFN or nucleotide analogues. For the meta-analysis of adverse events in the treatment of HBV carriers, as compared to the criteria of CHM analysis, there were three more criteria included: 1) the studies were randomized, controlled trials (RCTs); 2) Any adverse event was reported in the study; 3) the control groups were treated either with WM or placebo and the WM treatment contained not only IFN or nucleotide analogues but also other kinds of WM.

2.2. Outcome measures

The following outcomes were determined after treatment was complete and after the final follow-up:
• Primary outcome measures and definitions: HBeAg seroconversion or loss. HBeAg seroconversion was defined by the loss of HBeAg and the presence of anti-HBeAg antibody.
• Secondary outcome measures and definitions: HBsAg seroconversion or loss and virological response. HBsAg seroconversion was defined by the loss of HBsAg and the presence of anti-HBsAg antibody. The virological response was defined as HBV DNA less than the lower detectable limit or a reduction of HBV DNA in comparison to the baseline level.
• Adverse events: all adverse events reported in the studies were sought.

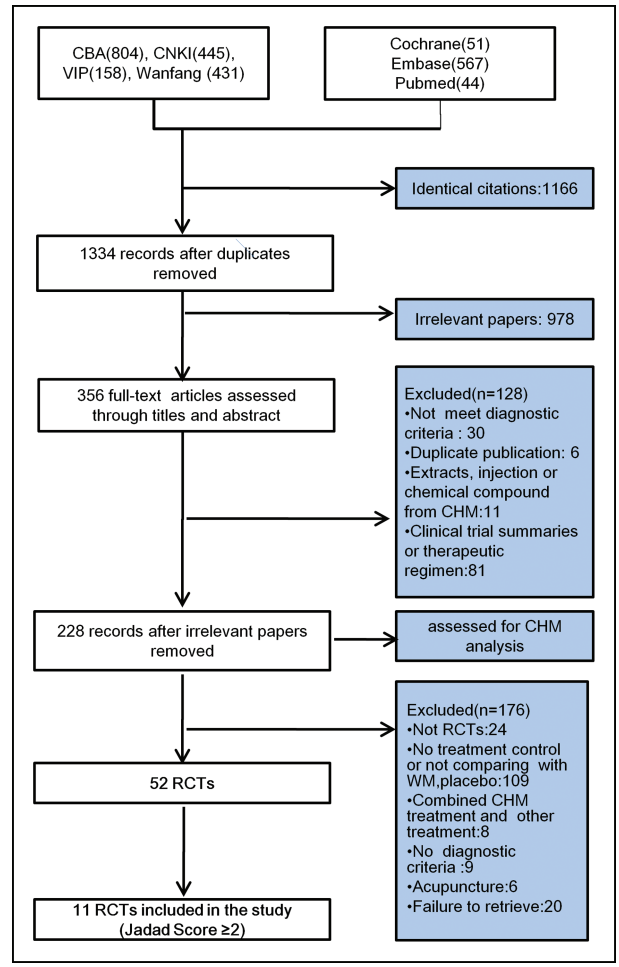

Fig. 1: Flowchart depicting the inclusion criteria for trials evaluated in this study.

2.3. Quality assessment

The quality of the studies was assessed using the Jadad scale (Jadad 1996) by measuring the allocation concealment, the blinding of the participants and the outcome assessors, the completeness of collection, and the outcome data reporting. Moreover, we evaluated in detail the bias of the studies with a Jadad score greater than or equal to two using the Cochrane risk of bias assessment tool in the following domains: allocation concealment, blinding of participants, personnel and outcome assessors, completeness of collection, and the outcome data reporting. Each domain was rated as "yes" (low risk of bias), "no" (high risk of bias) or "unclear" (uncertain risk).

2.4. Data extraction

One author (YY) extracted the data and JHY checked the extracted data. Any disagreement regarding the study data extraction was resolved by consensus. The following variables in each study were entered into a standardized spreadsheet: the first author, the year of study, the sample size, age/sex, the course of the disease, ALT, HBV DNA, CHM treatment, WM treatment, treatment course/follow-up.

2.5. Data analysis

Meta-analyses were conducted using the Cochrane Collaboration Review Manager software (RevMan 5.0). The effect was measured with consideration of the relative risks (RRs) for binary data with a corresponding 95% confidence interval (CI). The studies that met the above criteria were selected for

Table 1: Study design and Jadad score of 52 RCTs

Design	No. of studies	No. of studies showing herbeffect	No. of patients	No. of studies with different Jadad scores					No. of studies with Jadad score≥ 2
				I	II	III	IV	V	
CHM + WM *vs.*WM	21	20	2993	14	7	0	0	0	7
CHM *vs.* WM	16	13	2128	13	2	1	0	0	3
CHM *vs.*placebo	7	7	1394	1	2	0	3	1	6
3-arm design	8	7	1068	5	2	1	0	0	3
Total(%)	52 (100)	47 (90.38)	7583	33 (63.46)	13 (25)	2 (3.85)	3 (5.77)	1 (1.92)	19 (36.54)

RCTs: randomized, controlled trial; CHM: Chinese herbal medicine; WM: Western medicine.

the meta-analysis examining CHM usage and efficacy. A fixed effects model (Mantel–Haenszel) was used for pooling homogenous data if significant heterogeneity was absent ($P < 0.1$ or $P > 0.1$ but $I^2 > 50\%$–70%); however, a random effects model was used to reduce bias. The potential risk of publication bias was detected by Begg's test and Egger's test. It was considered that publication bias exists when $P < 0.1$. The trim and fill method was further used to analyze publication bias. Sensitivity analysis was conducted to validate the reliability of the primary meta-analysis by excluding RCT one by one and comparing the low quality (Jadad score = 2) with the high quality (Jadad score $\geq$ 3) RCTs.

3. Results

3.1. Study selection, description and quality assessment

A total of 356 full text articles were initially obtained. After title and abstract assessment, 128 articles were excluded based on duplicate records and irrelevance to this study. The remaining 228 studies examined the use of CHM and 52 were RCTs. Eleven RCTs were examined by meta-analysis (Fig. 1).

All the trials were performed in China and published in Chinese journals from 1985 to September 2012. The sample size of the 52 studies ranged from 40–460 with a total of 7,583 subjects. Fifty-two RCTs were assessed *via* their Jadad score. Thirty seven (71.15 %) of the fifty-two RCTs used WM as a control and seven RCTs used placebo as a control (Table 1). Table 2 (patient characteristics) and Table 3 (treatment protocols) present some specific details about the 11 articles that were used for efficacy analysis during our meta-analysis. The treatment course of the 11 RCTs ranged from 30 days to 364 days. Due to poor quality, there was a high risk of bias in the randomization and blindness. Only five studies of the 11 RCTs described their randomization method (He et al. 2010; He and Zhou 2012; Li 2012; Wei 2011; Zheng et al. 2012). Six trials were double-blind studies (Chen et al. 2012; He et al. 2010; He and Zhou 2012; Li 2012; Xing et al 2012; Zheng et al. 2012), of which only one trial described their double-blind method (Li and Tong 2012). Three RCTs with follow-ups (Wang 2008; Wei 2012; Zhao 1988) were CHM + WM *vs.* WM studies, four RCTs with follow-ups were CHM *vs.* placebo trials, and one was CHM *vs.* WM *vs.* placebo study. All the 11 studies did not describe the follow-up processes

Table 2: RCTs assessing CHMs in the treatment of HBV carriers with Jadad Score $\geq$ 2

Studies	Subjects (CHM/control)	Mean age in years (range)/female%	Mean course of disease in years (yr) or months (mo) (range)	ALT (U/L)	HBV DNA
Wang (2008)	30/30	27.5 (10–40)/31.7%	Nil (1–5yr)	No	NR
Wei (2012)	80/80	26.5 (10–40)/37.5%	Nil (1–5yr)	No	NR
Zhao (1988)	30/30	27.5 (10–40)/31.7%	Nil (1–5yr)	No	NR
Wei (2011)	20/20	40.43 (32–49)/55.9%	7.8 yr (1–15yr)	No	NR
Chen (2012)	60/60	NR (NR)/38.3%	NR (NR)	No	8.11 ± 1.12 *vs.* 8.13 ± 1.07 (lgIU mL^{-1})
He (2010)	60/30	35.4 (20–65)/22.2%	6.2 yr (1.5–38yr)	30–40 (male), 20–40 (female)	$> 10^{(7)}$ copies/mL
He (2012)	200/100	33.6 (30–52)/34.3%	93 mo (36–409 mo)	30–40 (male), 20–40 (female)	8.15 ± 1.13 *vs.* 8.17 ± 1.02 (lgIU mL^{-1})
Li (2012)	200/100	> 30 (NR)/41%	94 mo (NR)	28.16 ± 11.5 (30–40) *vs.* 29.62 ± 13.1 (19–40)	$> 1 \times 10^{(6)}$ copies/L
Xing (2012)	200/200	34.33 (NR)/40.5%	90.40 mo (NR)	28.23 ± 11.70 *vs.* 29.36 ± 12.50	$(1.585 \pm 6.386) \times 10^{(9)}$*vs.* $(0.749 \pm 1.766) \times 10^{(9)}$ IU mL^{-1}
Zheng (2012)	60/60	35.0 (30–52)/27.5%	115 mo (36–409 mo)	29.4 ± 6.80 *vs.* 28.54 ± 6.14	$> 10^{(5)}$ U mL^{-1}
Chen (1993)	34/35/30	NR (NR)/NR	NR (NR)	No	NR

RCTs: randomized, controlled trial; CHM: Chinese herbal medicine; HBV: hepatitis B virus; NR: not reported.

Table 3: Treatment intervention

Studies	CHM treatment	WM treatment	Treatment course/follow-up in weeks (wk), months (mo) or years (yr)
Wang (2008)	Wen Shen Jie Du Fang, 1 dose/d; interferon 40,000 U/time/2d	Interferon 40,000 U/time/2d	3 mo/6 mo
Wei (2012)	Yi Qi Hua Yu Jie Du Tang, 1dose/d; interferon 40,000 U/time/2d, lamivudine,100 mg/time/d	Interferon 40,000 U/time/2d, lamivudine, 100 mg/time/d	> 52 wk/12 wk
Zhao (1988)	Wen Shen Jie Du Fang, 1 dose/d; interferon, 40,000 U/time/2d	Interferon 40,000 U/time/2d	3 mo/6 mo
Wei (2011)	Jian Pi BuShenFang, 1 dose/d	Lamivudine 100 mg/time/d	6 mo/Nil
Chen (2012)	Bu Shen Jian Pi Qu XieFang,1 g/time, 3 times/d	Placebo, 1 g/time, 3 times/d	52 wk/Nil
He (2010)	Bu Shen Jian Pi Fang, 4 particles/time, 3 times/d	Placebo, 1 g/time, 3 times/d	48 wk/Nil
He (2012)	Bu Shen Jian Pi Fang, 1 dose/d, 2 times/d	Placebo, 1 dose/2 times/d	52 wk/Nil
Li (2012)	Bu Shen Qing TouFang, 1 dose/d, 2 times/d	Placebo, 1 dose/2 times/d	52 wk/1–3 yr
Xing (2012)	Bu Shen Qing TouFang, 2 times/d, 1 dose/time	Placebo, 1 dose/2 times/d	52 wk/Nil
Zheng (2012)	Bu Shen Jian Pi Fang, 1 dose/d, 2 times/d	Placebo, 1 dose/2 times/d	48 wk/Nil
Chen (1993)	Ling Bao Dan, 3–4 dose/time	Interferon 4–100,000 U; placebo	6 mo/1 yr

CHM: Chinese herbal medicine; WM: Western medicine.

and did not provide data with regards to the dropout rates. This lack of quality results in a risk of bias for reasons of incomplete data. All 11 trials had no intention-to-treat analysis.

3.2. CHM description

Two hundred and twenty eight trials were used to assess which were the most frequently used individual Chinese herbs. The number of different Chinese herbs in the 228 trials, with 179 CHM formulas, was 306 and the 20 most commonly used single herbs are listed in Table 4. As an example, *Radix Astragali* (Huang Qi) was present in 179 CHM formulas and was used 144 times in 10,323 subjects. The average number of individual Chinese herbs in each CHM formula was 9.92 (SD: 4.92; range: 1–31). In most cases, the formulas were given twice a day. We also evaluated the manner in which the herbs were given and found that 118 (46.46 %) of the 179 Chinese herbal formulas used in the trials were given as a decoction, 32 (12.60 %) were administered as pills, 32 (12.60 %) were capsules, 24 (9.45 %) were herb granules, 19 (7.48 %) were in tablet form and the remaining 29 (11.42 %) were administered as an oral liquid or ointment. The treatment course varied from 28 to 720 days, with a median of 164.53 days (SD = 111.45).

3.3. Efficacy assessment

Eleven RCTs were selected for detailed assessment *via* a meta-analysis and it should be noted that they had varying study designs as follows: three CHM + WM *vs*. WM (Wang 2008; Wei 2012; Zhao 1988); one CHM *vs*. WM) (Wei and Shen 2011); six CHM *vs*. placebo (Chen et al 2012; He et al. 2010; He and Zhou 2012; Li and Tong 2012; Xing et al. 2012; Zheng 2012); and one three-arm RCT (CHM *vs.* WM *vs.* placebo) (Chen et al. 1993).

3.3.1. CHM + WM vs. WM

• HBeAg loss and HBeAg seroconversion

Meta-analysis detected a significant difference in HBeAg loss (Fig. 2(A), RR: 3.24, 95 % CI: 2.38–4.39, $P < 0.00001$, $I^2 = 0\%$) (Wang 2008; Wei 2012; Zhao et al. 1988) and HBeAg seroconversion (Fig. 2(B), RR: 4.67, 95 % CI: 1.36–15.98, $P = 0.01$, $I^2 = 39\%$) (Wang 2008; Wei 2012; Zhao et al. 1988). Among them, there were two trials with no significant change in HBeAg

Table 4: The 20 most frequently used herbs in the treatment of HBV carriers

Herb Latin Name (Chinese Pinyin)	Frequency (n)	Patients (n)	Herb Latin Name (Chinese Pinyin)	Frequency (n)	Patients (n)
Radix Astragali (Huang Qi)	56.69 % (144)	10,323	Radix Paeoniae alba (Bai Shao)	16.54 % (42)	3,105
Radix Salviae miltiorrhizae (Dan Shen)	37.79 % (96)	7,454	*Fructus Lycii* (Gou Qi)	14.96 % (38)	3,105
Herba Hedyotidis diffusae (Bai Hua She She Cao)	36.22 % (92)	6,125	*Radix Isatidis* (Ban Lan Gen)	14.96 % (38)	2,595
Poria (Fuling)	35.83 % (91)	4,375	*Rhizoma Smilacis glabrae* (Tu Fu Ling)	14.57 % (37)	500
Rhizoma Atractylodis macrocephalae (Bai Zhu)	35.83 % (91)	6,182	*Herba Artemisiae scopariae* (Yin Chen)	13.38 % (34)	3,249
Rhizoma Polygoni cuspidate (Hu Zhang)	29.92 % (76)	2536	*Radix et Rhizoma Rhei* (Da Huang)	12.60 % (32)	1,052
Radix Bupleuri (Chai Hu)	27.56 % (70)	2,436	*Radix Paeoniae Rubra* (Chi Shao)	11.81 % (30)	1,477
Radix Glycyrrhizae (Gan Cao)	24.80 % (63)	4,972	*Herba Scutellariae barbatae* (Ban Zhi Lian)	11.42 % (29)	2,482
Radix Curcumae (Yu Jin)	18.90 % (48)	1,302	*Rhizoma Cyrtomii* (Guan Zhong)	11.02 % (28)	3,392
Radxix Codonopsis (Dang Shen)	18.11 % (46)	2,944	*Semen Cuscutae* (Tu Si Zi)	10.63 % (27)	2,021

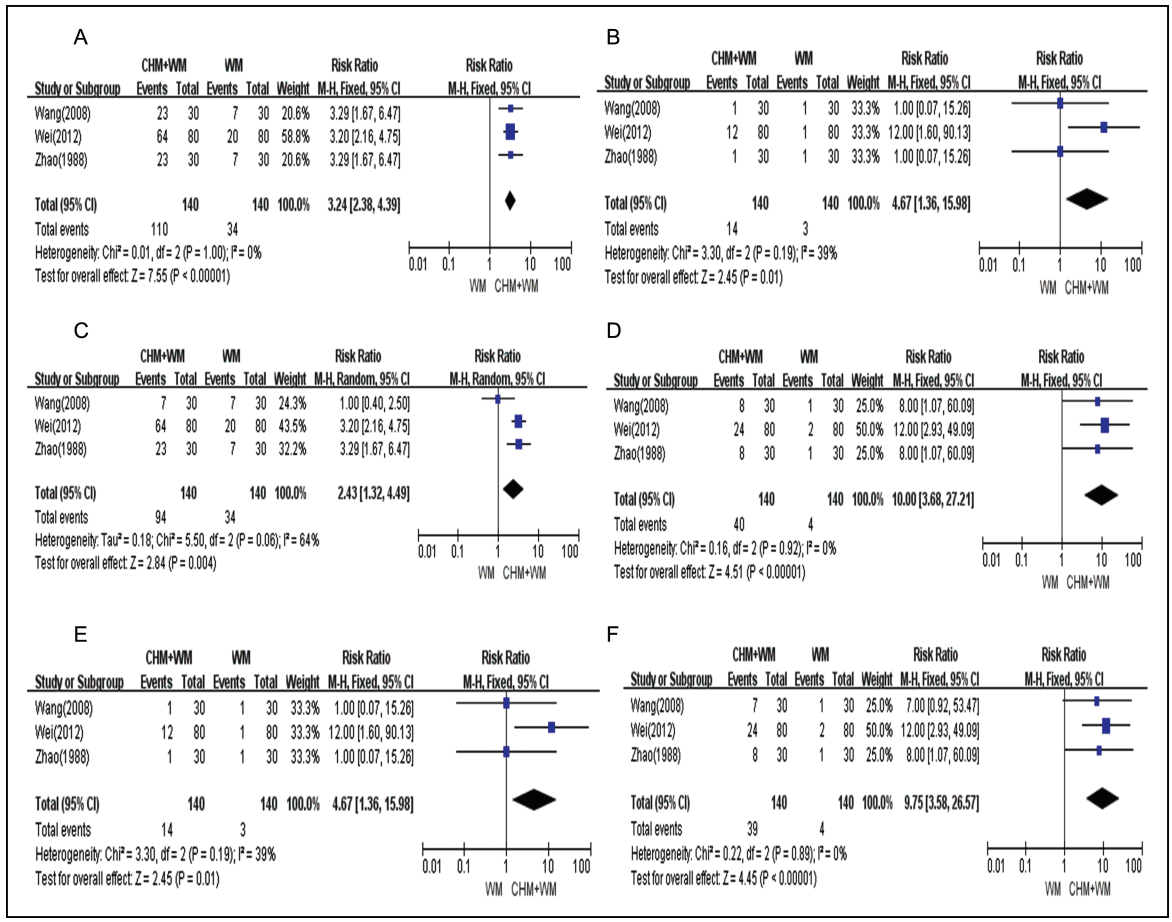

Fig. 2: Forest plots detailing the outcomes for CHM + WM *vs.* WM. (A) HBeAg loss; (B) HBeAg seroconversion; (C) HBeAg loss at follow-up; (D) HBsAg loss; (E) HBsAg seroconversion; (F) HBsAg loss at follow-up.

seroconversion (Wang 2008; Zhao et al. 1988). The mean (range) of the effective rates of HBeAg loss for CHM + WM and WM alone was 77.78 % *vs*. 23.89 % (76.67–80 % *vs*. 23.33–25 %) and the mean (range) HBeAg seroconversion, comparing again the CHM + WM against WM alone, was 7.22 % *vs*. 2.64 % (3.33–15 % *vs*. 1.25–3.33 %). Focusing on the CHM + WM *vs*. WM treatment groups, studies that employed this comparison show data on the follow-up efficacy with regards to HBeAg loss (Fig. 2(C), RR: 2.43, 95 % CI: 1.32–4.49, $P = 0.004$, $I^2 = 64$ %) (Wang 2008; Wei 2012; Zhao et al. 1988). The range of HBeAg losses were 23.33–80 % *vs*. 23.30–25 %, with a median of 60.01 % *vs*. 23.88 %.

• HBsAg loss and seroconversion

There was a significant difference in the HBsAg loss (Fig. 2(D), RR: 10.00, 95 % CI: 3.68–27.21, $P < 0.00001$, $I^2 = 0\%$) (Wang 2008; Wei 2012; Zhao et al. 1988) and HBsAg seroconversion (Fig. 2(E), RR: 4.67, 95 % CI: 1.36–15.98, $P = 0.01$, $I^2 = 39$ %) when CHM combined with WM was compared to WM alone and CHM + WM was found to be more effective (Wang 2008; Wei 2012; Zhao et al. 1988). The effective rates of HBsAg loss and HBsAg seroconversion [mean (range)] were 27.78 % *vs*. 3.05 % (26.67–30 % *vs*. 2.50–3.33 %) and 7.22 % *vs*. 2.64 % (3.33–15 % *vs*. 1.25–3.33 %), respectively. The follow-up efficacy with regards to HBsAg loss is shown in Fig. 2(F) (RR: 9.75, 95 % CI: 3.58–26.57, $P < 0.00001$, $I^2 = 0\%$) (Wang 2008; Wei 2012; Zhao et al. 1988) and the range of the effective rate of loss varied from 23.33 % to 30 % *vs*. 2.50 % to 3.33 %, with a median of 26.67 % *vs*. 3.05 %.

3.3.2. *CHM vs. placebo*

• HBeAg loss and seroconversion

The pooled analysis showed a significant difference in HBeAg loss (RR: 3.26, 95% CI: 1.81–5.86, $P < 0.0001$, $I^2 = 40\%$) (Fig. 3(A)) (Chen et al. 2012; Chen et al. 1993; He et al. 2010; He and Zhou 2012; Li and Tong 2012; Zheng et al. 2012) and HBeAg seroconversion (RR: 3.14, 95% CI: 1.80–5.47, $P < 0.0001$, $I^2 = 34\%$) (Fig. 3(B)) (Chen et al. 2012; Chen et al. 1993; He et al. 2010; He and Zhou 2012; Li and Tong 2012; Zheng et al. 2012). The mean of the effective rate of HBeAg loss was 25.10 % *vs.* 3.76 % (range: 3.66–70.60 % *vs*. 3.22–4.80 %) and, for HBeAg seroconversion, the mean rate was 25.17 % *vs*. 4.23 % (range: 3.66–60 % *vs.* 0–12 %).

• Virological response

Our meta-analysis showed that CHMs are significantly more effective than the placebo with regards to HBV DNA negativity (RR: 4.82, 95 % CI: 1.76–13.23, $P = 0.002$, $I^2 = 0\%$) (Fig. 3(C)) (Chen et al. 2012; He et al. 2010; He and Zhou 2012; Li and Tong 2012; Zheng et al. 2012) and at reducing HBV DNA levels (RR: 3.73, 95 % CI: 2.75–5.05, $P < 0.00001$, $I^2 = 39\%$) (Fig. 3(D)) (He and Zhou 2012; Li and Tong 2012; Zheng et al. 2012). However, it should be noted that two trials showed no significant differences between the groups with regards to in HBV DNA negativity (He and Zhou 2012; Li and Tong 2012). The mean (range) effective rates for HBV DNA negativity and the reduction in HBV DNA levels were 10.30% *vs.* 1.50% (0.57–21.67 % *vs.* 0–3.33%) and 37.61 % *vs*. 7.81 % (23.56–55.36 % *vs.* 7.02–8.60 %), respectively.

3.3.3. *CHM vs. WM*

Except one two-arm study and one three-arm study containing a CHM *vs.* WM group (Chen et al. 1993), there were no studies that compared CHM with WM. Due to an insufficient number

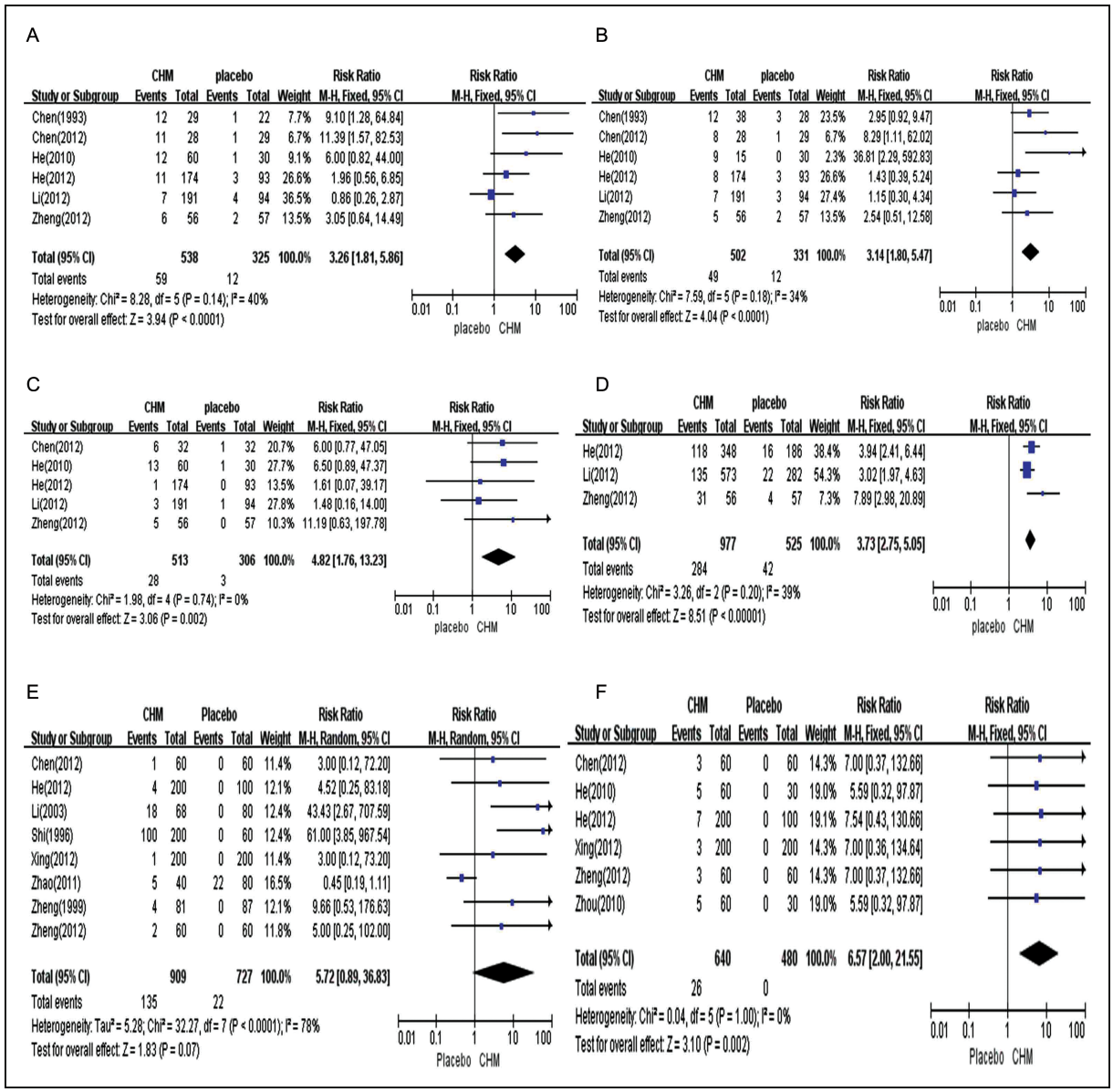

Fig. 3: Forest plots detailing the outcomes and safety of CHM *vs.* placebo. (A) HBeAg loss for CHM *vs.* placebo; (B) HBeAg seroconversion for CHM *vs.* placebo; (C) HBV DNA negativity for CHM *vs.* placebo; (D) reduction of HBV DNA levels for CHM *vs.* placebo; (E) liver function assessed *via* mildly elevated ALT; (F) loss of appetite, bloating and stomach discomfort.

of studies, no meta-analysis was performed. The two studies found significant between-group difference in HBeAg loss and HBeAg seroconversion rate.

3.4. Adverse events

Twenty of the fifty two RCTs did not report any adverse events (37.73 %) and nineteen studies (35.85 %) reported that there were no adverse events or obvious side effects. Fourteen RCTs (26.42 %) reported adverse events for CHM but they were mild and disappeared spontaneously without intervention. Only 11 studies reported the frequency of adverse events. The main types of adverse event were liver dysfunction and gastrointestinal reactions. Others symptoms included upper respiratory tract infections, headaches, nausea and intermittent puffiness of the face.

3.4.1. Liver dysfunction

There were eight studies that found the liver function ALT level to be slightly elevated: one study comparing CHM against WM (Li 2003), four studies comparing CHM against placebo (Chen et al. 2012; He and Zhou 2012; Xing et al. 2012; Zheng et al. 2012) and three three-arm studies (Shi 1996; Zhao et al. 2011; Zheng and Pan 1999). The CHM + WM *vs.* WM studies did not report this type of adverse event. Our meta-analysis detected no significant difference in the frequency of adverse events between CHM and the control groups (RR: 5.72, 95 % CI: 0.89–36.83, $P = 0.07$, $I^2 = 78$ %) (Fig. 3(E)); however, there was a significant difference ($P < 0.01$) after one study of the eight studies was excluded by a sensitivity analysis (Zhao et al. 2011).

3.4.2. Gastrointestinal reactions

Six of the fifty two RCTs provided the frequency of adverse events, which included loss of appetite, bloating and stomach discomfort (Chen et al. 2012; He et al 2010; He and Zhou 2012; Xing et al. 2012; Zheng et al. 2012; Zhou et al. 2010).

Our meta-analysis showed that these types of adverse event were significantly more frequently experienced by subjects that received the CHM compared to those in the control group (RR: 6.57, 95 % CI: 2.00–21.55, $P = 0.002$, $I^2 = 0$%) (Fig. 3(F)). These studies all followed a CHM *vs.* placebo design and all contained CHMs that aimed to tonify the kidney. Sensitivity analysis found the result was stable.

3.5. Publication bias and assessment of within-group heterogeneity

Due to a low number of meta-analysis trials, quantitative analysis for publication bias were performed by Stata11. Both Begg's test and Egger's test showed publication bias for HBeAg loss and HBeAg seroconversion in the CHM *vs*. placebo studies and for the studies that reported adverse effects on liver function, assessed *via* mildly elevated ALT, which was further confirmed by the trim and fill method. All of the other outcome measures showed no publication bias.

The heterogeneity in the efficacy at follow-up with regards to HBeAg loss in studies following a CHM + WM *vs.* WM design was derived from two studies (Wei 2012; Zhao et al. 1988). There was no heterogeneity for all the other outcomes of our meta-analysis.

3.6. Sensitivity analysis

Sensitivity analysis was performed by excluding each study included in the meta-analysis and, as a result, we found that the efficacy was mostly stable. The efficacy with regards to the HBsAg seroconversion in CHM + WM *vs*. WM studies was not stable (by excluding one study (Wei 2012) P changed from $P = 0.01$ to $P = 1$) and it is postulated that longer treatments, as used in the excluded study (Wei 2012), resulted in better efficacy. By excluding two studies (Wei 2012; Zhao et al. 1988), the significant difference for HBeAg loss resulting from CHM + WM *vs.* WM studies changed from $P > 0.05$ to $P > 0.2$.

In addition, a sensitivity analysis was conducted according to the Jadad score. For CHM *vs*. placebo studies (a total of 11 RCTs), three RCTs had a Jadad score of two (Chen et al. 2012; Chen et al. 1993; Xing et al. 2012) and were regarded as low quality; four RCTs had a Jadad score of greater than or equal to four (He et al. 2010; He and Zhou 2012; Li and Tong 2012; Zheng et al. 2012) and were considered to be high quality. In these cases, the sensitive analyses were stable (data not shown).

4. Discussion

4.1. Summary of findings

4.1.1. Efficacy and safety

This study is an updated meta-analysis to assess the efficacy and safety of CHM in the treatment of HBV carriers. The previous meta-analysis study in 2001 (Liu et al. 2001) included 11 RCTs ($n = 932$ HBV carriers) and did not specify the Jadad scores, whether the studies compared the herb to placebo, what interventions were necessary or whether IFN was used. The results of this meta-analysis showed that CHMs had a significant antiviral effect compared to WM; however, in comparison to placebo, CHMs did not have this same effect. The follow-up efficacy of eight RCTs (≤ 3 months) showed no significant benefit of CHMs in treating HBV carriers. Only one trial reported adverse events. There is disagreement between the previous analysis and our study. Our meta-analysis has demonstrated that CHM treatment alone or in combination with WM is more effective than the negative control (WM alone or placebo) and the follow-up efficacy showed CHM was effective. There may be several reasons for this difference. First, the design of the RCTs included in the study in 2001 was less rigorous; for example, the Jadad score of most RCTs (81.82 %) was less than two and no descriptions were given about the content, taste and appearance of the placebo; however, the RCTs included in our study had to meet this requirement. Second, our study included a larger number of patients ($n = 1749$ HBV carriers). Additionally, the herbal formulas included in our study may have been more effective as some of the most commonly used herbs were reported in separate studies to be quite effective against HBV in carriers. The CHMs included in our study were quite safe and most RCTs mentioned only temporarily elevated ALT levels and mild side effects, such as gastrointestinal disturbances. Notably, gastrointestinal disturbances were only reported in CHM *vs*. placebo RCTs (where the CHM contained tonifying kidney herbs). However, this evidence of safety is not sufficient as most studies reported no adverse events and the effects following long-term usage (treatment duration ≤ 6 months) were also not reported. Furthermore, overdose limits and whether the herbs are safe to take in pregnancy and during breastfeeding were also not reported. Hence, further research to confirm whether CHMs with efficacy against HBV can be used safely is required.

4.1.2. Formulas and individual herbs

Our study also examined the constituents of the Chinese herbal formulas and the individual herbs used for treatment. There exists a great variety of herbal combinations (179 different formulas used in the treatment of HBV carriers) and there may be two reasons for this. Firstly, the therapeutic rules that are used most frequently to guide the treatment of HBV carriers specify "tonifying the kidney and the spleen, clearing away heat and toxic materials, and promoting blood circulation to remove blood stasis"; thus, Chinese medical practitioners require different herbs to achieve these multiple effects. Secondly, there are shortcomings in the TCM diagnostic process, including disagreement among Chinese medicine practitioners regarding the patterns, if any, in the physiques of different groups (for example, obese and thin).

Consequently, the variety of herbal formulas prompted us to summarize the individual herbs that are most frequently used in the treatment of HBV carriers. Four herbs that have promising antiviral activity were frequently used for the treatment of HBV carriers; they are *Radix Astragali, Radix Salviae miltiorrhizae, Radix Bupleuri and Radix Glycyrrhizae. Radix Astragali* ranked most popular among the individual herbs for the treatment of HBV carriers. In general, this herb is widely used to treat liver disease in TCM and is considered to be quite safe. It has been reported that astragaloside IV, which is present in *Radix Astragali,* suppresses both HBsAg and HBeAg secretion *in vitro* and inhibits HBsAg and HBV DNA *in vivo*; in clinical evaluations, those receiving *Radix Astragali* showed more significant signs of improvement over conventional CHM formulations with regards to HBeAg loss and HBV DNA (Cui et al. 2010). *Radix Salviae miltiorrhizae* (SM) is a widely accepted herb that is used for the treatment of liver disease and was found in this study to be the second most commonly used herb. Its unique anti-HBV substance, protocatechuic aldehyde (PA), has been found to inhibit HBV both *in vitro* and *in vivo* (Cui et al. 2010). Several clinical trials have evaluated patients following treatment with SM and they have shown that this herb improves the loss of HBeAg and HBV DNA (Cui et al. 2010). The active compounds of *Radix Bupleuri* are saikosaponins, which have anti-inflammatory and antiviral activity and are also thought to be involved in immune regulation (Lu et al. 2012). Isoliquiritigenin and glycycoumarin, two compounds that have been extracted from *Radix Glycyrrhizae,* have been found to suppress HCV replication *in vitro* in a dose-dependent manner (Sekine-Osajima Y et al. 2009). As stated above, the clinical efficacy and mechanism of action of these four herbs have been reported in several studies, but most other herbs (Table 4) have not been the subjects of in-depth research with regards to liver disease. In order to gain additional information with regards to CHM efficacy and safety for HBV carriers, the herbs listed in Table 4 need to be thoroughly investigated to establish their optimal form, pharmacology and pharmacokinetics.

4.2. Limitations

There are several limitations in the evaluated studies as follows: the criteria, the poor methodology quality and the preparation of the formulas. Hence, it would be premature to draw conclusions regarding the use of CHM for HBV carriers.

First, the problems concerning the chosen criteria were: 1) due to the large time span (1989–2012), several versions of the guidelines on hepatitis were available and old versions did not specify HBeAg and/or HBV DNA levels and/or diagnosis following liver biopsy; 2) some studies did not describe the content of their criteria; 3) there is frequent disagreement in TCM diagnosis and the evaluation of syndromes according to the specifications of TCM. Furthermore, in some studies, no syndrome was present to diagnose.

Second, the methodological quality of most of the assessed RCTs was quite poor and it was frequently found that random methods were not described and some studies were not blind or double-blind (or failed to describe the blinding procedure).

Third, most of the CHMs used in the studies were prepared as a decoction; however, it is preferable to prepare herbal formulas and placebo in pill or granular form so that they appear similar. Studies should follow good manufacturing practice guidelines and the Chinese pharmacopoeia in order to ensure the pills or granules have the same efficacy as the decoction. The frequently used drug delivery method was 1–2 dosage(s) per day, which is a dosage protocol that has been used for more than 2,000 years. However, there have been no studies reporting whether this drug delivery approach is reasonable and there is a need for pharmacokinetic research to find the most appropriate drug delivery methods and doses.

5. Conclusion

The overall finding from the 52 RCTs and our meta-analysis of the RCTs with a Jadad score greater than or equal to two is that CHMs are more effective than the controls in treating HBV carriers. However, owing to the drawbacks of the included RCTs and the inadequate safety data, there is insufficient reliable data to allow definitive comment on the advantages of CHMs in the treatment of HBV. Rigorous randomized, double-blind, placebo-controlled trials examining the efficacy and safety of CHM are still required.

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