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Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B (Review)

Liang N, Kong DZ, Ma SS, Lu CL, Yang M, Feng LD, Shen C, Diao RH, Cui LJ, Lu XY, Nikolova D, Jakobsen JC, Gluud C, Liu JP

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Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B.
Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD013089.
DOI: [10.1002/14651858.CD013089.pub2](https://doi.org/10.1002/14651858.CD013089.pub2).

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[Intervention Review]

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B

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Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New, published in Issue 4, 2019.

Citation: Liang N, Kong DZ, Ma SS, Lu CL, Yang M, Feng LD, Shen C, Diao RH, Cui LJ, Lu XY, Nikolova D, Jakobsen JC, Gluud C, Liu JP. Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013089. DOI: [10.1002/14651858.CD013089.pub2](https://doi.org/10.1002/14651858.CD013089.pub2).

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ABSTRACT

Background

Hepatitis B virus (HBV) infection, a liver disease caused by hepatitis B virus, may lead to serious complications such as cirrhosis and hepatocellular carcinoma. People with HBV infection may have co-infections including HIV and other hepatitis viruses (hepatitis C or D), and co-infection may increase the risk of all-cause mortality. Chronic HBV infection increases morbidity and psychological stress and is an economic burden on people with chronic hepatitis B and their families. Radix Sophorae flavescentis, an herbal medicine, is administered most often in combination with other drugs or herbs. It is believed that it decreases discomfort and prevents replication of the virus in people with chronic hepatitis B. However, the benefits and harms of Radix Sophorae flavescentis for patient-centred outcomes are not known, and its wide usage has never been established with rigorous review methodology.

Objectives

To assess the benefits and harms of Radix Sophorae flavescentis versus placebo or no intervention in people with chronic hepatitis B.

Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded, Conference Proceedings Citation Index - Science, China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and SinoMed. We also searched the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictip), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry for ongoing or unpublished trials. We conducted the last search in December 2018.

Selection criteria

We included randomised clinical trials, irrespective of publication status, language, or blinding, comparing Radix Sophorae flavescentis versus no intervention or placebo in people with chronic hepatitis B. We excluded polyherbal blends containing Radix Sophorae flavescentis. We allowed co-interventions when the co-interventions were administered equally to all intervention groups.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Review authors in pairs retrieved data from individual published reports and after correspondence with investigators. Our primary outcomes were all-cause mortality, serious adverse events, and health-related quality of life. Our secondary outcomes were hepatitis B-related mortality, hepatitis B-related morbidity, and adverse events considered 'not to be serious'. We presented meta-analysed results as risk ratios (RRs) with 95% confidence intervals (CIs). We assessed risk of bias using domains with pre-defined definitions. We conducted Trial Sequential Analyses to control the risk of random errors. We used GRADE methodology to evaluate our certainty in the evidence (i.e. "the extent of our confidence that the estimates of the effect are correct or are adequate to support a particular decision or recommendation").

Main results

We included 35 randomised clinical trials with 3556 participants. One trial compared Radix Sophorae flavescentis with placebo; the remaining 34 trials compared effects of Radix Sophorae flavescentis in addition to a co-intervention versus the same co-intervention. The included trials assessed heterogenous forms and ways of administering Radix Sophorae flavescentis (e.g. oral capsules, oral tablets, intravenous infusion, intramuscular injection, acupoint (a specifically chosen site of acupuncture) injection) with treatment duration of 1 to 24 months. Two of the trials included children up to 14 years old. Participants in two trials had cirrhosis in addition to chronic hepatitis B. All trials were assessed at high risk of bias, and certainty of the evidence for all outcomes was very low.

Only one of the 35 trials assessed mortality; no deaths occurred. Ten trials assessed serious adverse events; no serious adverse events occurred. None of the trials reported health-related quality of life, hepatitis B-related mortality, or morbidity. Adverse events considered 'not to be serious' was an outcome in 19 trials; nine of these trials had zero events in both groups. Radix Sophorae flavescentis versus placebo or no intervention showed no difference in effects on adverse events considered 'not to be serious' (RR 1.10, 95% CI 0.76 to 1.59; $I^2 = 49\%$; 10 trials, 1050 participants). Radix Sophorae flavescentis showed a reduction in the proportion of participants with detectable HBV-DNA (RR 0.61, 95% CI 0.55 to 0.68; $I^2 = 56\%$; 29 trials, 2914 participants) and in the proportion of participants with detectable HBeAg (hepatitis B e-antigen) (RR 0.71, 95% CI 0.66 to 0.76; $I^2 = 19\%$; 20 trials, 2129 participants).

Seven of the 35 randomised clinical trials received academic funding from government or hospital. Four trials received no funding. The remaining 24 trials provided no information on funding.

Additionally, 432 trials lacked the methodological information needed to ensure inclusion of these trials in our review.

Authors' conclusions

The included trials lacked data on health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity. The effects of Radix Sophorae flavescentis on all-cause mortality and on the proportion of participants with serious adverse events and adverse events considered 'not to be serious' remain unclear. We advise caution in interpreting results showing that Radix Sophorae flavescentis reduced the proportion of people with detectable HBV-DNA and detectable HBeAg because the trials reporting on these outcomes are at high risk of bias and both outcomes are non-validated surrogate outcomes. We were unable to obtain information on the design and conduct of a large number of trials; therefore, we were deterred from including them in our review. Undisclosed funding may influence trial results and may lead to poor trial design. Given the wide usage of Radix Sophorae flavescentis, we need large, unbiased, high-quality placebo-controlled randomised trials in which patient-centred outcomes are assessed.

PLAIN LANGUAGE SUMMARY

Radix Sophorae flavescentis for chronic hepatitis B

Review question

To assess the benefits and harms of Radix Sophorae flavescentis versus placebo or no intervention in people with chronic hepatitis B.

Background

Chronic hepatitis B virus (HBV) infection is a common liver disease that is associated with high morbidity and death. It causes psychological stress and is a burden to people with chronic hepatitis B and their families. Radix Sophorae flavescentis has been used in treating people with chronic hepatitis B; it is believed that it decreases discomfort and prevents replication of the virus in people with chronic hepatitis B. However, its benefits and harms remain unclear.

Search date

December 2018 was the date of the last search.

Study characteristics

We included 35 randomised clinical trials with 3556 participants. One trial compared Radix Sophorae flavescentis with placebo; the remaining 34 trials compared effects of Radix Sophorae flavescentis in addition to a co-intervention versus the same co-intervention. The included trials assessed heterogenous forms and ways of administering Radix Sophorae flavescentis (e.g. oral capsules, oral tablets, intravenous infusion, intramuscular injection, acupoint (a specifically chosen site of acupuncture) injection) with treatment duration of 1

to 24 months. Two trials assessed children under 14 years of age. Participants in two trials had cirrhosis in chronic hepatitis B (late-stage scarring of the liver).

Study funding sources

Seven of the 35 randomised clinical trials received academic funding from government or hospital. Four trials received no funding. The remaining 24 trials provided no information on funding. Undisclosed funding may influence trial results and may lead to poor trial design.

Key results

Only one of the 35 trials assessed mortality; no deaths occurred. Ten trials assessed serious adverse events; no serious adverse events occurred. None of the trials assessed health-related quality of life, and no trials followed people who died from hepatitis B or were at risk of dying because of hepatitis B. Adverse events considered 'not to be serious' was an outcome in 19 trials. We cannot say if Radix Sophorae flavescentis versus placebo or no intervention is better or worse regarding the occurrence of adverse events considered 'not to be serious'. Radix Sophorae flavescentis reduced the proportion of people with detectable HBV-DNA and also the proportion of people with detectable HBeAg. However, caution is needed to understand these beneficial findings, as these trials were at high risk of bias, and these outcomes have not yet been proven relevant to patients. The 432 trials identified could not be included in the review because of lack of information required for the conduct of this review. Accordingly, more information from properly designed randomised clinical trials is needed before one can determine the benefits or harms of Radix Sophorae flavescentis for people with chronic hepatitis B.

Certainty of the evidence

'Certainty of evidence' means "the extent of one's confidence that review results are correct in supporting or rejecting a finding". The certainty of evidence on the use of Radix Sophorae flavescentis for people with chronic HBV in terms of its beneficial or harmful effects on death, health-related quality of life, risk of dying due to HBV infection, and serious adverse events cannot be determined, as only a few trials aimed to explore patient-relevant outcomes. Our certainty in the evidence that Radix Sophorae flavescentis, when compared with no intervention or placebo, decreases or increases adverse events considered not to be serious in people with chronic hepatitis B is very low. Our certainty in the evidence that Radix Sophorae flavescentis decreases the proportion of people with detectable HBV-DNA and the proportion of people with detectable HBeAg is also very low. These assessments of certainty of evidence are due to the poor design and reporting of the included trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B

Patient or population: chronic hepatitis B

Setting: hospitalised patients and outpatients

Intervention: Radix Sophorae flavescentis

Comparison: no intervention or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention or placebo	Risk with Radix Sophorae flavescentis				
All-cause mortality	No deaths	No deaths	-	86 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{a,b}	b) Number of events less than 300 and sample size very small Notes: pooled risk difference zero (95% CI -0.04 to 0.04)
Proportion of participants with 1 or more serious adverse events	No serious adverse events	No serious adverse events	-	1140 (10 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b}	b) Number of events less than 300 and sample size very small Notes: pooled risk difference zero (95% CI -0.01 to 0.01)
Health-related quality of life	No data					
Hepatitis B-related mortality	No data					
Hepatitis B-related morbidity	No data					
Proportion of participants with 1 or more adverse events considered 'not to be serious'	Study population		RR 1.10 (0.76 to 1.59)	1050 (10 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b,c}	b) Number of events less than 300; CI overlaps no effect and fails to exclude important harm (RR > 1.25) c) I ² = 49% could implicate moderate heterogeneity
	89 per 1000	98 per 1000 (68 to 142)				

(at maximum follow-up: 1 month to 24 months; median 6 months)					d) All included studies were small
Notes: 9 additional trials (952 participants) reported this outcome and there were 0 events in both arms					
Surrogate outcomes:	Study population	RR 0.61 (0.55 to 0.68)	2914 (29 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b,c,d}	b) Optimal information size criteria not met and sample size not very large (fewer than 4000 participants)
Proportion of participants with detectable HBV-DNA (at maximum follow-up: 1 month to 24 months; median 6 months)	630 per 1000 384 per 1000 (347 to 428)				c) $I^2 = 56\%$ could implicate substantial heterogeneity
Proportion of participants with detectable HBeAg (at maximum follow-up: 1 month to 24 months; median 6 months)	Study population	RR 0.71 (0.66 to 0.76)	2129 (20 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b}	d) Visual inspection of funnel plot showed some signs of asymmetry. Harbord's test showed a small-study effect ($P = 0.000$)
	794 per 1000 563 per 1000 (524 to 603)				b) Optimal information size criteria not met and sample size not very large (fewer than 4000 participants)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RCTs: randomised clinical trials; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by two levels because of within-study risk of bias: trials suffered from inadequate concealment of allocation and unblinded assessment of outcome by potentially biased people (e.g. participants).

^bDowngraded by two levels (for proportion of participants with one or more adverse events considered 'not to be serious' outcomes) or by one level (for surrogate outcomes) because of imprecision of the result.

^cDowngraded by one level because of heterogeneity or inconsistency of results. Trials included heterogeneous group of participants and covered different forms and ways of administration of Radix Sophorae flavescentis.

^dDowngraded by one level because of risk of publication bias.

BACKGROUND

Description of the condition

Hepatitis B infection is a liver disease caused by hepatitis B virus (HBV). Hepatitis B virus belongs to the Hepadnaviridae family of small, enveloped, primarily hepatotropic deoxyribonucleic acid (DNA) viruses and is classified into 10 genotypes (A through J) (Sunbul 2014; Tong 2016). Major modes of HBV transmission include mother-to-child transmission, sexual or close household contact with an infected person, injection drug use, and nosocomial exposure (Lee 1997; Hou 2005; WHO 2015).

In 2015, approximately 257 million people around the world, or 3.5% of the world's population, were infected with hepatitis B virus (WHO 2017). The estimated prevalence of HBV infection is highest in Africa and Western Pacific regions (WHO 2017). About 20% to 30% of chronically infected people could develop complications such as cirrhosis and hepatocellular carcinoma (WHO 2015). Based on data from 2015, approximately 887,000 people may have died because of chronic hepatitis B virus infection (WHO 2018). People with HBV infection may also have co-infections including HIV and other hepatitis viruses (hepatitis C and D) (Derikx 2011; Mallet 2017), and these co-infections may increase the risk of all-cause mortality (Puoti 2000; Mallet 2017). Chronic hepatitis B infection imposes substantial morbidity, psychological stress, and economic burden on people with chronic hepatitis B and their families (Alizadeh 2008; Lu 2013; Keshavarz 2015; Ezbarami 2017).

The initial evaluation of people with chronic hepatitis B virus infection includes a thorough history, physical examination, and assessment of liver disease activity and severity (e.g. liver biopsy, abdominal hepatic ultrasound, alanine transaminase assessments) and markers of HBV infection (e.g. HBV-DNA, HBeAg (hepatitis B e-antigen)) (Pellicelli 2008; Jones 2009; Shepherd 2009; AASLD 2016; Wang 2016; EASL 2017). Reducing mortality and hepatitis B-related morbidities such as liver cirrhosis, liver failure, and liver cancer; improving quality of life; and prolonging survival are the goals of long-term treatment of chronic hepatitis B (EASL 2012; WHO 2015; EASL 2017).

Description of the intervention

Sophora is a genus of the Fabaceae family, which includes several medicinal plants distributed in Asia, Oceania, and the Pacific Islands (Krishna 2012). *Sophora flavescens* Aiton, a perennial shrub, has been used for centuries for traditional medicine in China, Japan, and Korea (Tanabe 2015). Radix *Sophorae flavescentis* (Chinese name: Kushen) is the dried root of the shrub. It has been claimed that Radix *Sophorae flavescentis* has antibacterial, antiviral, anti-inflammatory, antitumour, and antipyretic effects; it is one of the commonly used traditional Chinese medicinal remedies for chronic hepatitis B (Zhu 1998; Chinese Herbal Dictionary 2006; Chinese Pharmacopoeia 2015). The extracts of Radix *Sophorae flavescentis* are dispensed as tablets, capsules, and injections (Long 2004a; Mao 2004; Zhu 2009; Zou 2009). The treatment period usually ranges from 1 month to 24 months (Yin 2011; Lu 2012; Zhang 2012d; Lai 2015; Wang 2015; Wang 2017).

Radix *Sophorae flavescentis* is likely associated with certain adverse events, such as abdominal pain, diarrhoea, nausea, vomiting, and fever (Gong 2000; Gu 2008; Zhang 2008; Li 2011; Li 2015a). Hepatotoxicity has been noted in people taking the Zhixue

capsule, which consists of Radix *Sophorae flavescentis* (ku shen) and Cortex *Dictamnus dasycarpus* (bai xian pi) (Chan 2011).

How the intervention might work

The Chinese Pharmacopoeia states that Radix *Sophorae flavescentis* is used to remove heat and dampness from the body and can be used in treating hepatitis and liver fibrosis (Chinese Pharmacopoeia 2015). Modern phytochemical studies have identified several active ingredients from Radix *Sophorae flavescentis* (Krishna 2012), among which matrine ($C_{15}H_{24}N_2O$) and oxymatrine ($C_{15}H_{24}N_2O_2$) are the main components (Liu 2003a). Animal studies have suggested that matrine may prevent liver fibrogenesis by inhibiting synthesis of platelet-derived growth factor (PDGF) and proliferation of transforming growth factor beta-1 (TGF- β 1) (Zhang 2001), and may inhibit hepatitis B virus replication by increasing Th1 cytokines and decreasing Th2 cytokines to trigger immune responses (Dong 2002). In cell studies, matrine has shown anticancer action by inhibiting telomerase and tumour proliferation, preventing tumour cell invasion, and inducing tumour cell apoptosis (Qin 2009a; Li 2017). Oxymatrine may inhibit HBV replication in vitro by interfering with the process of packaging pre-genomic ribonucleic acid (RNA) into the nucleocapsid, or by inhibiting viral DNA polymerase activity (Xu 2010).

Why it is important to do this review

The benefits and harms of Radix *Sophorae flavescentis* have never been established in systematic reviews with rigorous and reasonable methodology (Liu 2003b; He 2013a; Jiang 2013; Qi 2013; Song 2016; Wang 2017). Previously published reviews may have been limited by focusing only on a specific group in the chronic hepatitis B population (Qi 2013), or by assessing only a specific form or treatment duration of Radix *Sophorae flavescentis* (Qi 2013; Song 2016). These reviews are likely not able to provide dependable results because of possible flaws in their methodology, such as lack of protocol, inadequate technique for risk of bias assessment, or unjustified restriction in literature searching. Moreover, transfer of review results into practice was impossible, as review authors primarily focused on assessing effects of Radix *Sophorae flavescentis* on surrogate outcomes. It is questionable whether these surrogate outcome results do indeed lead to improvement in clinically important outcomes because validation of any association should be carried out in randomised clinical trials (Gluud 2007; Flemming 2012; Ciani 2017; Jakobsen 2017; Kemp 2017; Jakobsen 2018). Thus, the clinical benefits and harms of Radix *Sophorae flavescentis* remain vague. As benefits and harms of an intervention need to be established first against placebo or no intervention, we have planned to perform two reviews: "Radix *Sophorae flavescentis* versus no intervention or placebo for chronic hepatitis B" (the current one) and "Radix *Sophorae flavescentis* versus antiviral drugs for chronic hepatitis B" (Liang 2018a).

OBJECTIVES

To assess the benefits and harms of Radix *Sophorae flavescentis* versus placebo or no intervention in people with chronic hepatitis B.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised clinical trials irrespective of blinding, language, year, publication format, and publication status. We also considered quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms if retrieved during our searches for randomised clinical trials. We did this because adverse events are rarely reported in randomised clinical trials (Storebø 2018). Moreover, such observational studies may provide information on late occurring adverse events (Storebø 2018). We were aware that the decision not to search for all observational studies might have biased our review towards assessment of benefits and might have caused us to overlook certain harms, such as very late or very rare harms. If we demonstrate benefits derived from using *Radix Sophorae flavescentis* or its extractions in people with chronic hepatitis B, then a systematic review of harms of *Sophorae flavescentis* or its extractions in observational studies in people with chronic hepatitis B ought to be launched (Storebø 2018).

Types of participants

Inclusion criteria

We included trial participants of any sex and any age given the diagnosis of chronic hepatitis B, as defined by trialists or according to guidelines (HBsAg (hepatitis B surface antigen) positivity for longer than six months, serum HBV-DNA positivity > 2000 IU/mL (i.e. 10^4 copies/mL), persistent or intermittent elevation in levels of aspartate aminotransferase or alanine transaminase, and liver biopsy findings showing chronic hepatitis B with moderate or severe necro-inflammation) (AASLD 2016; EASL 2017).

In addition to chronic hepatitis B, trial participants could have had cirrhosis, hepatocellular carcinoma, concomitant HIV infection or AIDS, hepatitis C, hepatitis D, or any other concomitant disease.

Exclusion criteria

We applied no exclusion criteria.

Types of interventions

We included *Radix Sophorae flavescentis* or its extractions (e.g. matrine, oxymatrine) at any dose, form, and regimen, compared with placebo or no intervention. We excluded polyherbal blends containing *Radix Sophorae flavescentis*.

We allowed co-interventions in experimental and control intervention groups, when the co-interventions were administered equally to all intervention groups of a trial.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Proportion of participants with one or more serious adverse events, that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (ICH-E2A 1994; ICH-GCP E6(R2) 2016)

- Health-related quality of life: any scale used by trialists to assess participants' reporting of their quality of life

Secondary outcomes

- Hepatitis B-related mortality
- Hepatitis B-related morbidity (proportion of participants with one or more of the following events: cirrhosis, ascites, variceal bleeding, hepatorenal syndrome, hepatocellular carcinoma, hepatic encephalopathy, or needed liver transplantation, and who have not died)
- Proportion of participants with one or more adverse events considered 'not to be serious'

Exploratory outcomes

- Proportion of participants with detectable HBV-DNA in serum, plasma, or HBV-DNA viral load
- Proportion of participants with detectable HBeAg in serum or plasma
- Separately reported serious adverse events
- Separately reported hepatitis B-related morbidity
- Separately reported adverse events considered 'not to be serious'

We assessed all outcomes at maximal follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (Cochrane Hepato-Biliary Group Module), the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, MEDLINE Ovid, Embase Ovid, Latin American Caribbean Health Sciences Literature (LILACS) (Bireme), Science Citation Index - Expanded (Web of Science), and Conference Proceedings Citation Index - Science (Web of Science) (Royle 2003). We also searched four Chinese biomedical databases including China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and SinoMed. Appendix 1 provides the search strategies with the time spans for these searches.

Searching other resources

We searched the reference lists of meta-analyses on this topic and the reference lists of the retrieved studies. We also searched the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictpr), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry (ChiCTR) for ongoing or unpublished trials.

Data collection and analysis

We conducted our review according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the *Cochrane Hepato-Biliary Group Module*, and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines (MECIR 2018). We performed analyses using Review Manager 5 (Review Manager 2014), along with Trial Sequential Analysis version 0.9.5.10 Beta software (Thorlund 2011a; TSA 2011).

Selection of studies

Review authors in pairs (SSM, CLL, MY, LDF, XYL, LJC, RLD, CS) independently screened titles and abstracts to identify potentially eligible trials. We listed multiple reports of the same trial under the main reference, as well as ineligible studies with reasons for exclusion in the [Characteristics of excluded studies](#) section. We resolved disagreements through discussion, or we asked JPL to arbitrate. We recorded the selection process in a PRISMA flow diagram ([PRISMA 2009](#)).

Data extraction and management

Review authors in pairs (SSM, CLL, MY, LDF, XYL, LJC, RLD, CS) independently extracted data using a pre-piloted electronic data collection form created in Microsoft Excel. In case of discrepancies, we rechecked the extracted data. When disagreements persisted, we tried to resolve any disagreements through discussion. We contacted JPL to arbitrate when disagreements had not been resolved, before proceeding with the analyses.

We extracted the following information: publication data (i.e. year, country, authors); study characteristics and design; characteristics of trial participants; trial inclusion and exclusion criteria; interventions (e.g. duration, dose); outcomes; follow-up; and types of data analyses (i.e. intention-to-treat, modified intention-to-treat, per-protocol). We contacted the trial authors to request missing information. We extracted data at maximum follow-up.

Assessment of risk of bias in included studies

Review authors in pairs (NL, DZK) independently assessed the risk of bias in included studies. We assessed risk of bias according to the Cochrane 'risk of bias' tool ([Higgins 2011](#)), the [Cochrane Hepato-Biliary Group Module](#), and methodological studies ([Schulz 1995](#); [Moher 1998](#); [Kjaergard 2001](#); [Wood 2008](#); [Savović 2012a](#); [Savović 2012b](#); [Lundh 2017](#); [Savović 2018](#)), using the following definitions.

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person, not otherwise involved in the study, performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We planned to include such studies only for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.

- High risk of bias: it was likely that the investigators who assigned the participants knew the allocation sequence. We planned to include such studies only for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: any of the following: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or no blinding or incomplete blinding, but the review authors judged that the outcome (such as mortality) was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias: any of the following: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or no blinding of outcome assessment, but the review authors judged that the outcome measurement (such as mortality) was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of low risk or high risk; or the study did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias into the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial protocol is available on e.g. ClinicalTrials.gov or other full-available databases, and all pre-specified outcomes of interest in the review (all-cause mortality, serious adverse events, and health-related quality of life) have been reported in the pre-specified way; or the trial protocol is not available or was registered after the trial began, but all expected outcomes are reported in the trial publication.
- Unclear risk of bias: not all pre-defined outcomes in the trial protocol or clinically relevant and reasonably expected outcomes such as all-cause mortality, serious adverse events, and health-related quality of life were reported fully in the trial publication; or it was unclear whether or not the data on these outcomes were reported.

- High risk of bias: one or more outcomes in the trial protocol were not reported as pre-specified or expected in the trial publication; or outcomes in the trial publication were missing or added, only subsets of outcomes were reported, or there were unexpected measurements or methods; or all-cause mortality, serious adverse events, and health-related quality of life outcomes were reported incompletely so they cannot be entered in a meta-analysis.

Other bias

- Low risk of bias: the study appeared to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the study may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the study that could put it at risk of bias.

Overall risk of bias

- Low risk of bias: the outcome result will be classified at overall low risk of bias if all of the bias sources described in the above paragraphs are classified as at low risk of bias.
- High risk of bias: the outcome result will be classified at overall high risk of bias when any of the bias risk sources described above are classified as at unclear risk of bias or high risk of bias.

We tried to reach consensus through discussion. We contacted JPL to arbitrate when disagreements had not been resolved.

We planned to base our primary conclusions on all of our primary and secondary outcome results at overall low risk of bias; however, we found no trials at overall low risk of bias.

Measures of treatment effect

We used risk ratios (RRs) to measure dichotomous outcomes, and we intended to use mean differences (MDs) for continuous data with 95% confidence intervals (CIs) for head-to-head comparison meta-analysis. If different instruments were used to measure the same continuous outcome, we intended to calculate standardised mean differences (SMDs) with 95% CIs.

Unit of analysis issues

We followed the guidelines set forth in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The unit of analysis was the participants randomised into trial intervention groups. For trials with multiple intervention groups, we included the groups in which our experimental and control interventions were compared. We intended to divide the control group into two or more groups to avoid double-counting, in case it was a common comparator.

For cluster-randomised trials, we intended to directly extract data from the analysis that properly account for the cluster design. We planned to determine the inflated standard errors, which account for clustering, if there was no control of the clustering. We planned to use the inverse-variance method in Review Manager 5 (Higgins 2011; Review Manager 2014). We found no cluster-randomised trials.

For cross-over trials, we intended to extract only data from the first period to avoid residual treatment effects (Higgins 2011). We found no cross-over trials.

Dealing with missing data

We attempted to contact trial authors to ask for missing data or information that was not clearly presented.

We performed all analyses using the intention-to-treat method whenever possible. When not possible, we used the data that were available to us. We planned to include participants with incomplete or missing data, for all outcomes in the sensitivity analyses by imputing them as follows.

For dichotomous outcomes:

- best- and worst-case scenarios: we assumed that all participants lost to follow-up in the experimental group had survived, had improvement in clinical symptoms, had no serious adverse event, and had no morbidity (for all dichotomous variables); and that all participants lost to follow-up in the control group had not survived, had no improvement in clinical symptoms, had a serious adverse event, and had morbidities (for all dichotomous variables); and
- worst- and best-case scenarios: we assumed that all participants lost to follow-up in the experimental group had not survived, had no improvement in clinical symptoms, had a serious adverse event, and had morbidities (for all dichotomous variables); and that all participants lost to follow-up in the control group had survived, had improvement in clinical symptoms, had no serious adverse event, and had no morbidity (for all dichotomous variables).

For continuous outcomes:

- we planned to base the 'beneficial' outcome on the group mean plus 2 standard deviations (SDs), or 1 SD, and the 'harmful' outcome on the group mean minus 2 SDs, or 1 SD (Jakobsen 2014).

We intended to request the information from trial authors or to calculate SDs using data from the trial, if not reported.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining trial participant characteristics and the design of the included trials. We attempted to assess the presence of clinical heterogeneity by comparing effect estimates (please see [Subgroup analysis and investigation of heterogeneity](#)) in trial reports in terms of participants diagnosed with only chronic hepatitis B comparing to participants diagnosed with concomitant disease, intervention forms and administration ways, duration and dosages of the intervention, co-interventions, different control interventions, and follow-up. Different study designs and risk of bias can contribute to methodological heterogeneity. We assessed statistical heterogeneity by comparing results of the fixed-effect model meta-analysis and the random-effects model meta-analysis. We started by looking at the forest plots for signs of statistical heterogeneity. Next, we used the Chi² test with significance threshold set as $P < 0.10$, and we measured the amount of heterogeneity using the I² statistic to assess to what extent heterogeneity is present (Higgins 2002; Higgins 2003; Higgins

2011). A rough guide for the I^2 statistic was as follows: 0% to 40%: might not be important; 30% to 60%: might represent moderate heterogeneity; 50% to 90%: might represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins 2011).

For the heterogeneity adjustment of the diversity-adjusted required information size (DARIS) in the Trial Sequential Analysis, we used diversity (D^2) because I^2 statistics used for this purpose might underestimate the required information size (Wetterslev 2009).

Assessment of reporting biases

We assessed reporting bias using funnel plots when we had data from at least 10 trials per comparison. To assess bias risk, we looked for symmetry or asymmetry in each funnel plot. For dichotomous outcomes, we assessed asymmetry using Harbord's test (Harbord 2006). For continuous outcomes, we intended to apply the regression asymmetry test (Egger 1997).

Data synthesis

Meta-analysis

We performed meta-analyses according to the instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* - Higgins 2011 - and the *Cochrane Hepato-Biliary Group Module*. We analysed data using Review Manager 5 software (Review Manager 2014).

We assessed our intervention effects using both fixed-effect model and random-effects model meta-analyses, and we reported both results when results differed (e.g. one giving a significant intervention effect, the other no significant intervention effect); otherwise, we reported the estimate closest to zero effect (the highest P value) (Jakobsen 2014).

We assessed the three primary outcomes with a P value of 0.025 or less as statistically significant, and the three secondary outcomes with a P value of 0.025 or less as statistically significant, to secure a family-wise error rate below 0.05 (Jakobsen 2014). For exploratory outcomes, we considered a P value less than 0.05 as statistically significant because we viewed these outcomes as only hypothesis-generating outcomes. Whether we presented our data synthesis as a meta-analysis or in a narrative way depended on our assessment of statistical and clinical heterogeneity of the meta-analysed trial data per comparison.

We did not plan to impute missing data in our primary analyses; instead, we imputed missing data in our sensitivity analysis of continuous and dichotomous data (see *Sensitivity analysis*) (Jakobsen 2014).

When data were available from only one trial, we planned to use Fisher's exact test, as presented in Fisher 1922, for dichotomous data, and Student's t-test, as presented in Student 1908, for continuous data.

Trial Sequential Analysis

As cumulative meta-analysis involves risk of producing random errors due to sparse data and repetitive testing, we performed Trial Sequential Analysis. To minimise random errors, we calculated the required information size (i.e. the number of participants

needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008; TSA 2011). The required information size calculation should also account for the diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa (Thorlund 2011a; TSA 2011).

We controlled the risks of type I errors and type II errors for both dichotomous and continuous outcomes (Brok 2008; Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2010; Castellini 2017; Wetterslev 2017). For dichotomous outcomes, we estimated the DARIS based on the event proportion in the control group; a relative risk reduction of 15%; an alpha of 2.5% for primary outcomes, 2.5% for secondary outcomes, and 5.0% for exploratory outcomes; a beta of 10% (Castellini 2017); and diversity suggested by trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014). For continuous outcomes, we intended to estimate the DARIS based on the SD observed in the control group; a minimal relevant difference of 50% of this SD; an alpha of 2.5%; a beta of 10% (Castellini 2017); and diversity suggested by trials in the meta-analysis (Wetterslev 2009; Jakobsen 2014).

We tested statistical significance using 'trial sequential monitoring boundaries' for benefit, harm, and futility (Thorlund 2011a). If the Z-curve crosses the trial sequential monitoring boundaries for benefit or harm before reaching DARIS, the effect of the intervention is considered superior or inferior to the control intervention. If the Z-curve crosses the futility monitoring boundaries before reaching the DARIS, this would mean that the intervention does not possess the postulated effect, and further randomised trials might be futile. Furthermore, if the trial sequential monitoring boundaries are not surpassed, and if the trial monitoring boundaries for futility are not crossed, it is probably necessary to continue doing trials to detect or reject a certain intervention effect (Wetterslev 2008; Thorlund 2011b). In our cases where the trial monitoring boundaries were not reached, we also displayed the Trial Sequential Analysis-adjusted CI.

Subgroup analysis and investigation of heterogeneity

In case of available data, we planned to perform the following subgroup analyses.

- Trials at low risk of bias compared to trials at high risk of bias.
- Trials at low risk of bias compared to trials at high risk of bias on blinding of outcome assessment.
- Trials at low risk of bias compared to trials at high risk of bias on incomplete outcome data.
- Trials at low risk of bias compared to trials at high risk of bias on selective outcome reporting.
- Trials with for-profit funding compared to trials without for-profit funding (Lundh 2017).
- Different control interventions: no intervention compared to placebo intervention.
- Different administration ways for *Radix Sophorae flavescentis*.
- Different duration of the intervention stratified according to the medians observed (less than or more than six months).
- Participants diagnosed only with chronic hepatitis B compared to participants diagnosed with concomitant diseases (HIV infection, AIDS, hepatitis C, hepatitis D, or a combination of these). We planned to analyse each concomitant disease separately.

- Participants with uncomplicated chronic hepatitis B compared to participants with severe chronic hepatitis B disease, cirrhosis, and hepatocellular carcinoma.

Sensitivity analysis

In addition to the sensitivity analysis described under [Dealing with missing data](#), we compared our GRADE imprecision assessments to those conducted via Trial Sequential Analysis ([Jakobsen 2014](#)). Furthermore, we used sensitivity analyses whenever we wanted to test the robustness of our findings ([Jakobsen 2014](#); [Castellini 2018](#); [Gartlehner 2018](#)). We reported this in the [Differences between protocol and review](#) section of the review.

'Summary of findings' table

We constructed a 'Summary of findings' table to show our results and confidence in the evidence on all [Primary outcomes](#) and [Secondary outcomes](#). The 'Summary of findings' table displayed information on assumed control group risk, corresponding intervention group risk, relative effect, confidence interval, statistically significant relative effect, number of participants, and certainty of the evidence. We calculated the corresponding risk (and its 95% CI) using the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Using GRADEpro GDT software ([GRADEpro GDT](#)), we assessed five factors of the evidence referring to limitations in study design and implementation that suggest the certainty of evidence: within-study risk of bias; indirectness of the evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results; and risk of publication bias ([Balshem 2011](#); [Guyatt 2011a](#); [Guyatt 2011b](#); [Guyatt 2011c](#); [Guyatt 2011d](#); [Guyatt 2011e](#); [Guyatt 2011f](#); [Guyatt 2011g](#); [Guyatt 2011h](#); [Guyatt 2013a](#); [Guyatt 2013b](#); [Guyatt 2013c](#); [Guyatt 2013d](#); [Mustafa 2013](#); [Guyatt 2017](#)).

The certainty of the evidence grades were defined as follows.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Description of studies

Results of the search

We identified 4044 references through searching the databases and the reference lists of meta-analyses on this topic ([Figure 1](#)). After excluding 1432 duplicates and 1818 clearly irrelevant references, we read the full text of the remaining 794 references. Of these 794, 159 references comparing Radix Sophora flavescens versus other antiviral drugs are of interest to another Cochrane systematic review ([Liang 2018a](#)); we excluded 166 references with reasons listed in the [Characteristics of excluded studies](#), and 432 references failed to provide a clear description of random sequence generation even after we asked study authors for missing information, so we prepared an online [Appendix](#) with summary information on these trials and urged study authors to contact us if the trial indeed was a properly randomised trial. We found no ongoing and unpublished trials.

Figure 1. Study flow diagram.

Figure 1. (Continued)

Included studies

We included 35 randomised clinical trials as reported in 37 publications (Gao 2003; Duan 2004; Huang 2004a; Huang 2004b; Lu 2004; Huang 2005; Liu 2005; Li 2006; Wang 2006; Li 2008; Xue 2008; Li 2010; Lv 2010; Wang 2010; Wei 2010; Xi 2010; Xie 2010; Lv 2011; Sun 2011; Wang 2011; Yan 2011; Zhang 2011a; Zhang 2011b; He 2013; Zhou 2013; Mao 2014; Su 2014; Ye 2015; Zhang 2015; Liu 2016; Zhang 2017; Chai 2018; Huang 2018; Luo 2018; Wu 2018; Yang 2018; Zhu 2018). Twenty-nine of these trials provided data for meta-analyses. The remaining six trials did not study the outcomes of interest in our review, hence we used the provided information only in a narrative way (Gao 2003; Lv 2010; Wang 2011; Mao 2014; Huang 2018; Zhu 2018). For two randomised trials, each with four groups, we split each trial into two comparisons for analysis (Huang 2004a; Huang 2004b; Zhang 2011a; Zhang 2011b). These trials were all conducted in China and were published as full papers. Lu 2004 was a multi-centre trial. For further details on included trials, see [Characteristics of included studies](#). Seven of the 35 randomised clinical trials received academic funding from government or hospital. Four trials received no funding. The remaining 24 trials provided no information on funding. Undisclosed funding may influence trial results and may lead to poor trial design.

Participants

The 35 trials randomised 3556 participants with chronic hepatitis B (Gao 2003; Duan 2004; Huang 2004a; Huang 2004b; Lu 2004; Huang 2005; Liu 2005; Li 2006; Wang 2006; Li 2008; Xue 2008; Li 2010; Lv 2010; Wei 2010; Xi 2010; Xie 2010; Wang 2010; Lv 2011; Sun 2011; Wang 2011; Yan 2011; Zhang 2011a; Zhang 2011b; He 2013; Zhou 2013; Mao 2014; Su 2014; Ye 2015; Zhang 2015; Liu 2016; Zhang 2017; Chai 2018; Huang 2018; Luo 2018; Wu 2018; Yang 2018; Zhu 2018). The number of participants in these trials ranged from 28 to 200. Age of participants was reported in 26 trials, and mean age of participants in these trials was 37 years old (Duan 2004; Huang 2004a; Huang 2004b; Huang 2005; Wang 2006; Li 2008; Li 2010; Wei 2010; Xi 2010; Xie 2010; Lv 2011; Wang 2011; Yan 2011; Zhang 2011a; Zhang 2011b; He 2013; Zhou 2013; Mao 2014; Su 2014; Ye 2015; Zhang 2015; Liu 2016; Zhang 2017; Chai 2018; Huang 2018; Luo 2018; Wu 2018; Yang 2018). Two trials included children up to 14 years old (Xi 2010; Zhang 2011a). The sex of participants was reported in all but two trials, and the

ratio of male to female participants was 2229:1120 (Lu 2004; Wang 2010). Participants in all trials received a diagnosis of chronic hepatitis B in accordance with diagnostic criteria as described in the guidelines. In addition to the diagnosis of chronic hepatitis B, two trials included participants with cirrhosis (Xie 2010; Zhang 2017), and one trial included participants with or without decompensated cirrhosis (Zhang 2015). Even though these three studies did not report data on mortality, they are the only studies that could realistically assess the primary outcomes in light of the prognosis of participants (Xie 2010; Zhang 2015; Zhang 2017). Eight trials excluded pregnant and lactating women, and the others did not specify whether they did this (Lu 2004; Wang 2006; Wei 2010; Yan 2011; Ye 2015; Luo 2018; Wu 2018; Yang 2018).

Interventions and comparisons

Lu 2004 compared Radix Sophorae flavescentis versus placebo, and the remaining 34 trials explored effects of Radix Sophorae flavescentis in addition to a co-intervention versus the same co-intervention.

We identified 16 trials evaluating oral capsules of Radix Sophorae flavescentis (Huang 2004a; Lu 2004; Wang 2006; Li 2010; Lv 2010; Xie 2010; Lv 2011; Yan 2011; He 2013; Zhou 2013; Su 2014; Ye 2015; Liu 2016; Zhang 2017; Wu 2018; Zhu 2018); one trial evaluated an oral dispersible tablet (Zhang 2015), one evaluated intramuscular injection (Gao 2003), 12 evaluated intravenous infusion (Mao 2004; Huang 2005; Li 2006; Wang 2010; Wei 2010; Xi 2010; Sun 2011; Wang 2011; Zhang 2011a; Chai 2018; Huang 2018; Yang 2018), one evaluated acupoint injection (Xue 2008), and four evaluated mixed ways of administering Radix Sophorae flavescentis (i.e. intravenous infusion followed by oral capsules/tablets in Duan 2004, Liu 2005, and Luo 2018; intravenous infusion or intramuscular injection in Li 2008). The duration of treatment ranged from 1 month to 24 months. Five trials had post-treatment follow-up ranging from three to six months (Huang 2004a; Lu 2004; Huang 2005; Li 2010; He 2013).

Thirty-four trials had equally implemented co-interventions. Twenty-three trials received antiviral drugs as co-interventions (adefovir in seven trials (Li 2008; Lv 2010; Wei 2010; Lv 2011; Yan 2011; Zhou 2013; Su 2014), entecavir in seven trials (Wang 2010; Xie 2010; Ye 2015; Liu 2016; Huang 2018; Wu 2018; Zhu 2018),

lamivudine in two trials (Duan 2004; Wang 2006), telbivudine in one trial (Zhang 2015), tenofovir disoproxil in one trial (Yang 2018), lamivudine plus adefovir in one trial (He 2013), and recombinant interferon α -2b in four trials (Huang 2004b; Wang 2011; Chai 2018; Luo 2018)); 10 trials received antiviral and liver protective drugs including Chinese herbal medicine (glycyrrhizin in seven trials (Gao 2003; Huang 2005; Liu 2005; Li 2006; Li 2010; Zhang 2011a; Zhang 2011b), silymarin in two trials (Huang 2004a; Xue 2008), and tanshinone IIA in one trial (Mao 2014)); and three trials received liver protective drugs such as vitamin C, thymosin, and inosine as co-interventions (Xi 2010; Sun 2011; Zhang 2017).

Outcomes

Only one trial reported results on mortality (Su 2014). Ten trials reported results on serious adverse events (Lu 2004; Wang 2006; Li 2010; Wei 2010; Lv 2011; Sun 2011; Yan 2011; He 2013; Ye 2015; Zhang 2017). None of the included trials reported outcome results for health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity. Nineteen trials evaluated adverse events considered 'not to be serious' (Duan 2004; Lu 2004; Liu 2005; Li 2006; Wang 2006; Li 2008; Li 2010; Wei 2010; Xi 2010; Lv 2011; Sun 2011; Yan 2011; He 2013; Su 2014; Ye 2015; Zhang 2017; Luo 2018; Wu 2018; Yang 2018). Twenty-nine trials reported the proportion of participants with detectable HBV-DNA (Duan 2004; Huang 2004a; Huang 2004b; Lu 2004; Huang 2005; Liu 2005; Li 2006; Wang 2006; Li 2008; Xue 2008; Li 2010; Wang 2010; Wei 2010; Xi 2010; Xie 2010; Lv 2011; Sun 2011; Yan 2011; Zhang 2011a; Zhang 2011b; He 2013;

Zhou 2013; Su 2014; Ye 2015; Zhang 2015; Liu 2016; Zhang 2017; Chai 2018; Luo 2018; Wu 2018; Yang 2018), and 20 trials reported the proportion of participants with detectable HBeAg (Duan 2004; Huang 2004a; Huang 2004b; Lu 2004; Huang 2005; Liu 2005; Li 2006; Wang 2006; Li 2008; Xue 2008; Li 2010; Wei 2010; Xi 2010; Lv 2011; Sun 2011; Zhang 2011a; Zhang 2011b; He 2013; Zhou 2013; Zhang 2017; Wu 2018; Yang 2018).

Included trials also reported other biomarkers such as serum liver fibrosis indexes (e.g. type III procollagen), liver function biomarkers (e.g. aspartate transaminase), and serum inflammatory cytokines indexes (e.g. tumour necrosis factor- α) (Gao 2003; Lv 2010; Wang 2011; Mao 2014; Huang 2018; Zhu 2018).

Excluded studies

We excluded 166 studies after reading the full text of the articles. We explained the reasons for their exclusion under [Characteristics of excluded studies](#). As stated above, we excluded 432 further references because of insufficient information (online [Appendix](#)).

Risk of bias in included studies

We carried out the risk of bias assessment based on information retrieved from the publications and some from trial authors (Figure 2; Figure 3). We judged many trials to have unclear risk of bias in certain domains because we could not obtain additional information from the trial authors after we contacted them.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chai 2018	+	?	-	?	+	-	+
Duan 2004	+	?	-	?	+	-	+
Gao 2003	+	?	-	?	-	-	+
He 2013	+	+	-	?	+	?	+
Huang 2004a	+	-	-	+	-	-	+
Huang 2004b	+	-	-	+	-	-	+
Huang 2005	+	-	-	+	-	-	+
Huang 2018	+	?	-	?	+	-	+
Li 2006	+	?	-	?	+	-	+
Li 2008	+	-	-	-	+	-	+
Li 2010	+	?	-	?	+	?	+
Liu 2005	+	?	-	?	+	-	+
Liu 2016	+	?	-	?	+	-	+
Lu 2004	+	?	+	?	-	?	+
Luo 2018	+	?	-	?	+	-	+
Lv 2010	+	-	-	?	?	-	+
Lv 2011	+	+	-	?	+	?	+
Mao 2014	+	?	-	?	+	-	+
Su 2014	+	?	-	?	+	?	+
Sun 2011	+	?	-	?	+	?	+

Figure 3. (Continued)

Sun 2011	+	?	-	?	+	?	+
Wang 2006	+	?	-	+	?	?	+
Wang 2010	+	?	-	?	+	-	+
Wang 2011	+	?	-	?	+	-	+
Wei 2010	+	?	-	?	+	?	+
Wu 2018	+	?	-	+	+	-	+
Xi 2010	+	?	-	?	+	-	+
Xie 2010	+	?	-	?	?	-	+
Xue 2008	+	?	-	?	+	-	+
Yan 2011	+	?	-	?	?	?	+
Yang 2018	+	?	-	?	+	-	+
Ye 2015	+	?	-	?	+	?	+
Zhang 2011a	+	?	-	?	+	-	+
Zhang 2011b	+	?	-	?	+	-	+
Zhang 2015	+	?	-	?	+	-	+
Zhang 2017	+	?	-	?	+	?	+
Zhou 2013	+	?	-	?	+	-	+
Zhu 2018	+	?	-	?	+	-	+

Allocation

All trials generated a randomisation sequence by using a random numbers table, tossing a coin, drawing lots, or grabbing balls. The method used to conceal allocation was adequate in two trials (Lv 2011; He 2013). Three trials did not implement any method to conceal the allocation, and therefore we assessed them at high risk of bias (Huang 2004a; Li 2008; Lv 2010). We assessed the remaining 30 trials at unclear risk of bias, as trial authors did not report how the allocation concealment was performed. Therefore, they were also at high risk of bias.

Blinding

Only one trial adequately performed blinding of participants and personnel (Lu 2004). The remaining 34 trials did not describe any blinding method of participants and personnel. As all 34 trials compared Radix Sophorae flavescentis in addition to a co-intervention versus a co-intervention alone, and there was no blinding, we assessed the 34 trials to be at high risk of bias regarding blinding of participants and personnel.

Blinding of outcome assessors was adequately performed in four trials (Huang 2004a; Huang 2005; Wang 2006; Wu 2018). One trial did not blind the outcome assessors; therefore we assessed it at high risk of bias (Li 2008). The remaining 30 trials did not describe

the method used for blinding of outcome assessors, resulting in our assessments of unclear risk of bias. Therefore, they were also at high risk of bias.

Incomplete outcome data

Twenty-seven trials reported having no missing data and included all participants in data analyses, showing low risk of attribution bias (Duan 2004; Liu 2005; Li 2006; Li 2008; Xue 2008; Li 2010; Wang 2010; Wei 2010; Xi 2010; Lv 2011; Sun 2011; Wang 2011; Zhang 2011a; He 2013; Zhou 2013; Mao 2014; Su 2014; Ye 2015; Zhang 2015; Liu 2016; Zhang 2017; Chai 2018; Huang 2018; Luo 2018; Wu 2018; Yang 2018; Zhu 2018). The remaining eight trials had dropouts and excluded the dropouts from the analyses, so we assessed them at high risk of bias, as they did not properly deal with the missing data.

Selective reporting

Twenty-four trials seem to be at high risk of bias regarding the selective reporting domain because of lack of pre-published trial protocols and lack of data reporting on all-cause mortality, serious adverse events, and health-related quality of life (Gao 2003; Duan 2004; Huang 2004a; Huang 2005; Liu 2005; Li 2006; Li 2008; Xue 2008; Lv 2010; Wang 2010; Xi 2010; Xie 2010; Wang 2011; Zhang 2011a; Zhou 2013; Mao 2014; Zhang 2015; Liu 2016; Chai 2018; Huang 2018; Luo 2018; Wu 2018; Yang 2018; Zhu 2018). The remaining 11

trials reported either all-cause mortality or serious adverse events; therefore were assessed them to be at unclear risk of bias.

Other potential sources of bias

All the included randomised clinical trials appeared to be free of other factors that could put them at risk of bias. We classified all 35 trials at low risk of other biases.

Overall risk of bias

We assessed the included randomised clinical trials to be at overall high risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Radix Sophorae flavescens versus no intervention or placebo for chronic hepatitis B](#)

Lu 2004 compared Radix Sophorae flavescens versus placebo, and the other 34 trials compared Radix Sophorae flavescens in addition to a co-intervention versus a similar co-intervention. Only one trial compared Radix Sophorae flavescens versus placebo, and subgroup analyses showed no evidence of differences between different control interventions (i.e. no intervention compared to placebo) ([Analysis 1.5](#); [Analysis 1.35](#); [Analysis 1.25](#)); therefore our primary analysis combined them. Below, in accordance with our protocol ([Liang 2018a](#)), we have presented all outcomes through the random-effects model, as the random-effects model in this review provided similar but more conservative results compared to the fixed-effect model.

Primary outcomes

All-cause mortality

Only one trial with 86 participants randomised to Radix Sophorae flavescens plus a co-intervention versus a similar co-intervention assessed mortality; no deaths occurred (risk difference 0.00, 95% confidence interval (CI) -0.04 to 0.04; [Analysis 1.1](#)) ([Su 2014](#)).

Proportion of participants with one or more serious adverse events

Ten trials with 1140 participants randomised to Radix Sophorae flavescens plus a co-intervention versus a similar co-intervention assessed serious adverse events; no serious adverse events occurred (risk difference 0.00, 95% CI -0.01 to 0.01; [Analysis 1.2](#) ([Lu 2004](#); [Wang 2006](#); [Li 2010](#); [Wei 2010](#); [Lv 2011](#); [Sun 2011](#); [Yan 2011](#); [He 2013](#); [Ye 2015](#); [Zhang 2017](#))).

Health-related quality of life

None of the included trials reported health-related quality of life.

Secondary outcomes

Hepatitis B-related mortality

None of the included trials reported hepatitis B-related mortality.

Hepatitis B-related morbidity

None of the included trials reported hepatitis B-related morbidity.

Proportion of participants with one or more adverse events considered 'not to be serious'

Adverse events considered 'not to be serious' was an outcome in 19 trials with 2002 participants; 9 out of 19 trials reported zero events in both groups; 111/1018 (10.9%) participants in the Radix Sophorae flavescens group experienced one or more adverse events considered 'not to be serious' versus 88/984 participants (8.9%) in the no intervention/placebo group ([Duan 2004](#); [Lu 2004](#); [Liu 2005](#); [Li 2006](#); [Wang 2006](#); [Li 2008](#); [Li 2010](#); [Wei 2010](#); [Xi 2010](#); [Lv 2011](#); [Yan 2011](#); [Sun 2011](#); [He 2013](#); [Su 2014](#); [Ye 2015](#); [Zhang 2017](#); [Luo 2018](#); [Wu 2018](#); [Yang 2018](#)). We found no statistical evidence of a difference in effect between Radix Sophorae flavescens versus no intervention/placebo (risk ratio (RR) 1.10, 95% CI 0.76 to 1.59; $P = 0.62$; $I^2 = 49\%$; 10 trials, 1050 participants; [Analysis 1.8](#)).

Heterogeneity

The primary meta-analysis showed statistically significant heterogeneity ($I^2 = 49\%$; $P = 0.04$; [Analysis 1.8](#)). Visual inspection of the forest plot revealed that two trials, accounting for 43.3% weight, showed beneficial effects for the no intervention/placebo group. The post hoc sensitivity analysis by excluding these two trials showed that heterogeneity became zero (analysis not shown). However, these two trials are small, and the probability of exaggerating an intervention effect exists ([Li 2006](#); [Xi 2010](#)). Our planned subgroup analyses could not explain it. Then, we post hoc analysed the studies with the hypothesis of differences between participants. Participants in four trials ([Liu 2005](#); [Li 2006](#); [Xi 2010](#); [Sun 2011](#)), unlike participants in the remaining trials, were symptomatic (as in liver pain) at the time of randomisation, and if these four trials are removed from the analysis, heterogeneity becomes zero (analysis not shown). So this may suggest that heterogeneity may be due to presentation of asymptomatic disease among participants in these four trials.

Trial Sequential Analysis

The DARIS obtained through Trial Sequential Analysis for the proportion of participants with adverse events considered 'not to be serious' was 21,209 participants. For calculation of DARIS, we used an event rate in the control group of 8.9%, a risk ratio reduction of 15%, a two-sided alpha of 2.5%, a beta of 10%, and observed diversity of 0%. Trial Sequential Analysis showed that the Z-curve did not cross any of the boundaries for benefit, harm, or futility. This indicates that evidence was insufficient to support or refute a 15% risk reduction for Radix Sophorae flavescens versus no intervention/placebo regarding the proportion of participants with adverse events considered 'not to be serious'. The Trial Sequential Analysis-adjusted CI was 0.57 to 3.09 ([Figure 4](#)).

Figure 4. Trial Sequential Analysis on proportion of participants with one or more adverse events considered 'not to be serious' in 19 high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 8.9%, risk ratio reduction of 15%, type I error of 2.5%, type II error of 10% (90% power), and diversity of 0%. The required information size was 21,209 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit, harm, or futility (red inward sloping lines), as well as the required information size. The green dotted line shows conventional boundaries (2.5%). We performed constant continuity correction method using 1.0 to handle zero events. The Trial Sequential Analysis-adjusted confidence interval was 0.57 to 3.09.

Sensitivity analysis

We had to impute data for only one trial on the outcome of proportion of participants with one or more adverse events considered 'not to be serious' (Wang 2006). 'Best-worst' and 'worst-best' case scenario meta-analyses showed that incomplete outcome data bias did not influence our results ('best-worst' meta-analysis: RR 1.11, 95% CI 0.77 to 1.58; $P = 0.58$, $I^2 = 43\%$; 10 trials, 1053 participants; Analysis 1.15; 'worst-best' meta-analysis: RR 1.13, 95% CI 0.78 to 1.61; $P = 0.52$, $I^2 = 44\%$; 10 trials; 1053 participants; Analysis 1.3).

Our GRADE and Trial Sequential Analysis assessments on imprecision for the proportions of participants with one or more adverse events considered 'not to be serious' did not differ: we downgraded the evidence for imprecision by two levels with GRADE because the number of events was less than 300 and the CI overlapped no effect, failing to exclude important harm ($RR > 1.25$) (GRADE 2013; Schunemann 2016). If Trial Sequential Analysis was used to assess imprecision, we would have downgraded the evidence also by two levels because none of the sequential boundaries for benefit, harm, or futility were crossed (Jakobsen 2014).

Post hoc sensitivity analysis

Nine out of 19 trials reported zero events in both groups (Duan 2004; Wang 2006; Li 2008; Li 2010; Wei 2010; Lv 2011; He 2013; Zhang 2017; Wu 2018).

Using risk difference (rather than risk ratio) showed no evidence of a difference in effect between Radix Sophorae flavescentis and no intervention/placebo (risk difference 0.00, 95% CI -0.02 to 0.02; $P = 0.74$, $I^2 = 52\%$; 19 trials, 2002 participants). The problem with the precision of our results seemed to disappear.

Subgroup analysis

We could not perform all of the pre-specified subgroup analyses because of insufficient data (Subgroup analysis and investigation of heterogeneity).

We found no statistically significant subgroup differences when trials at low risk of bias were compared to trials at high risk of bias regarding the incomplete outcome data domain (test for subgroup difference: $P = 0.69$, $I^2 = 0\%$; Analysis 1.4); when trials on Radix Sophorae flavescentis versus no intervention were compared to trials on Radix Sophorae flavescentis versus placebo (test for subgroup difference: $P = 0.82$, $I^2 = 0\%$; Analysis 1.5); when trials

with treatment duration less than six months were compared to trials with treatment duration longer than six months (test for subgroup difference: $P = 0.94$, $I^2 = 0\%$; [Analysis 1.7](#)); when trials that compared participants with chronic hepatitis B concomitant with other diseases were compared with trials with participants with only a diagnosis of chronic hepatitis B or trials with unclear status of concomitant disease (test for subgroup difference: $P = 0.28$, $I^2 = 14.4\%$; [Analysis 1.17](#)); and when trials comparing different co-interventions were compared (test for subgroup difference: $P = 0.37$, $I^2 = 4.6\%$; [Analysis 1.9](#)).

We found a statistically significant subgroup difference when trials assessing intravenous infusion of *Radix Sophorae flavescentis* were compared to trials assessing oral capsules and trials assessing mixed forms and ways of administration of *Radix Sophorae flavescentis* (test for subgroup difference: $P = 0.004$, $I^2 = 82.2\%$; [Analysis 1.6](#)). The subgroup receiving intravenous infusion of *Radix Sophorae flavescentis* showed a significant increase in the risk of adverse events considered 'not to be serious' (RR 1.58, 95% CI 1.26 to 2.00; $P = 0.0001$, $I^2 = 0\%$; 5 trials, 480 participants) compared to the subgroup given oral capsules (RR 0.80, 95% CI 0.39 to 1.61; $P = 0.52$, $I^2 = 0\%$; 10 trials, 1080 participants) and the subgroup with mixed forms and means of administration (RR 0.54, 95% CI 0.28 to 1.05; $P = 0.07$, $I^2 = 0\%$; 4 trials, 442 participants). However, we must acknowledge the uncertainty in the evidence for all three subgroups due to inconsistency between individual trial results, which might be due to insufficient numbers of participants and small trials in general, the latter of which do not allow detection of subgroup differences.

Publication bias

As we included no more than 10 trials with usable data in the meta-analysis, we did not construct a funnel plot. In light of the small

sample size of the included trials and the scant data reported on adverse events, we could not exclude the risk of publication bias.

Exploratory outcomes

Proportion of participants with detectable HBV-DNA

Twenty-nine trials with 2914 randomised participants reported data on proportions of participants with detectable HBV-DNA: 567/1476 (38.4%) participants in the *Radix Sophorae flavescentis* group had detectable HBV-DNA versus 906/1438 participants (63.0%) in the no intervention/placebo group ([Duan 2004](#); [Huang 2004a](#); [Huang 2004b](#); [Lu 2004](#); [Huang 2005](#); [Liu 2005](#); [Li 2006](#); [Wang 2006](#); [Li 2008](#); [Xue 2008](#); [Li 2010](#); [Wang 2010](#); [Wei 2010](#); [Xi 2010](#); [Xie 2010](#); [Lv 2011](#); [Sun 2011](#); [Yan 2011](#); [Zhang 2011a](#); [Zhang 2011b](#); [He 2013](#); [Zhou 2013](#); [Su 2014](#); [Ye 2015](#); [Zhang 2015](#); [Liu 2016](#); [Zhang 2017](#); [Chai 2018](#); [Luo 2018](#); [Wu 2018](#); [Yang 2018](#)). *Radix Sophorae flavescentis* showed a better effect in reducing the proportion of participants with detectable HBV-DNA when compared with no intervention/placebo (RR 0.61, 95% CI 0.55 to 0.68; $P < 0.00001$, $I^2 = 56\%$; [Analysis 1.10](#)).

Trial Sequential Analysis

We calculated the DARIS to be 3395 participants, based on an event rate in the control group of 63.0%, a risk ratio reduction of 15%, a two-sided alpha of 5.0%, a beta of 10%, and observed diversity of 66%. Trial Sequential Analysis showed that the Z-curve crossed the boundary for benefit but did not reach the required information size. This indicates that *Radix Sophorae flavescentis* versus no intervention/placebo results in a 15% or greater risk ratio reduction among participants with detectable HBV-DNA. The Trial Sequential Analysis-adjusted CI was 0.54 to 0.69 ([Figure 5](#)).

Figure 5. Trial Sequential Analysis on proportion of participants with detectable HBV-DNA in 29 high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 63.0%, risk ratio reduction of 15%, type I error of 5%, type II error of 10% (90% power), and diversity of 66%. The required information size was 3395 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundary for benefit (red inward sloping lines) before reaching the required information size. The green dotted line shows conventional boundaries (5.0%). The Trial Sequential Analysis-adjusted confidence interval was 0.54 to 0.69.

Sensitivity analysis

We had to impute data for three trials on the outcome of proportion of participants with detectable HBV-DNA (Lu 2004; Huang 2005; Wang 2006). 'Best-worst' and 'worst-best' case scenario meta-analyses showed that incomplete outcome data bias did not influence the results ('best-worst' meta-analysis: RR 0.60, 95% CI 0.54 to 0.67; $P < 0.00001$, $I^2 = 58\%$; 29 trials, 2944 participants; Analysis 1.11; 'worst-best' random-effects meta-analysis: RR 0.63, 95% CI 0.56 to 0.70; $P < 0.00001$, $I^2 = 57\%$; 29 trials, 2944 participants; Analysis 1.12).

GRADE and Trial Sequential Analysis assessments on imprecision for the proportion of participants with detectable HBV-DNA outcomes differed: we downgraded the evidence for imprecision by one level with GRADE because the optimal information size criteria were not met and the sample size was not very large (fewer than 4000 participants) (GRADE 2013; Schunemann 2016). If we used Trial Sequential Analysis to assess imprecision, we would not downgrade the evidence because the sequential boundary for benefit was crossed (Jakobsen 2014).

Subgroup analysis

We could not perform all of the pre-specified subgroup analyses because of insufficient data (Subgroup analysis and investigation of heterogeneity).

We found no statistically significant subgroup differences in the effect of Radix Sophorae flavescentis on the proportion of participants with detectable HBV-DNA, when trials at low risk of bias were compared to trials at high risk of bias regarding the blinding of outcome assessors domain (test for subgroup difference: $P = 0.41$, $I^2 = 0\%$; Analysis 1.13) and regarding the incomplete outcome data domain (test for subgroup difference: $P = 0.26$, $I^2 = 19.6\%$; Analysis 1.14); when trials assessing Radix Sophorae flavescentis versus no intervention were compared to trials assessing Radix Sophorae flavescentis versus placebo (test for subgroup difference: $P = 0.92$, $I^2 = 0\%$; Analysis 1.35); when trials compared different forms and means of administration of Radix Sophorae flavescentis (test for subgroup difference: $P = 0.27$, $I^2 = 22.5\%$; Analysis 1.16); when trials with treatment duration less than six months were compared to trials with treatment duration longer than six months (test for subgroup difference: $P = 0.54$, $I^2 = 0\%$; Analysis 1.27); when trials where participants who had concomitant other diseases were compared to trials where participants received the diagnosis only of chronic hepatitis B or trials with unclear status of concomitant

disease among participants (test for subgroup difference: $P = 0.17$, $I^2 = 40.3\%$; [Analysis 1.18](#)); and when trials comparing different co-interventions were compared (test for subgroup difference: $P = 0.64$, $I^2 = 0\%$; [Analysis 1.19](#)).

Publication bias

Visual inspection of the funnel plot revealed some signs of asymmetry ([Figure 6](#)). Harbord's test showed small-study effect ($P = 0.000$) ([Harbord 2006](#)). Based on visual inspection of the funnel plot and Harbord's test results, we assessed the risk of publication bias as high.

Figure 6. Funnel plot of comparison: 1 Radix Sophorae flavescens versus no intervention or placebo, outcome: 1.10 Proportion of participants with detectable HBV-DNA - overall.

Proportion of participants with detectable HBeAg

Twenty trials with 2129 participants reported data on proportions of participants with detectable HBeAg: 597/1078 (55.4%) participants in the Radix Sophorae flavescens group had detectable HBeAg versus 834/1051 (79.4%) participants in the no intervention/placebo group ([Duan 2004](#); [Huang 2004a](#); [Huang 2004b](#); [Lu 2004](#); [Huang 2005](#); [Liu 2005](#); [Li 2006](#); [Wang 2006](#); [Li 2008](#); [Xue 2008](#); [Li 2010](#); [Wei 2010](#); [Xi 2010](#); [Lv 2011](#); [Sun 2011](#); [Zhang 2011a](#); [Zhang 2011b](#); [He 2013](#); [Zhou 2013](#); [Zhang 2017](#); [Wu 2018](#); [Yang 2018](#)). Radix Sophorae flavescens showed a better effect in reducing the proportion of participants with detectable HBeAg (RR 0.71, 95% CI 0.66 to 0.76; $P < 0.00001$, $I^2 = 19\%$; [Analysis 1.20](#)).

Trial Sequential Analysis

We calculated the DARIS to be 751 participants based on an event rate in the control group of 79.4%, a risk ratio reduction of 15%, a two-sided alpha of 5.0%, a beta of 10%, and observed diversity of 23%. Trial Sequential Analysis showed that the Z-curve crossed the boundary for benefit and the required information size. This indicates that comparison of Radix Sophorae flavescens versus no intervention/placebo results in a 15% risk ratio reduction in detectable HBeAg. The Trial Sequential Analysis-adjusted CI was 0.66 to 0.76 ([Figure 7](#)).

Figure 7. Trial Sequential Analysis on proportion of participants with detectable HBeAg in 20 high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 79.4%, risk ratio reduction of 15%, type I error of 5%, type II error of 10% (90% power), and diversity of 23%. The required information size was 751 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundary for benefit (red inward sloping lines), as well as the required information size. The green dotted line shows conventional boundaries (5.0%). The Trial Sequential Analysis-adjusted confidence interval was 0.66 to 0.76.

Sensitivity analysis

We had to impute data for three trials on the outcome of proportion of participants with detectable HBeAg (Lu 2004; Huang 2005; Wang 2006). 'Best-worst' and 'worst-best' case scenario meta-analyses showed that incomplete outcome data bias did not influence the results ('best-worst' random-effects meta-analysis: RR 0.70, 95% CI 0.65 to 0.74; $P < 0.00001$, $I^2 = 23\%$; 20 trials; 2159 participants; Analysis 1.21; 'worst-best' random-effects meta-analysis: RR 0.72, 95% CI 0.67 to 0.78; $P < 0.00001$, $I^2 = 33\%$; 20 trials; 2159 participants; Analysis 1.22).

GRADE and Trial Sequential Analysis assessments on imprecision for the proportions of participants with detectable HBeAg outcomes differed: we downgraded the evidence for imprecision by one level with GRADE because the optimal information size criteria were not met and the sample size was not very large (fewer than 4000 participants) (GRADE 2013; Schunemann 2016). If we used Trial Sequential Analysis to assess imprecision, we would not downgrade the evidence because the sequential boundary for benefit was crossed (Jakobsen 2014).

Subgroup analysis

We could not perform all of the pre-specified subgroup analyses because we had insufficient data (Subgroup analysis and investigation of heterogeneity).

We found no statistically significant subgroup differences when trials at low risk of bias were compared to trials at high risk of bias regarding the blinding of outcome assessors domain (test for subgroup difference: $P = 0.95$, $I^2 = 0\%$; Analysis 1.23) and regarding the incomplete outcome data domain (test for subgroup difference: $P = 0.42$, $I^2 = 0\%$; Analysis 1.24); when trials on Radix Sophorae flavescens versus no intervention were compared to trials on Radix Sophorae flavescens versus placebo (test for subgroup difference: $P = 0.27$, $I^2 = 18.1\%$; Analysis 1.25); when trials comparing different forms and means of administration of Radix Sophorae flavescens were compared (test for subgroup difference: $P = 0.39$, $I^2 = 0.1\%$; Analysis 1.26); when trials with treatment duration less than six months were compared to trials with treatment duration longer than six months (test for subgroup difference: $P = 0.13$, $I^2 = 57.4\%$; Analysis 1.43); when trials with participants with concomitant other diseases were compared to trials in which participants received only the diagnosis of chronic hepatitis B or trials with unclear status of concomitant disease of participants (test for subgroup difference: $P = 0.17$, $I^2 = 43.6\%$; Analysis 1.28); and

when trials comparing different co-interventions were compared (test for subgroup difference: $P = 0.64$, $I^2 = 0\%$; [Analysis 1.29](#)).

Publication bias

Visual inspection of the funnel plot revealed no signs of asymmetry ([Figure 8](#)). Harbord's test showed no small-study effects ($P = 0.45$)

([Harbord 2006](#)). Based on visual inspection of the funnel plot and Harbord's test results, we determined that the risk of publication bias might be low.

Figure 8. Funnel plot of comparison: 1 Radix Sophorae flavescentis versus no intervention or placebo, outcome: 1.20 Proportion of participants with detectable HBeAg - overall.

Separately reported adverse events considered 'not to be serious'

In keeping with our protocol, we had to present the results of dichotomous outcomes from one trial, using Fisher's exact test. Due to the limitations of the algorithm, we were unable to calculate Fisher's statistic for values for digestive symptoms, dizziness and fatigue, and increased serum phosphorus; instead, we performed χ^2 tests. As the results derived from Fisher's exact tests/ χ^2 tests (not shown) did not differ from those obtained via RevMan analysis, and in view of future updates of the review, we present here only the analysis results obtained via RevMan.

- **Proportion of participants with nausea:** only one trial with 132 participants provided these results; thus the direction of effect of Radix Sophorae flavescentis on proportion of participants with nausea is still unclear (RR 2.51, 95% CI 0.10 to 60.43; $P = 0.57$; [Analysis 1.30](#)) ([Yan 2011](#)).
- **Proportions of participants with nausea and vomiting:** two trials with 186 participants reported the data on proportions of participants with nausea and vomiting; therefore the direction

of effect of Radix Sophorae flavescentis on this outcome remains unclear (RR 0.62, 95% CI 0.12 to 3.13; $P = 0.56$, $I^2 = 50\%$; [Analysis 1.31](#)) ([Su 2014](#); [Ye 2015](#)).

- **Proportion of participants with upper abdomen discomfort:** only one trial with 132 participants reported these results; thus the direction of effect of Radix Sophorae flavescentis on proportion of participants with upper abdomen discomfort is still unclear (RR 1.67, 95% CI 0.15 to 17.93; $P = 0.67$; [Analysis 1.32](#)) ([Yan 2011](#)).
- **Proportion of participants with digestive symptoms:** one trial with 80 participants showed that Radix Sophorae flavescentis was associated with higher risk of digestive symptoms (RR 1.47, 95% CI 1.00 to 2.16; $P = 0.05$; [Analysis 1.33](#)) ([Li 2006](#)).
- **Proportions of participants with loss of appetite:** three trials with 320 participants showed no evidence of a difference with Radix Sophorae flavescentis on proportions of participants with loss of appetite (RR 0.82, 95% CI 0.30 to 2.21; $P = 0.70$, $I^2 = 84\%$; [Analysis 1.34](#)) ([Liu 2005](#); [Xi 2010](#); [Sun 2011](#)).
- **Proportions of participants with abdominal distension:** two trials with 225 participants reported data on proportions of

participants with abdominal distension, indicating that Radix Sophorae flavescentis may be associated with lower risk of abdominal distension when compared with control (RR 0.29, 95% CI 0.14 to 0.62; $P = 0.001$, $I^2 = 0\%$; [Analysis 1.52](#)) (Liu 2005; Sun 2011).

- **Proportions of participants with diarrhoea:** two trials with 192 participants showed no evidence of a difference with Radix Sophorae flavescentis in proportions of participants with diarrhoea (RR 1.27, 95% CI 0.33 to 4.92; $P = 0.73$, $I^2 = 0\%$; [Analysis 1.36](#)) (Ye 2015; Yang 2018).
- **Proportions of participants with dizziness and headache:** three trials with 288 participants showed no evidence of a difference with Radix Sophorae flavescentis on proportions of participants with dizziness and headache (RR 0.70, 95% CI 0.27 to 1.81; $P = 0.47$, $I^2 = 0\%$; [Analysis 1.37](#)) (Ye 2015; Luo 2018; Yang 2018).
- **Proportion of participants with dizziness and fatigue:** only one trial with 86 participants reported the direction of effect of Radix Sophorae flavescentis on the proportion of participants with dizziness and fatigue; thus this finding remains unclear (RR 0.33, 95% CI 0.07 to 1.56; $P = 0.16$; [Analysis 1.38](#)) (Su 2014).
- **Proportions of participants with fatigue:** six trials with 596 participants reported data on the proportions of participants with fatigue; Radix Sophorae flavescentis may be associated with higher risk of fatigue when compared with control (RR 1.45, 95% CI 1.13 to 1.86; $P = 0.003$, $I^2 = 0\%$; [Analysis 1.39](#)) (Liu 2005; Li 2006; Xi 2010; Sun 2011; Ye 2015; Luo 2018).
- **Proportions of participants with fever:** three trials with 288 participants showed no evidence of a difference with Radix Sophorae flavescentis on proportions of participants with fever (RR 1.63, 95% CI 0.60 to 4.46; $P = 0.34$, $I^2 = 0\%$; [Analysis 1.40](#)) (Ye 2015; Luo 2018; Yang 2018).
- **Proportion of participants with rash:** because only one trial with 100 participants reported this outcome, the direction of effect of Radix Sophorae flavescentis on the proportion of participants with rash is still unclear (RR 0.50, 95% CI 0.05 to 5.34; $P = 0.57$; [Analysis 1.41](#)) (Ye 2015).
- **Proportion of participants with yellow urine:** researchers found that Radix Sophorae flavescentis may be associated with higher risk of yellow urine; however, because only one trial with 80 participants reported these results, we are not certain of the effect (RR 1.89, 95% CI 1.31 to 2.73; $P = 0.0007$; [Analysis 1.42](#)) (Li 2006).
- **Proportion of participants with creatine kinase increase:** only one trial with 86 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with creatine kinase increase is still unclear (RR 0.33, 95% CI 0.04 to 3.08; $P = 0.33$; [Analysis 1.51](#)) (Su 2014).
- **Proportion of participants with serum creatinine increase:** only one trial with 86 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with creatinine increase remains unclear (RR 0.33, 95% CI 0.04 to 3.08; $P = 0.33$; [Analysis 1.44](#)) (Su 2014).
- **Proportion of participants with increased serum phosphorus:** only one trial with 86 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with phosphorus

increase is still unclear (RR 0.20, 95% CI 0.02 to 1.64; $P = 0.13$; [Analysis 1.45](#)) (Su 2014).

- **Proportion of participants with liver pain:** four trials with 400 participants reported data on proportions of participants with liver pain; we did not find evidence of a difference in effect of Radix Sophorae flavescentis on this outcome (RR 0.99, 95% CI 0.45 to 2.19; $P = 0.98$; [Analysis 1.46](#)) (Liu 2005; Li 2006; Xi 2010; Sun 2011).
- **Proportion of participants with hepatomegaly:** only one trial with 80 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with hepatomegaly is still unclear (RR 0.69, 95% CI 0.28 to 1.70; $P = 0.42$; [Analysis 1.47](#)) (Liu 2005).
- **Proportion of participants with jaundice:** only one trial with 95 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with jaundice is still unclear (RR 2.66, 95% CI 1.03 to 6.86; $P = 0.04$; [Analysis 1.48](#)) (Xi 2010).
- **Proportion of participants with splenomegaly:** only one trial with 80 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with splenomegaly remains unclear (RR 0.96, 95% CI 0.35 to 2.67; $P = 0.94$; [Analysis 1.49](#)) (Liu 2005).
- **Proportion of participants with muscle pain:** only one trial with 96 participants reported on this outcome; thus the direction of effect of Radix Sophorae flavescentis on the proportion of participants with muscle pain is still unclear (RR 0.33, 95% CI 0.01 to 7.98; $P = 0.50$; [Analysis 1.50](#)) (Luo 2018).

'Summary of findings' tables

We planned to construct a 'Summary of findings' table for all primary and secondary outcomes ([Primary outcomes](#); [Secondary outcomes](#)). However, because of lack of data, we listed all outcomes but could perform our GRADE assessment only on the outcome of the proportion of participants with one or more adverse events considered 'not to be serious'. Our data were derived from 19 trials assessing Radix Sophorae flavescentis versus no intervention/placebo (Duan 2004; Lu 2004; Liu 2005; Li 2006; Wang 2006; Li 2008; Li 2010; Wei 2010; Xi 2010; Lv 2011; Sun 2011; Yan 2011; He 2013; Su 2014; Ye 2015; Zhang 2017; Luo 2018; Wu 2018; Yang 2018). Post hoc, we decided to present the results on our surrogate outcomes of proportion of participants with detectable HBV-DNA and proportion of participants with detectable HBeAg because physicians consider administration of Radix Sophorae flavescentis helpful in decreasing discomfort and preventing replication of the virus in people with chronic hepatitis B.

[Summary of findings for the main comparison](#) presents details on how we assessed the evidence. We have defined the certainty of evidence for all outcomes with data as very low.

DISCUSSION

Summary of main results

This review included a total of 35 randomised clinical trials with 3556 participants. All trials were assessed at high risk of bias. For our meta-analyses, we could gather quantitative data from 29 out of the 35 trials. One trial compared Radix Sophorae flavescentis versus placebo, and the other 34 trials compared Radix Sophorae flavescentis plus co-intervention versus a similar

co-intervention. One trial assessed all-cause mortality; no deaths occurred. Ten trials assessed serious adverse events; no serious adverse events occurred. None of the included trials aimed to assess health-related quality of life, hepatitis B-related mortality, or hepatitis B-related morbidity. The evidence on the proportion of participants with one or more adverse events considered 'not to be serious', based on data from 19 randomised clinical trials (nine trials had zero events in both groups), showed no evidence of a difference. Trial Sequential Analysis suggested that more information is needed. Subgroup analysis showed that intravenous infusion might increase the risk of adverse events when compared to oral administration and when compared to combined ways of administering Radix Sophorae flavescentis. This might be a reason for the significant 49% heterogeneity shown in the meta-analysis. A sensitivity analysis on imprecision showed no evidence of a difference between GRADE imprecision assessments and Trial Sequential Analysis imprecision assessments (Castellini 2018; Gartlehner 2018). The 'best-worst' and 'worst-best' analyses did not show that there was impact of missing data on the results. We could not prepare the funnel plot as we included no more than 10 trials in the meta-analysis. Regarding our surrogate outcomes - the proportion of participants with detectable hepatitis B virus (HBV)-deoxyribonucleic acid (DNA) and the proportion of participants with detectable hepatitis B e-antigen (HBeAg) - meta-analyses showed evidence of a difference in these two outcomes favouring Radix Sophorae flavescentis. Trial Sequential Analyses confirmed the results. None of the subgroup analyses found evidence of a difference in the effects of Radix Sophorae flavescentis on proportion of participants with detectable HBV-DNA nor on the proportion of participants with detectable HBeAg regarding trial quality and pre-specified clinical factors. Sensitivity analyses showed no impact of missing data on the results. Regarding our surrogate outcomes on adverse events considered 'not to be serious', analysed separately, we found that Radix Sophorae flavescentis was associated with lower risk of abdominal distension and higher risk of digestive symptoms, fatigue, yellow urine, and jaundice; we found no evidence of a difference regarding other adverse events.

Overall completeness and applicability of evidence

We searched for published and unpublished trials irrespective of publication type, publication date, and language. We also searched reference lists of relative reviews for any trials we might have missed. Overall, we included 35 completed randomised clinical trials in our systematic review. We found no unpublished or ongoing trials comparing Radix Sophorae flavescentis with no intervention or placebo randomising people with chronic hepatitis B. In addition, 432 studies provided no description of the random generation method used. Contacting study authors did not lead to complete information. Because it was uncertain whether these trials were indeed randomised, we displayed the summary of these 432 studies in an online Appendix, and urged study authors to contact us if their trial was indeed a properly randomised trial.

Participants included in the 35 trials generally represented the characteristics of the general chronic hepatitis B population. Two trials included an adolescent population (under 14 years old). Two trials recruited participants with cirrhosis. The included trials covered oral capsules, oral tablets, intravenous infusion, intramuscular injection, acupoint injection, and various ways of administering Radix Sophorae flavescentis with a variety

of treatment durations ranging from 1 month to 24 months. We found no strong evidence to show that the effects we observed were influenced by type or duration of Radix Sophorae flavescentis administration. We could find limited evidence on patient-centred outcomes and could perform meta-analyses only on adverse events considered 'not to be serious'. Data from 19 trials showed no evidence of a difference with Radix Sophorae flavescentis on adverse events considered 'not to be serious'. In contrast, we obtained beneficial results on surrogate outcomes such as proportion of participants with detectable HBV-DNA and proportion of participants with detectable HBeAg in the serum (regarded only as hypothesis-generating outcomes), and unless these outcomes become validated, we cannot be certain of their effects. We also conducted subgroup analyses and sensitivity analyses in an attempt to identify differences in treatment effects, depending on pre-defined clinical factors.

Quality of the evidence

Lack or insufficiency of clinically relevant data is a serious limitation of our review and findings. Below, we describe our assessments for each of the five GRADE factors.

Within-study risk of bias

Risk of bias is known to be responsible for overestimation of intervention benefits and underestimation of harms in randomised clinical trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018). Of the 35 randomised clinical trials, all (100%) used adequate generation of randomisation sequence, but only two trials (6%) had adequate allocation concealment; only one (3%) had blinding of participants, and four (11%) had binding of outcome assessments; 27 (77%) appeared to be uninfluenced by incomplete outcome data; none (0%) appeared to be free from selective reporting; and all appeared to be free from other bias. Therefore, we considered all trials to be at high risk of bias.

Indirectness of the evidence

All of the trials included in our review assessed Radix Sophorae flavescentis in a chronic hepatitis B population. We found trial participants to be similar to a clinical population. Hence, we found no serious problems in indirectness of the evidence.

Heterogeneity or inconsistency of results

We explored statistical heterogeneity using the Chi² test, and we quantified heterogeneity using the I² statistic (Higgins 2002). We observed moderate statistical heterogeneity regarding the outcome adverse events considered 'not to be serious' (I² = 49%). We performed subgroup analyses regarding trial quality, forms and ways of administering Radix Sophorae flavescentis, duration of treatment, control intervention, co-intervention, and concomitant diseases of participants, in an attempt to explain heterogeneity. Subgroup tests did not indicate any statistical differences, except when trials with different forms and ways of administering Radix Sophorae flavescentis were compared, which showed that intravenous infusion of Radix Sophorae flavescentis significantly increased the risk of adverse events compared to oral capsules and mixed administration methods (Analysis 1.6). This might be a reason for the obvious heterogeneity.

We considered the proportion of participants with detectable HBV-DNA outcomes to have a substantial level of heterogeneity ($I^2 = 56\%$) and the proportion of participants with detectable HBeAg outcomes to have minor heterogeneity ($I^2 = 19\%$). Our attempts to analyse heterogeneity through subgroup analyses while taking into consideration the adequacy of blinding of outcome assessment and incomplete outcome data reporting, as well as pre-specified clinical factors, did not reveal the sources of heterogeneity. However, one explanation could be that the included trials were small.

We applied both fixed-effect and random-effects meta-analysis models, and we found the results of these two models to be consistent with all outcome results.

Imprecision of results

Following the GRADE criteria for assessment of imprecision, we downgraded the evidence by two levels for the proportion of participants with one or more adverse events considered 'not to be serious' outcome because the number of events was less than 300 and the confidence interval (CI) overlapped no effect, failing to exclude important harm (risk ratio (RR) > 1.25); for the proportion of participants with the detectable HBV-DNA outcome, we downgraded the evidence by one level because optimal information size criteria were not met and the sample size was not very large (fewer than 4000 participants); for the proportion of participants with the detectable HBeAg outcome, we downgraded the evidence by one level because optimal information size criteria were not met and the sample size was not very large (fewer than 4000 participants) (GRADE 2013; Schunemann 2016).

We also performed Trial Sequential Analysis to assess imprecision and found that results were consistent with the GRADE assessment for the proportion of participants with the one or more adverse events considered 'not to be serious' outcome; we downgraded the evidence for imprecision by two levels because none of the sequential boundaries for benefit, harm, or futility were crossed. However, for the proportion of participants with the detectable HBV-DNA outcome and the proportion of participants with the detectable HBeAg outcome, we did not downgrade the evidence for imprecision because the trial sequential boundary for benefit was crossed (Jakobsen 2014).

Risk of publication bias

We could not construct the funnel plot on adverse events considered 'not to be serious', because no more than 10 trials provided usable data. The funnel plot constructed on the outcome detectable HBV-DNA showed some signs of asymmetry, and Harbord's test showed a small-study effect. We assessed the risk of publication bias as high. For the proportion of participants with the detectable HBeAg outcome, the risk of publication bias might be low based on the funnel plot with no signs of asymmetry and Harbord's test showing no small-study effect.

Additionally, we used an error matrix tool to assess the validity of the included randomised clinical trials (Keus 2010), and we found that all 35 trials were at high risk of systematic errors, at moderate or high risk of random errors, and at high risk of design errors (Liang 2018b).

Potential biases in the review process

We performed our systematic review based on recommended methodology (Higgins 2011; GRADE 2013; Cochrane Hepato-Biliary Group Module). We followed our pre-published and peer-reviewed protocol with pre-defined participants, interventions, comparisons, and outcomes to avoid biases in the review process (Liang 2018a). We performed comprehensive search strategies that covered published and unpublished studies, and we combined electronic data searches with manual searches of the reference lists of identified review publications. We included trials regardless of language of publication, and regardless of whether they reported data on the outcomes we needed. We contacted relevant study authors for additional information. We extracted all available data to perform our pre-defined analyses, including Trial Sequential Analysis and several subgroup analyses. We also tested the robustness of our results by performing sensitivity analyses ('best-worst', 'worst-best', 'zero event' trials).

Unpublished trials with negative results, which we did not identify during preparation of this review, are a possible source of bias. We have in the online Appendix listed the 432 trials that did not clearly report the randomisation method used. Our attempts to receive information from the authors of these 432 trials failed for the reasons listed in the online Appendix. Previous studies have demonstrated misuse of randomisation in Chinese medicine trials, which might significantly influence the quality of clinical evidence (Liu 2002a; Wu 2009). Thus, we did not include these 432 trials for analysis at this stage and will not include them until necessary methodology information is supplemented. On the other hand, there is a possibility that some true randomised trials were limited by poor reporting; therefore we might 'throw the baby out with the bathwater'. Trial authors should realise the importance of research promotion and should report the trial clearly, provide effective contact information in the publication, respond actively to inquiries, and thus reduce research waste (Chalmers 2009; Al-Shahi Salman 2014; Chalmers 2014; Glasziou 2014; Ioannidis 2014; Macleod 2014; Moher 2016).

All the trials we have identified, were carried out in China. It could be because *Radix Sophorae flavescentis* is mostly used in Asian countries. Although we have designed explicit strategies to search for all available trials, no matter the language, our search strategies might not have identified studies published in languages other than Chinese and English. In the future, if possible, Japanese and Korean medical databases should also be searched, and experts asked to find out if there are more studies on this topic.

Observational studies may provide information on rare late-occurring adverse events and health-related quality of life, which are outcomes of our interest. We planned to consider quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms of *Radix Sophorae flavescentis* if retrieved with our searches for randomised clinical trials. Four-hundred thirty-two studies, that are on the waiting list due to lack of information on trial design, might be a valuable source of data on adverse events. Our decision not to search all observational studies and not to assess potential data on adverse events from studies on the waiting list may bias our reviews towards assessment of benefits and might overlook certain harms such as late or rare harms. This decision may currently appear less problematic as we have found no beneficial effect of *Radix Sophorae flavescentis* on patient-centred outcomes in this review.

Moreover, to conduct a systematic review of observational studies on harms of *Sophora flavescens* is desirable.

Another possible limitation of our review could be that we did not define a minimum duration of treatment with *Radix Sophorae flavescens*. We did this to avoid arbitrary choice of a cut-off value. We have, instead, in subgroup tests, analysed whether the intervention effect was influenced by the duration of treatment. These analyses showed no difference when trials with *Radix Sophorae flavescens* interventions for six months or longer were compared to trials with the intervention for less than six months. Subgroups regarding duration of treatment were divided according to our pre-defined definitions using median as the cut-off value, but this choice of cut-off value might be questionable.

We have included a number of subgroup analyses and numerous outcomes. There could have been problems with multiplicity in terms of the seven subgroup analyses conducted for each outcome (Imberger 2011). We did not adjust the threshold for subgroups analyses, as we considered subgroup analysis results as exploratory and only hypothesis-generating.

Another potential limitation of this review involved dealing with adverse events. We used the proportion of participants with one or more adverse events at maximum follow-up for measurement. For trials reporting adverse events, we selected the highest number of events among the separately reported number of events that had occurred in experimental or control groups for calculation. This may have been problematic, as it might have led to underestimation of adverse events. Furthermore, the different events for this composite outcome often have different severity, such as headache compared to hepatomegaly, so that even with a neutral result, there might be in reality a significant difference in severity between groups. Using composite outcomes increases power, but the limitations as mentioned here must be considered when review results are interpreted.

In this review, we hoped to be able to assess the benefits and harms of *Radix Sophorae flavescens* compared with matching placebo for patient-centred outcomes in people with chronic hepatitis B. However, we included only one trial comparing *Radix Sophorae flavescens* with placebo. Thirty-four trials assessed the effects of *Radix Sophorae flavescens* in addition to a co-intervention compared to a co-intervention alone. In our primary analysis including both types of trials, it is assumed that no interaction occurred between the co-intervention and the *Radix Sophorae flavescens*. If no interaction occurred, the effects of the co-intervention will even out between groups, and trial results will reflect the effects of *Radix Sophorae flavescens*. If there is interaction, however, it will be essential to show such interaction (e.g. in subgroup analyses).

This review is inconclusive, as the evidence of any effect - benefit or harm - remains uncertain. This result is surely due to the poor design and reporting of the included trials. However, there could also have been problems with a relatively 'broad' review question. So it is important to conduct certain subgroup analyses to deal with these problems.

Agreements and disagreements with other studies or reviews

We found seven published reviews with meta-analyses of *Radix Sophorae flavescens* for people with chronic hepatitis B (Liu 2003b; Wu 2011b; He 2013; Jiang 2013; Qi 2013; Song 2016; Wang 2017).

Both Liu 2003b and Wu 2011b tried to assess the effects of *Radix Sophorae flavescens* compared with placebo, no intervention, or antiviral drugs (e.g. interferon, adefovir, lamivudine). Both reviews showed beneficial effects of *Radix Sophorae flavescens* on surrogate outcomes detectable HBV-DNA and detectable HBeAg. No data were obtained on quality of life and adverse events. Only one randomised trial reported mortality and showed that oxymatrine plus hepatocyte growth factor in addition to basic treatment reduced mortality compared with basic treatment alone (36.4% (8/22) with combination treatment vs 73.3% (11/15) with basic treatment alone) (Liu 2003b). Moreover, Liu 2003b used the Jadad score to assess methodological quality (this is now abandoned) (Higgins 2011).

He 2013 compared the effects of *Radix Sophorae flavescens* plus lamivudine versus lamivudine monotherapy; the combination therapy showed better effects on reduction of HBV-DNA, HBeAg, and alanine aminotransferase levels and on development of anti-HBeAg antibodies (nine trials, 570 participants).

Qi 2013 assessed the effects of *Radix Sophorae flavescens* administered for at least six months plus entecavir versus entecavir alone for HBeAg-positive chronic hepatitis B. Participants with the diagnosis of chronic hepatitis B could not have had other concomitant diseases. The combination therapy showed a better effect on reduction of HBV-DNA, HBeAg, and alanine aminotransferase levels and on development of anti-HBeAg antibodies (10 trials, 756 participants).

Jiang 2013 and Wang 2017 assessed the add-on effect of *Radix Sophorae flavescens* to interferon, and showed a better effect of combination therapy on reduction of HBV-DNA and HBeAg. Jiang 2013 also showed beneficial effects of combination therapy on liver fibrosis (26 trials, 2068 participants). Wang 2017 showed that combination therapy had lower risks of leucopenia and thrombocytopenia but was no different with interferon monotherapy regarding influenza-like symptoms. Both reviews applied unjustified language restrictions when searching the literature (Jiang 2013; Wang 2017).

Song 2016 focused only on oral *Radix Sophorae flavescens*, excluded trials with participants with other concomitant diseases, and included only trials with full-text publications. The results showed that *Radix Sophorae flavescens* was associated with significant effects on clearance of HBV-DNA and hepatitis B virus surface antigen, and it was beneficial for liver function improvement when compared to no intervention/placebo (52 trials, 5227 participants).

These reviews were limited by primarily focusing on surrogate outcomes, not using rigorous methodology, and having high risk of bias of the included trials without taking that into consideration. Compared with the risk of bias tool used in the seven identified reviews, we found that our bias risk assessment tool is more rigorous. We did not use scores to assess bias risk, as this is

the case with the Jadad scale, and we used more domains to assess possible risk of reporting bias. We used Trial Sequential Analyses to control random errors, and we performed GRADE assessments to define the certainty of evidence. In our review, we found one trial reporting that no one died in both Radix Sophorae flavescentis and control groups and 10 trials reporting that no serious adverse events had occurred in both groups. We found no evidence of a difference between Radix Sophorae flavescentis and no intervention/placebo on adverse events considered 'not to be serious'. The Trial Sequential Analysis indicated that more information is needed. Our results on the surrogate outcomes detectable HBV-DNA and detectable HBeAg were in agreement with those of previously published reviews, which showed a better effect of Radix Sophorae flavescentis on reduction of these outcomes compared to no intervention/placebo. The certainty of the evidence was very low, and the benefits and harms of Radix Sophorae flavescentis remain vague.

AUTHORS' CONCLUSIONS

Implications for practice

The included trials lacked data on health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity. The effects of Radix Sophorae flavescentis on all-cause mortality, proportion of participants with serious adverse events, and adverse events considered 'not to be serious' remain unclear. We advise caution in interpreting the results of Radix Sophorae flavescentis showing reduction in the proportion of people with detectable HBV-DNA and detectable HBeAg, because these trials are at high risk of bias, and both outcomes are non-validated surrogate outcomes (hypothesis-generating). As we were unable to obtain information on a large number of trials regarding their design and conduct, we were deterred from including them in our review. Undisclosed funding might have influenced trial results and led to poor trial design.

Implications for research

In view of the wide usage of Radix Sophorae flavescentis, large, unbiased, high-quality, placebo-controlled randomised trials with proper design are needed, in which patient-centred outcomes are assessed (Brown 2006).

Evidence (what is the current state of the evidence)?

We included 35 randomised clinical trials involving 3556 participants. All trials were assessed at high risk of bias, and the certainty of evidence was assessed as very low. In total, 432 trials failed to provide the randomisation method used, and we will need supplementary methodology information before we can include them in future updates of this review. Only one trial assessed Radix Sophorae flavescentis versus placebo, and the remaining 34 trials assessed the effects of Radix Sophorae flavescentis plus a co-intervention versus a similar co-intervention alone. Very few data were provided on clinical important outcomes including mortality, health-related quality of life, adverse events, and hepatitis B-related morbidity. We found no evidence of a difference between Radix Sophorae flavescentis versus no intervention/placebo on adverse events considered 'not to be serious'. Also, the fact that the diversity-adjusted required information size (DARIS) was not reached indicates that more randomised clinical trials are needed. The evidence shows beneficial effects of Radix Sophorae flavescentis on the outcomes proportion of participants with

detectable HBV-DNA and proportion of participants with detectable HBeAg; however, these surrogate outcomes were not validated, and the evidence was of very low certainty.

Participants (what is the population of interest)?

Our review focused on people with chronic hepatitis B. Two trials included children up to 14 years old (Xie 2010; Zhang 2011a), and two trials assessed participants with concomitant cirrhosis (Xie 2010; Zhang 2017). Subgroup analyses showed no differences when trials where participants had concomitant diseases were compared to trials where participants received only the diagnosis of chronic hepatitis B, or where information on concomitant diseases was unclear. However, the certainty of evidence was very low; therefore we are very uncertain about this finding. Future trials should be well designed and should clearly report the effects of Radix Sophorae flavescentis in varied groups of people. When concomitant diseases are present, stratified randomisation should be employed.

Interventions (what are the interventions of interest)?

Our review covered oral capsules, oral tablets, intravenous infusion, intramuscular injection, acupoint injection, and mixed forms and administration ways of Radix Sophorae flavescentis, with treatment duration ranging from one month to 24 months. Subgroup analysis by comparing trials with different forms and administration ways suggested that intravenous infusion of Radix Sophorae flavescentis might increase the risk of adverse events considered 'not to be serious' compared to oral capsules and mixed administration ways. Subgroup analyses comparing trials with treatment duration longer than six months versus trials with treatment duration less than six months showed no difference in the effects of Radix Sophorae flavescentis. However, because we identified few trials and because we found very low-certainty evidence, future randomised clinical trials should be designed to look for differences between different forms, administration ways, and treatment durations for Radix Sophorae flavescentis.

Comparisons (what are the comparisons of interest)?

In this review, we hoped to be able to assess the benefits and harms of Radix Sophorae flavescentis compared with matching placebo for patient-centred outcomes in people with chronic hepatitis B. However, we included only one trial comparing Radix Sophorae flavescentis versus placebo. Randomised clinical trials comparing Radix Sophorae flavescentis versus matching placebo are needed. Thirty-four trials assessed the effects of Radix Sophorae flavescentis in addition to a co-intervention compared to a co-intervention alone. In our primary analysis including both types of trials, it is assumed that there is no interaction between the co-intervention and Radix Sophorae flavescentis. If there is no interaction, the effects of the co-intervention will even out between groups, and trial results will reflect the effects of Radix Sophorae flavescentis. If there is interaction, it will be essential to show such interaction (e.g. in subgroup analyses). Hence, there is a need for both trials comparing Radix Sophorae flavescentis with placebo and trials comparing Radix Sophorae flavescentis with a co-intervention and with a similar co-intervention.

We will discuss the comparison between Radix Sophorae flavescentis and other antiviral drugs in another Cochrane systematic review (Liang 2018a).

Outcomes (what are the outcomes of interest)?

The primary outcomes planned to be assessed in this review (all-cause mortality, proportion of participants with one or more serious adverse events, and quality of life) should be included as primary outcomes in all future trials. Future randomised clinical trials also need to validate the relationship between surrogate outcomes and patient-centred outcomes.

Time stamp (date of recommendation)

October 2018

Further randomised clinical trials ought to be designed according to the SPIRIT standards ([Chan 2013](#)), and should be reported according to the CONSORT standards ([Moher 2001](#)).

ACKNOWLEDGEMENTS

We acknowledge the great help of the Information Specialist for the Cochrane Hepato-Biliary Group, Sarah Klingenberg, in designing the search strategies. We also acknowledge Dr. L. Susan Wieland

of the Cochrane Complementary Medicine Field (USA), who co-ordinated the peer review process.

Peer reviewers: Zhao-Xiang Bian, China

Contact editor: Giovanni Casazza, Italy

Associate editor: Liz Bickerdike, UK

Sign-off editor: Agostino Colli, Italy

Cochrane Review Group funding acknowledgement: The Danish State is the largest single founder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. Disclaimer: the views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

This work was partially funded by Grant Number R24 AT001293 from the National Center for Complementary and Integrative Health (NCCIH). The contents of this systematic review are solely the responsibility of the authors and do not necessarily represent the official views of the NCCIH or the National Institutes of Health.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chai 2018

Methods	Randomised clinical trial, China Parallel-group design
Participants	90 participants with diagnosis of chronic hepatitis B with HBV-DNA level higher than 1×10^4 copies/ mL, abnormal liver function indexes, 25 to 65 years old, and had not used hormone and immune inhibitors during the past 6 months Male:Female = 52:38 Mean age: 49.2 years (experimental group), 48.5 years (control group) Exclusion criteria: malignant tumour, acute infection, and heart-kidney dysfunction; abnormal coagulation; thyroid dysfunction; history of abdominal surgery and congenital malformation of chest and abdomen; cannot co-operate with researchers
Interventions	Experimental intervention: kushensu injection, 500 mg, once daily, intravenous infusion, 6 months (n = 45) Control intervention: no intervention (n = 45) Co-intervention: recombinant interferon α -2b, intramuscular injection, 5M IU, once daily, 6 months
Outcomes	HBV-DNA; liver function tests (ALT level, AST level); liver fibrosis tests (IVC, LN, HA)
Notes	Study dates: January 2014 to January 2017 Funding information: the study authors stated that researchers had no conflicts of interest. Notes: we contacted study authors on 26 December 2018 by phone, but no one answered the phone
Risk of bias	
Bias	Authors' judgement Support for judgement

Chai 2018 (Continued)

Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescens</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Duan 2004

Methods	Randomised clinical trial, China Parallel-group design
Participants	120 participants with diagnosis of chronic hepatitis B for longer than 6 months and with HBV-DNA positive and HBeAg positive in serum according to Chinese guidelines 2000 (CMA 2000) Male:Female = 80:40 Mean age: 35 years Exclusion criteria: not stated
Interventions	Experimental intervention: oxymatrine, 600 mg, once daily, intravenous infusion, 2 months; then oxymatrine, 200 mg, 3 times daily, oral administration, 4 months (n = 60) Control intervention: no intervention (n = 60) Co-intervention: lamivudine, 100 mg, once daily, oral administration, 6 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function test (ALT level)
Notes	Study dates: November 2001 to June 2002 Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 18 April 2018 by phone. Study authors said they could not remember the details, as it was a long time ago

Risk of bias

Duan 2004 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; the number of participants analysed was equal to the number of participants randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Gao 2003

Methods	Randomised clinical trial, China Parallel-group design
Participants	80 participants with diagnosis of chronic hepatitis B who had not used any antiviral drugs before Male:Female = 68:12 Age: 30 years (experimental group), 28 years (control group) Exclusion criteria: concomitant with hepatitis C virus infection, schistosomiasis, hyperlipidaemia; serum bilirubin > 51 µmol/ L; long-term drinking history
Interventions	Experimental intervention: kushensu, 600 mg, intramuscular injection, once daily, 3 months; then kushensu, every other day, 3 months (n = 40) Control intervention: no intervention (n = 40) Co-intervention: glycyrrhizin, 150 mg, 3 times daily, oral administration, 6 months
Outcomes	Liver fibrosis serum markers (HA, PCIII, LN)
Notes	Study dates: not stated Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 18 April 2018 by phone, but no one answered the phone

Gao 2003 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessment of liver fibrosis serum markers was conducted by a specific person
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data was 3%. Two participants could not bear the injection pain and dropped out. No participants in the control group were reported to drop out. Dropout rate incomparable between groups
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

He 2013

Methods	Randomised clinical trial, China Parallel-group design
Participants	116 participants with diagnosis of chronic hepatitis B infection (HBeAg positive or negative type) according to Chinese guidelines 2000 (CMA 2000): HBeAg positive type defined as HBsAg, HBeAg, and HBV-DNA positive, anti-HBe negative, persistently or repeatedly elevated ALT level, or liver histological tests showing pathological lesion; HBeAg negative type defined as HBsAg and HBV-DNA positive, HBeAg negative, anti-HBe positive, persistently or repeatedly elevated ALT level, or liver histological tests showing pathological lesion Male:Female = 65:51 Mean age: 42.3 years (experimental group), 38.5 years (control group) Exclusion criteria: concomitant with other hepatic viral infection such as HCV, HDV, HAV, HEV, and HGV; liver cancer; used immunomodulatory drugs or interferon during past 6 months
Interventions	Experimental intervention: kushensu, 600 mg, 3 times daily, oral administration, 12 months (n = 54) Control intervention: no intervention (n = 62) Co-intervention: lamivudine tablets, 100 mg each day, oral administration; plus adefovir capsules, 10 mg each day, oral administration, 12 months

He 2013 (Continued)

Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBeAg sero-conversion; liver function test (ALT level)	
Notes	Study dates: February 2007 to February 2012 Funding information: the study was supported by hospital funding. Notes: we contacted study authors on 1 June 2018 by phone and received their reply on missing data	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors allocated participants by tossing a coin
Allocation concealment (selection bias)	Low risk	Study authors used a sealed opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors mentioned that surrogate outcomes were assessed by nurses and by personnel in other departments, but we were unclear about outcome assessment blinding for other outcomes such as non-serious adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number of participants randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Huang 2004a

Methods	Randomised clinical trial, China Parallel-group design	
Participants	146 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBeAg positive, HBV-DNA positive, and ALT level > 100 U Male:Female = 120:26 Mean age: 35.7 years (experimental group), 39.5 years (control group) Exclusion criteria: concomitant with jaundice and other viral infection such as HAV, HCV, HDV, HEV, and HFV infection	
Interventions	<u>Comparison 1</u> Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 6 months (n = 36)	

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Huang 2004a (Continued)

Control intervention: no intervention (n = 36)

Co-intervention: liver protective drugs (e.g. silymarin, vitamin C), oral administration, 6 months

Follow-up: 6 months

Outcomes	HBV-DNA; HBeAg; liver function test (ALT level); serum TGF-β; serum liver fibrosis tests (HA, LN, IVC, PCIII); liver histology tests
Notes	<p>Study dates: June 2001 to May 2003</p> <p>Funding information: the study received no funding.</p> <p>Notes: we contacted study authors on 28 June 2018 by phone and received the reply on missing data</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	High risk	Study authors said they did not conceal the allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Study authors reported dropouts but did not remember the number and did not include those people in the analysis
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Huang 2004b

Methods	<p>Randomised clinical trial, China</p> <p>Parallel-group design</p>
Participants	<p>146 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBeAg positive, HBV-DNA positive, and ALT level > 100 U</p> <p>Male:Female = 120:26</p> <p>Mean age: 37.4 years (experimental group), 41.2 years (control group)</p>

Huang 2004b (Continued)

Exclusion criteria: concomitant with jaundice and other viral infection such as HAV, HCV, HDV, HEV, and HFV infection

Interventions	<p><u>Comparison 2</u></p> <p>Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 6 months (n = 37)</p> <p>Control intervention: no intervention (n = 37)</p> <p>Co-intervention: interferon a-2b, 5MU, intramuscular injection, every other day; plus liver protective drugs (e.g. silymarin, vitamin C), oral administration, 6 months</p> <p>Follow-up: 6 months</p>
Outcomes	HBV-DNA; HBeAg; liver function test (ALT level); serum TGF- β ; serum liver fibrosis tests (HA, LN, IVC, PCIII); liver histology tests
Notes	<p>Study dates: June 2001 to May 2003</p> <p>Funding information: the study received no funding.</p> <p>Notes: we contacted study authors on 28 June 2018 by phone and received their reply on missing information</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	High risk	Study authors said they did not conceal the allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Study authors reported dropouts but did not remember the number and did not include those people in the analysis
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Huang 2005

Methods	Randomised clinical trial, China
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Huang 2005 (Continued)

Parallel-group design

Participants	<p>120 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBeAg positive, HBV-DNA positive</p> <p>Male:Female = 80:40</p> <p>Mean age: 35.3 years (experimental group), 35.7 years (control group)</p> <p>Exclusion criteria: concomitant with other viral infection such as HAV, HCV, HDV, HEV, and HFV infection; had used antiviral drug or other immunomodulators during the past 6 months</p>
Interventions	<p>Experimental intervention: kushensu intravenous infusion, 600 mg, once daily, 3 months (n = 64)</p> <p>Control intervention: no intervention (n = 56)</p> <p>Co-intervention: thymosin intravenous infusion, 80 mg, once daily, plus liver protective drugs (e.g. di-ammonium glycyrrhizinate, vitamin C), 3 months</p> <p>Follow-up: 6 months</p>
Outcomes	HBV-DNA; HBeAg; liver function test (ALT level); serum TGF- β
Notes	<p>Study dates: October 2001 to January 2004</p> <p>Funding information: the study received no funding.</p> <p>Notes: we contacted study authors on 28 June 2018 by phone and received their reply on missing information</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	High risk	Study authors said they did not conceal the allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Study authors reported dropouts but did not remember the number and did not include those people in the analysis
Selective reporting (reporting bias)	High risk	We could not find the protocol; study authors did not report any of the primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Huang 2018

Methods	Randomised clinical trial, China Parallel-group design
Participants	104 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2010 (CMA 2010), who had not received antiviral or immune-modulating treatment during the past 6 months and had signed the consent for information Male:Female = 62:42 Mean age: 45.12 years (experimental group), 45.20 years (control group) Exclusion criteria: concomitant with other viral infection; heart, liver, or kidney dysfunction; allergic constitution; withdrew from the research
Interventions	Experimental intervention: oxymatrine injection, 150 mg, once daily, intravenous infusion, 6 months (n = 52) Control intervention: no intervention (n = 52) Co-intervention: entecavir, 0.5 mg, once daily, 6 months
Outcomes	Liver function tests (ALT, AST, TBIL); serum inflammatory cytokine indexes (tumour necrosis factor- α , interleukin-6, interleukin-8)
Notes	Study dates: July 2015 to June 2016 Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 26 April 2018 by phone but found the phone number did not exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for the study; study authors did not report any of the 3 primary outcomes

Huang 2018 (Continued)

Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias
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Li 2006

Methods	Randomised clinical trial, China Parallel-group design
Participants	80 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2000 (CMA 2000) Male:Female = 54:26 Age: 13 to 75 years (experimental group); 15 to 71 years (control group) Exclusion criteria: not stated
Interventions	Experimental intervention: kushensu injection, 600 mg, once daily, intravenous infusion, 2 months (n = 40) Control intervention: no intervention (n = 40) Co-intervention: diammonium glycyrrhizinate, 150 mg, intravenous infusion with 250 mL 10% glucose solution; routine liver protective drugs (e.g. intravenous infusion of vitamin C, gantaile, potassium aspartate, and magnesium aspartate), 2 months
Outcomes	Non-serious adverse events; HBV-DNA; HBeAg; liver function tests (ALT, TBIL); serum liver fibrosis tests (HA, LN, PC III, VIC)
Notes	Study dates: January 2004 to June 2005 Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 24 April 2018 by phone but found the phone number did not exist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used simple randomisation method to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias)	Low risk	No missing data; number of participants analysed was equal to number randomised

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Li 2006 (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Li 2008

Methods	Randomised clinical trial, China Parallel-group design
Participants	146 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000) Male:Female = 107:39 Mean age: 30.2 years Exclusion criteria: not stated
Interventions	Experimental intervention: kushensu, 600 mg, intravenous or intramuscular injection, once daily, 6 months (n = 70) Control intervention: no intervention (n = 76) Co-intervention: adefovir capsules, 10 mg, once daily, 6 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function test (ALT level)
Notes	Study dates: January 2005 to June 2006 Funding information: the study was funded by municipal health bureau projects. Notes: we contacted study authors on 15 August 2018 by email and received their reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors allocated participants by grabbing balls
Allocation concealment (selection bias)	High risk	Study authors did not seal the allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study authors said that researchers collected and assessed the data
Incomplete outcome data (attrition bias)	Low risk	No missing data; number of participants analysed was equal to number of participants randomised

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B (Review)

Li 2008 (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Li 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	120 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with abnormal ALT levels (< 2 times normal level), HBeAg positive, HBV-DNA > 10 ⁵ copies/ mL, unwilling to take liver biopsy for diagnosis Male:Female = 71:49 Mean age: 35 years (experimental group), 37 years (control group) Exclusion criteria: acute hepatitis, other viral infection, ascites, liver cirrhosis, or liver cancer; had used antiviral drugs, immunoregulators, immunosuppressives, or cytotoxic drugs in the past 6 months; concomitant with drug-induced hepatitis, autoimmune hepatitis, or other severe disease
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, 3 months (n = 61) Control intervention: no intervention (n = 59) Co-intervention: routine liver protection drugs including compound glycyrrhizin, potassium magnesium aspartate, and vitamin C, 3 months
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBeAg sero-conversion; liver function test (ALT level)
Notes	Study dates: not stated Funding information: the study did not provide any information on study support or sponsorship. Notes: article had only 1 author. We contacted the study author on 9 November 2015 by email but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study author used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study author did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group received Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding

Li 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study author did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number of participants randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study author assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Liu 2005

Methods	Randomised clinical trial, China Parallel-group design
Participants	80 hospitalised participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBsAg, HBeAg, HBcAb, HBV-DNA positive; HBeAg positive for at least 6 months; serum ALT > 1.5× upper limit of normal, and serum total bilirubin < 85.5 mol/L Male:Female = 60:20 Age: 22 to 56 years (experimental group), 20 to 50 years (control group) Exclusion criteria: not stated
Interventions	Experimental intervention: oxymatrine injection, 600 mg, once daily, intravenous infusion, 1 month; then oxymatrine capsules, 200 mg, 3 times daily, oral administration, 5 months (n = 50) Control intervention: no intervention (n = 30) Co-intervention: routine liver protection treatment (intravenous infusion of diammonium glycyrrhizinate and panangin, oral administration of vitamin C and glucurone), 6 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function tests (ALT, AST, TBIL)
Notes	Study dates: August 2002 to August 2003 Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 18 April 2018 by phone but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information

Liu 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experiment group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Liu 2016

Methods	Randomised clinical trial, China Parallel-group design	
Participants	80 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2005 (CMA 2005) Male:Female = 41:39 Mean age: 48.2 years (experimental group), 48.2 years (control group) Exclusion criteria: history of drug allergy	
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 6 months (n = 40) Control intervention: no intervention (n = 40) Co-intervention: entecavir, 0.5 mg, once daily, oral administration, 6 months	
Outcomes	HBV-DNA; HBsAg; HBeAg seroconversion; liver function test (ALT level); serum liver fibrosis tests (PCIII, CIV, HA, LN)	
Notes	Study dates: March 2013 to March 2016 Funding information: the study did not provide any information on study support or sponsorship. Notes: study had only one author. We contacted study author on 20 March 2018 by email but received no reply	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study author used random numbers table to allocate participants

Liu 2016 (Continued)

Allocation concealment (selection bias)	Unclear risk	Study author did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group received <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study author did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study author did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Lu 2004

Methods	Randomised clinical trial, China Parallel-group design
Participants	144 participants with diagnosis of chronic hepatitis B infection with HBsAg and HBV-DNA positive for at least 6 months, abnormal ALT ($> 1.2 \times$ upper limit of normal) 2 or more times within 6 months before enrolling, serum total bilirubin $< 85.5 \mu\text{mol/L}$, had not used antiviral drugs and immunomodulators within past 6 months Male:Female = not stated Age: 18 to 65 years Exclusion criteria: serum ALT level $> 10 \times$ upper limit of normal, human immunodeficiency virus positive, serum anti-HCV and/or HCV RNA positive, decompensated liver disease suggestive of autoimmune disease (antinuclear antibody titre $> 1:160$ dilution), serum creatinine $> 1.5 \times$ upper limit of normal, or other severe disease; hypersensitivity to oxymatrine; pregnancy and breast-feeding
Interventions	Experimental intervention: oxymatrine capsules, 300 mg, 3 times daily, oral administration, 16 months (n = 72) Control intervention: placebo intervention (size, colour, shape, and taste of vacant placebo capsule were consistent with oxymatrine capsules), 16 months (n = 72) Co-intervention: no co-intervention
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBsAg; HBeAg seroconversion; liver function tests (ALT, AST, TB); serum hepatic fibrosis tests (HA, LN, PCIII, IVC); liver histological examination results
Notes	Study dates: not stated

Lu 2004 (Continued)

Funding information: the trial was supported by academic association: the Key Project of Shanghai Medical Development Foundation (NO: 99ZDI001), and grants from the 1999 Foundation of Chinese Liver Diseases Association for Young Scholars.

Notes: we contacted study authors on 25 April 2018 by email but received no reply. We called study authors on 8 April and 22 April, but no one answered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Vacant placebo with magnitude, colour, shape, and taste consistent with the oxyamtrine capsule was used as control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal rate was 10%, with 7 cases in intervention group and 7 cases in control group. Study authors did not specify reasons for withdrawal in each group
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study, but study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Luo 2018

Methods	Randomised clinical trial, China Parallel-group design
Participants	96 participants with diagnosis of chronic hepatitis B who had not received antiviral treatment during the past 6 months and were not allergic to the drugs used in this research Male:Female = 63:33 Mean age: 47.13 years (experimental group), 46.57 years (control group) Exclusion criteria: concomitant with autoimmune disease or severe internal disease; pregnant or lactating women
Interventions	Experimental intervention: kushensu injection, 600 mg, intravenous infusion, once daily, 3 months; then kushensu tablets, 200 mg, 3 times daily, oral administration, 3 months (n = 48) Control intervention: no intervention (n = 48) Co-intervention: recombinant interferon α -2b, 5M IU, once daily, intramuscular injection, 6 months

Luo 2018 (Continued)

Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; liver function tests (ALT, AST); serum liver fibrosis indexes (LN, HA, PCIII); serum immune indexes (natural killer cells, CD4+, CD8+)	
Notes	Study dates: March 2015 to June 2017 Funding information: the study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 28 December 2019 by phone, but no one answered the phone	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Lv 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	<p>164 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2004 (no reference), with anti-HBV-DNA positive, ALT level > 2× upper limit of normal and < 10× upper limit of normal, total bilirubin < 5 mg/dL (85.5 μmol/L)</p> <p>Male:Female = 118:46</p> <p>Age: 16 to 60 years</p> <p>Exclusion criteria: concomitant with other viral infection such as HAV, HCV, HDV, and HEV infection; decompensated cirrhosis; obvious heart, brain, and kidney disease; psychological disease; diabetes; history of alcohol and drug abuse; had used antiviral drugs, immunomodulators, and glucocorticoid during past 6 months</p>

Lv 2010 (Continued)

Interventions	Experimental intervention: kushensu capsule, 200 mg, 3 times daily, oral administration, 12 months (n = 82) Control intervention: no intervention (n = 82) Co-intervention: adefovir capsules, 10 mg, once daily, oral administration, 12 months	
Outcomes	HBV-DNA; liver function tests (ALT, AST, TBIL, DBIL); liver biopsy tests	
Notes	Study dates: June 2006 to June 2007 Funding information: the study authors said they did not accept any funding Notes: we contacted study authors on 1 June 2018 by phone and received their reply	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors allocated participants by drawing lots
Allocation concealment (selection bias)	High risk	Study authors said they did not take measures to conceal the allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Surrogate outcomes were assessed by nurses and by personnel in other departments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two participants dropped out during the trial; study authors did not specify which group had dropouts and did not state reasons for dropout
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Lv 2011

Methods	Randomised clinical trial, China
	Parallel-group design
Participants	<p>104 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2005 (CMA 2005), with HBsAg, HBeAg, and HBV-DNA positive for at least 6 months, HBV-DNA > 1 × 10⁵ copies/mL, ALT level > 2 × upper limit of normal, TBIL < 3 × upper limit of normal, and repeatedly elevated ALT, and had not used antiviral drugs and immunoregulators in the past 6 months</p> <p>Male:Female = 81:23</p> <p>Mean age: 32.5 years (experimental group), 33.5 years (control group)</p>

Lv 2011 (Continued)

Exclusion criteria: concomitant with cardiovascular disease, cerebrovascular disease, nephropathy, diabetes, autoimmune disease, psychosis, liver cancer, or any other hepatitis viral infection such as hepatitis A, C, D, and E virus infection

Interventions	<p>Experimental intervention: kushensu capsule, 300 mg, 3 times daily, oral administration, 9 months (n = 54)</p> <p>Control intervention: no intervention (n = 50)</p> <p>Co-intervention: adefovir capsules, 10 mg, once daily, oral administration, 9 months</p>
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBsAg; liver function tests (ALT, TBIL); serum liver fibrosis indicators (HA, LN, IVC)
Notes	<p>Study dates: August 2006 to January 2009</p> <p>Funding information: the study was funded by the hospital.</p> <p>Notes: we contacted study authors on 25 April 2018 by phone and received their reply</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We contacted study authors, who said they used a random numbers table
Allocation concealment (selection bias)	Low risk	Study authors said they used numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Surrogate outcomes were assessed by nurses and by personnel in other departments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Mao 2014

Methods	<p>Randomised clinical trial, China</p> <p>Parallel-group design</p>
Participants	<p>70 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000)</p> <p>Male:Female = 40:30</p>

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B (Review)

Mao 2014 (Continued)

Mean age: 44 years

Exclusion criteria: concomitant with other hepatic viral infection

Interventions	<p>Experimental intervention: kushensu injection, 600 mg, intravenous infusion with 250 mL 5% glucose solution, once daily, 1 month (n = 36)</p> <p>Control intervention: no intervention (n = 34)</p> <p>Co-intervention: tanshinone IIA, 60 mg, intravenous infusion with 250 mL 5% glucose solution, once daily; antiviral and liver protective drugs (vitamin, liver protective tablets, oral administration; potassium aspartate and magnesium aspartate, vitamin K, intravenous infusion), 1 month</p>
Outcomes	Liver function tests (ALT, AST, TBIL); serum liver fibrosis indexes (HA, LN, PCIII, IVC)
Notes	<p>Study dates: August 2012 to June 2013</p> <p>Funding information: the study authors did not provide any information on study support or sponsorship.</p> <p>Notes: we contacted study authors on 9 November 2015 by email but received no reply</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Su 2014

Methods	<p>Randomised clinical trial, China</p> <p>Parallel-group design</p>
Participants	86 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2010 (CMA 2010)

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B (Review)

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Su 2014 (Continued)

Male:Female = 58:28

Mean age: 53.6 years (experimental group), 54.1 years (control group)

Exclusion criteria: not stated

Interventions	<p>Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 1 month (n = 43)</p> <p>Control intervention: no intervention (n = 43)</p> <p>Co-intervention: adefovir, 10 mg, once daily, oral administration, 1 month</p>
Outcomes	All-cause mortality; adverse events considered 'not to be serious'; HBV-DNA; liver function tests (ALT, AST); serum liver fibrosis indexes (HA, LN, IVC, PCIII)
Notes	<p>Study dates: January 2009 to December 2012</p> <p>Funding information: the study did not provide any information on study support or sponsorship.</p> <p>Notes: we contacted study authors on 9 November 2015 by email but received no reply</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed all-cause mortality
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Sun 2011

Methods	<p>Randomised clinical trial, China</p> <p>Parallel-group design</p>
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Sun 2011 (Continued)

Participants	145 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with no apparent ascites and in relatively stable condition	
	Male:Female = 103:42	
	Mean age: 37.9 years (experimental group), 38.4 years (control group)	
	Exclusion criteria: concomitant with drug-induced liver disease, alcoholic liver disease, serious disease in heart, brain, lung, kidney, and endocrine; had received antiviral drugs and immunomodulators in the past 6 months; had used bidentate, schisandra preparations, or hormones during the past month; younger than 16 years of age; pregnant women	
Interventions	Experimental intervention: matrine injections, 150 mg, intravenous infusion with 250 mL 10% glucose solution, once daily, 3 months (n = 75)	
	Control intervention: no intervention (n = 70)	
	Co-intervention: liver protection compounds including vitamin C, vitamin B6, inosine, gantaile, hutianbao, and branched chain amino acids, once daily, 3 months	
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBsAg; liver function test (ALT, TBIL)	
Notes	Study dates: May 2009 to February 2011	
	Funding information: this study did not provide any information on study support or sponsorship.	
	Notes: we contacted study authors on 16 July 2018 by email but received no reply	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was said to be a double-blinded trial, but the study author did not mention who were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study, but study author assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Wang 2006

Methods	Randomised clinical trial, China Parallel-group design
Participants	115 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with serum HBsAg positive for at least 6 months, HBeAg positive, HBV-DNA positive, and ALT level < 10× upper limit of normal Male:Female = 72:40 Mean age: 37.6 years (experimental group), 35.1 years (control group) Exclusion criteria: concomitant with other hepatitis virus infection, autoimmune liver disease, drug-induced liver disease, alcoholic liver disease, decompensated liver cirrhosis, liver cancer, or any serious disease; pregnant or lactating women; people who had received antiviral drugs and immunomodulators in the past 6 months
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 12 months (n = 59) Control intervention: no intervention (n = 56) Co-intervention: lamivudine, 100 mg, once daily, oral administration, 12 months
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBeAg sero-conversion; liver function test (ALT level)
Notes	Study dates: March 2003 to December 2004 Funding information: this study did not provide any information on study support or sponsorship. Notes: we tried to contact study authors through their working department on 16 July 2018 by phone, but no one answered the phone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data was 3%. One participant in the intervention group stopped taking drugs because of upper abdomen discomfort, and both groups lost 1 participant during follow-up. Missing data seemed to be comparable between groups. Study authors reported per-protocol analysis

Wang 2006 (Continued)

Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Wang 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	60 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000) Male:Female = not stated Mean age: not stated Exclusion criteria: concomitant with cirrhosis, liver cancer, or autoimmune disease
Interventions	Experimental intervention: kushensu injection, 600 mg, intravenous infusion, once daily, 6 months (n = 30) Control intervention: no intervention (n = 30) Co-intervention: entecavir, 0.5 mg, once daily, oral administration, 6 months
Outcomes	HBV-DNA; serum liver fibrosis tests (HA, LN, PCIII, IVC)
Notes	Study dates: October 2006 to January 2009 Funding information: this study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 28 December 2018 by phone, but no one answered the phone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study author did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised

Wang 2010 (Continued)

Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Wang 2011

Methods	Randomised clinical trial, China Parallel-group design
Participants	60 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with at least 6-month history of hepatitis B infection, ALT/AST > 60 U/L and < 80 U/L, HBV-DNA < 10 ⁷ copies/mL, and HBeAg < 500 s/co Male:Female = 47:13 Mean age: 38.5 years Exclusion criteria: had used any drugs during the past 6 months
Interventions	Experimental intervention: matrine, 150 mg, intravenous infusion, once daily, 1 month (n = 30) Control intervention: no intervention (n = 30) Co-intervention: recombinant human interferon α -2b, 5M IU, subcutaneous injection, once daily, 3 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function tests (ALT, AST)
Notes	Study dates: January 2007 to December 2009 Funding information: the study was supported by Shandong provincial funds on education and technology (J07YE13) Notes: we contacted study authors on 9 November 2015 by email but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information

Wang 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Wei 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	68 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBV-DNA, HBsAg, and HBeAg positive for at least 6 months, serum ALT level > 2× upper limit of normal for at least 3 months Male:Female = 42:26 Mean age: 35.9 years (experimental group), 35.2 years (control group) Exclusion criteria: concomitant with autoimmune hepatitis, malignant tumour, serum creatinine > 133 µmol/L, or other severe disease; pregnant or lactating women; had used any viral drugs and immunoregulators in the past 3 months
Interventions	Experimental intervention: kushensu, intravenous infusion, 600 mg, once daily, 12 months (n = 36) Control intervention: no intervention (n = 32) Co-intervention: adefovir tablets, 10 mg, once daily, 12 months
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function test (ALT level)
Notes	Study dates: not stated Funding information: this study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 9 November 2015 by email but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding

Wei 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	HBV-DNA was detected by another medical centre; no information on other outcomes was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study, but study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Wu 2018

Methods	Randomised clinical trial, China Parallel-group design
Participants	70 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2015 (CMA 2015), with history of hepatitis B infection or serum HBsAg positive for at least 6 months and/or serum HBV-DNA positive, and with other serological or virological indexes and biochemical tests: serum ALT level 120 to 400 U/L, HBV-DNA level > 1 × 10 ⁵ copies/mL. Participants with compensated liver cirrhosis were also included Male:Female = 46:24 Mean age: 56.32 years (experimental group), 55.81 years (control group) Exclusion criteria: had used antiviral drugs during past 3 months; concomitant with hepatitis A, C, D, E, or F infection; decompensated liver cirrhosis; liver cancer; human immunodeficiency virus infection; severe heart, liver, or kidney dysfunction; pregnant or lactating women
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 12 months (n = 35) Control intervention: no intervention (n = 35) Co-intervention: entecavir, 0.5 mg, once daily, oral administration, 12 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function tests (ALT level); peripheral blood immunoglobulin A, M, and G; serum immunological indicators (tumour necrosis factor-α, interleukin-6)
Notes	Study dates: March 2015 to September 2016 Funding information: this study did not provide any information on study support or sponsorship. Notes: we contacted study authors on 28 December 2018 by phone, but no one answered the phone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants

Wu 2018 (Continued)

Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Xi 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	95 children (5 to 14 years old) with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBV-DNA, HBeAg, and HBsAg positive for at least 6 months, ALT > 2× upper limit of normal Male:Female = 65:30 Mean age: 10.23 years (experimental group), 10.51 years (control group) Exclusion criteria: concomitant with other disease that may affect liver function; had used oxymatrine injections and liver protective drugs during the past 6 months; had adverse events when taking these drugs
Interventions	Experimental intervention: kushensu injections, 50 to 100 mg (5- to 10-year-old children), 100 to 150 mg (11 to 14 years old); intravenous infusion with 10% glucose solution, once daily, 2 months; kushensu capsules, 3 times daily, 4 months (n = 47) Control intervention: no intervention (n = 48) Co-intervention: liver protective drug, 1 to 2 tablets (1- to 8-year-old children), 2 to 3 tablets (9- to 14-year-old children), oral administration, 6 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function tests (ALT, AST)
Notes	Study dates: February 2007 to May 2009 Funding information: this study did not provide any information on study support or sponsorship Notes: we contacted study authors on 9 November 2015 by email but received no reply

Xi 2010 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Xie 2010

Methods	Randomised clinical trial, China Parallel-group design
Participants	61 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2000 (CMA 2000), with obvious hepatitis symptoms such as fatigue, loss of appetite, nausea, abdominal pain, liver pain, spider nevus, abnormal liver function, abnormal serum liver fibrosis indexes, and cirrhosis by ultrasound tests Male:Female = 42:19 Mean age: 42.83 years (experimental group), 44.13 years (control group) Exclusion criteria: concomitant with severe hepatitis, hepatic coma, hepatic encephalopathy, other serious complications, liver cancer, severe primary disease in heart, brain, kidney, and hematopoietic system, or mental disorder; younger than 18 years or older than 60 years; pregnant or lactating women; hypersensitivity to drugs; not taking drugs as required, or researchers could not judge effects; incomplete data; had splenectomy before enrolment
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, 24 months (n = 30) Control intervention: no intervention (n = 31) Co-intervention: entecavir, 0.5 mg, once daily, 24 months

Xie 2010 (Continued)

Outcomes	HBV-DNA; HBeAg seroconversion; liver function tests (ALT, AST, TBIL, ALB, albumin/globulin, gamma-glutamyltransferase); serum liver fibrosis tests (HA, LN, PCIII, ICV)	
Notes	Study dates: March 2005 to June 2009 Funding information: this study did not provide any information on study support or sponsorship Notes: trial has only one study author. We contacted study authors on 9 November 2015 by email but received no reply	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study authors excluded participants if they were not taking drugs as required, researchers could not judge the effects, or data were incomplete. Whether there were dropouts remains unclear
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Xue 2008

Methods	Randomised clinical trial, China
	Parallel-group design
Participants	<p>74 participants with diagnosis of chronic hepatitis B according to Chinese guidelines 2000 (CMA 2000), with HBsAg, hepatitis B core antigen, anti-hepatitis B core antigen, HBV-DNA positive, and abnormal ALT level</p> <p>Male:Female = 50:24</p> <p>Age: 18 to 50 years</p> <p>Exclusion criteria: have used antiviral drugs and immunoregulators in the past 6 months</p>

Xue 2008 (Continued)

Interventions	<p>Experimental intervention: acupoint injection of kushensu solution, 4 acupoints (bilateral Zusanli (ST36) and bilateral Sanyinjiao (SP 6)), 1 mL for each acupoint per time, 6 times a week, 6 months (n = 37)</p> <p>Control intervention: no intervention (n = 37)</p> <p>Co-intervention: liver protective drugs (e.g. vitamin C, yiganling, multi-vitamin B), 6 months</p>
Outcomes	HBV-DNA; HBeAg; liver function tests (ALT, TBIL)
Notes	<p>Study dates: April 2000 to October 2005</p> <p>Funding information: the study authors did not provide any information on study support or sponsorship</p> <p>Notes: we contacted study authors on 3 April 2018 by phone; study authors replied regarding random sequence generation method but said they had no time to answer other questions. We sent emails on 3 April and 10 April 2018 but received no reply</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Yan 2011

Methods	<p>Randomised clinical trial, China</p> <p>Parallel-group design</p>
Participants	132 participants with diagnosis of HBeAg-positive chronic hepatitis B according to Chinese guidelines 2005 (CMA 2005), with HBsAg, HBeAg, hepatitis B core antibody (HBcAb) positive for at least 6 months,

Yan 2011 (Continued)

HBsAb negative, HBV-DNA more than 10^5 copies/mL, ALT level $> 2 \times$ upper limit of normal, and elevated ALT during past 6 months before enrolling

Male:Female = 101:31

Mean age: 32 years (experimental group), 32 years (control group)

Exclusion criteria: concomitant with acute hepatitis B, severe hepatitis, liver failure, cirrhosis, primary hepatocellular carcinoma, drug-induced hepatitis, alcoholic hepatitis, fatty liver, other viral (HAV, HCV, HDV, HEV, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus) infection, severe disease (e.g. severe heart, lung, or kidney disease; psychology; malignant carcinoma; diabetes), autoimmune liver disease, or systematic autoimmune disease; pregnant or lactating women; not using drugs as required or not finishing overall treatments; not using any other antiviral drugs and immunoregulators

Interventions	<p>Experimental intervention: kushensu capsules, 150 mg, 3 times daily, 13 months (n = 70)</p> <p>Control intervention: no intervention (n = 62)</p> <p>Co-intervention: adefovir, 10 mg, once daily, 13 months</p>
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg seroconversion; liver function tests (ALT, AST)
Notes	<p>Study dates: October 2007 to October 2009</p> <p>Funding information: the study authors did not provide any information on study support or sponsorship</p> <p>Notes: we contacted study authors on 28 April and 16 July 2018 by Wechat but received no reply</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study authors excluded participants if not taking drugs as required or if not finishing overall treatments; we were not sure whether there were dropouts
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Yang 2018

Methods	Randomised clinical trial, China Parallel-group design
Participants	92 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2015 (CMA 2015), who have taken lamivudine for at least 12 months, with HBV-DNA level increasing 11 g IU/mL over lowest level of treatment or HBV-DNA changing to positive from negative Male:Female = 55:37 Mean age: 42.37 years Exclusion criteria: concomitant with HAV, HCV, HEV, HDV infection, or acquired immune deficiency syndrome infection; liver cancer, liver cirrhosis, alcoholic liver disease, or autoimmune liver disease; severe heart, brain, or kidney dysfunction; pregnant or lactating women
Interventions	Experimental intervention: matrine injection, 150 mg, once daily, 12 months (n = 46) Control intervention: no intervention (n = 46) Co-intervention: tenofovir disoproxil, 300 mg, once daily, 12 months
Outcomes	Adverse events considered 'not to be serious'; HBV-DNA; HBeAg; liver function tests (ALT, AST, TBIL); liver fibrosis indexes (HA, LN, PCIII, IVC)
Notes	Study dates: February 2014 to October 2016 Funding information: this study did not provide any information on study support or sponsorship Notes: we tried to contact study authors on 28 December 2018 by phone, but no one answered the phone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescens and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study author did not report any of the 3 primary outcomes

Yang 2018 (Continued)

Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias
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Ye 2015

Methods	Randomised clinical trial, China Parallel-group design
Participants	100 participants with diagnosis of chronic hepatitis B infection according to Chinese guidelines 2005 (CMA 2005), with HBeAg and HBV-DNA positive and normal liver function Male:Female = 59:41 Mean age: 31.3 years (experimental group), 33.7 years (control group) Exclusion criteria: concomitant with HAV, HCV, HEV, HDV infection, acquired immune deficiency syndrome infection, alcoholic liver disease, autoimmune liver disease, liver cirrhosis, or liver cancer; pregnant or lactating women
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, 12 months (n = 50) Control intervention: no intervention (n = 50) Co-intervention: entecavir, 0.5 mg, once daily, 12 months
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; liver function tests (ALT, AST, TBIL)
Notes	Study dates: January 2011 to January 2013 Funding information: the trial was supported by Zhejiang Provincial TCM Science Program (2010ZA118) Notes: we tried to contact study authors on 3 April and 28 April 2018 by phone, but no one answered the phone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias)	Low risk	No missing data; number of participants analysed was equal to number randomised

Radix Sophorae flavescentis versus no intervention or placebo for chronic hepatitis B (Review)

Ye 2015 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhang 2011a

Methods	Randomised clinical trial, China Parallel-group design
Participants	200 children with diagnosis of chronic hepatitis B according to guidelines 2000 (CMA 2000), with HBsAg, HBeAg, HBV-DNA positive for at least 6 months, and ALT/AST > 2× upper limit of normal Male:Female = 112:88 Mean age: 11.59 years Exclusion criteria: have used antiviral drugs such as kushensu and lamivudine; concomitant with other hepatic viral (HAV, HCV, HDV) infection
Interventions	<u>Comparison 1</u> Experimental intervention: matrine injections, 50 to 100 mg (5- to 10-year-old children), 100 to 150 mg (11- to 14-year-old children), intravenous injection with 10% glucose solution, once daily, 6 months (n = 50) Control intervention: no intervention (n = 50) Co-intervention: diammonium glycyrrhizinate capsules, 3 mg/kg/d, twice daily (the weight of the participants was used to calculate the dosage); plus inosine tablets, 100 to 400 mg, 3 times daily, oral administration, 6 months
Outcomes	HBV-DNA; HBeAg; HBeAg seroconversion; liver function test (ALT level)
Notes	Study dates: not stated Funding information: the study authors did not provide any information on study support or sponsorship Notes: we contacted study authors on 9 November 2015 by email but received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias)	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding

Zhang 2011a (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhang 2011b

Methods	Randomised clinical trial, China Parallel-group design	
Participants	200 children with diagnosis of chronic hepatitis B according to guidelines 2000 (CMA 2000), with HBsAg, HBeAg, HBV-DNA positive for at least 6 months, and ALT/ AST > 2× upper limit of normal Male:Female = 112:88 Mean age: 11.59 years Exclusion criteria: have used antiviral drugs such as kushensu and lamivudine; concomitant with other hepatic viral (HAV, HCV, HDV) infection	
Interventions	<u>Comparison 2</u> Experimental intervention: matrine injections, 50 to 100 mg (5- to 10-year-old children), 100 to 150 mg (11- to 14-year-old children), intravenous injection with 10% glucose solution, once daily, 6 months (n = 50) Control intervention: no intervention (n = 50) Co-intervention: diammonium glycyrrhizinate capsules, 3 mg/kg/d, twice daily (the dosage is calculated on the weight of the participants); plus inosine tablets, 100 to 400 mg, 3 times daily; plus lamivudine, 3 mg/kg-d, once daily, oral administration, 6 months	
Outcomes	HBV-DNA; HBeAg; HBeAg seroconversion; liver function test (ALT level)	
Notes	Study dates: not stated Funding information: this study did not provide any information on study support or sponsorship Notes: we contacted study authors on 9 November 2015 by email but received no reply	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers tables to allocate participants

Zhang 2011b (Continued)

Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhang 2015

Methods	Randomised clinical trial, China Parallel-group design
Participants	80 participants with diagnosis of chronic hepatitis B with HBeAg positive for at least 6 months, HBV-DNA < 10 ⁹ copies/ mL, ALT > 2× upper limit of normal. 21 participants concomitant with decompensated cirrhosis Male:Female = 57:23 Mean age: 41.33 years Exclusion criteria: concomitant with other hepatic viral infection, human immunodeficiency virus infection, alcoholic liver disease, fatty liver disease, autoimmune liver disease, liver cirrhosis, and any other liver disease; allergic to drugs; lactating and pregnant women
Interventions	Experimental intervention: kushensu dispersible tablets, 200 mg, 3 times daily, oral administration, 12 months (n = 40) Control intervention: no intervention (n = 40) Co-intervention: telbivudine, 600 mg daily, oral administration, 12 months
Outcomes	HBV-DNA; liver function tests (ALT, AST, TBIL, DBIL)
Notes	Study dates: March 2011 to June 2012 Funding information: this study did not provide any information on study support or sponsorship Notes: article has only one author. We contacted study author on 20 April and 24 April 2018 by phone, but study author said he was too busy and refused to answer questions

Risk of bias

Zhang 2015 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study author allocated participants by drawing lots
Allocation concealment (selection bias)	Unclear risk	Study author did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study author did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study author did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhang 2017

Methods	Randomised clinical trial, China Parallel-group design
Participants	96 participants with diagnosis of chronic hepatitis B according to guidelines 2010 (CMA 2010), with concomitant liver cirrhosis Male:Female = 64:32 Mean age: 63.5 years (experimental group), 62.9 years (control group) Exclusion criteria: concomitant with HAV, HCV, or HDV infection, immune hepatitis, drug-induced hepatitis, alcoholic hepatitis, fatty liver disease, severe disease in heart, lung, and kidney, malignant tumour
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 6 months (n = 48) Control intervention: no intervention (n = 48) Co-intervention: routine liver protection and nutritional support treatments, 6 months
Outcomes	Serious adverse events; adverse events considered 'not to be serious'; HBV-DNA; HBeAg; HBeAg sero-conversion; serum liver fibrosis tests (HA, IVC, PCIII, LN); portal haemodynamics indexes (diameter of portal vein; diameter of splenic vein; velocity of portal vein; velocity of splenic vein; quantity of blood flow in the portal vein; quantity of blood flow in the splenic vein)
Notes	Study dates: January 2014 to October 2016

Zhang 2017 (Continued)

Funding information: the study authors did not provide any information on study support or sponsorship

Notes: we tried to contact study authors on 16 April and 25 April by phone, but no one answered the phone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used <i>Radix Sophorae flavescentis</i> and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number of participants randomised
Selective reporting (reporting bias)	Unclear risk	We could not find the protocol for this study; study authors assessed serious adverse events
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhou 2013

Methods	Randomised clinical trial, China Parallel-group design
Participants	28 participants with diagnosis of chronic hepatitis B according to China national guidelines 2000 (CMA 2000), who used interferon for average 11.4 months before enrolment but still with HBeAg and HBV-DNA positive Male:Female = 16:12 Mean age: 45.2 years Exclusion criteria: concomitant with other hepatic viral infection such as HAV, HCV, HEV infection; metabolic, drug-induced, autoimmune liver disease; heart, kidney, and lung disease
Interventions	Experimental intervention: kushensu, 300 mg, 3 times daily, oral administration, 24 months (n = 14) Control intervention: no intervention (n = 14) Co-intervention: adefovir, 10 mg daily, oral administration, 24 months

Zhou 2013 (Continued)

Outcomes	HBV-DNA; HBeAg; liver function tests (ALT, AST, ALB, TBIL, DBIL)	
Notes	Study dates: January 2011 to January 2013 Funding information: this study did not provide any information on study support or sponsorship Notes: this article had only 1 author. We tried to contact the study author on 8 April and 20 April 2018 by phone, but no one answered the phone	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study author used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study author did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals and dropouts; study authors reported data for all participants randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

Zhu 2018

Methods	Randomised clinical trial, China Parallel-group design	
Participants	134 participants with diagnosis of chronic hepatitis B who never used antiviral drugs before Male:Female = 78:56 Age: 42 to 62 years (experimental group), 44 to 63 years (control group) Exclusion criteria: concomitant with other hepatic viral infection; decompensated liver cirrhosis; liver fibrosis and other liver disease	
Interventions	Experimental intervention: kushensu capsules, 1 capsule daily, oral administration, 6 months (n = 67) Control intervention: no intervention (n = 67)	

Zhu 2018 (Continued)

Co-intervention: entecavir, 1 tablet daily, oral administration, 6 months

Outcomes	Serum liver fibrosis indexes (PCIII, IVC, TGF- β 1, angiotensin-II), cellular immune indexes
Notes	<p>Study dates: March 2015 to June 2017</p> <p>Funding information: the study was supported by National Science Foundation for Young Scientists of China (No.81600476)</p> <p>Notes: we tried to contact study authors on 28 December 2018 by phone, but no one answered the phone</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used random numbers table to allocate participants
Allocation concealment (selection bias)	Unclear risk	Study authors did not report such information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Except for equally implemented co-interventions, experimental group used Radix Sophorae flavescentis and control group received nothing, which can easily unseal the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study author did not report such information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; number of participants analysed was equal to number randomised
Selective reporting (reporting bias)	High risk	We could not find the protocol for this study; study authors did not report any of the 3 primary outcomes
Other bias	Low risk	We did not identify any other potential sources of bias that would put the study at risk of bias

ALB: serum albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBIL:direct bilirubin; HA: hyaluronic acid; HAV: hepatitis A virus; HBcAb: hepatitis B core antibody; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HEV: hepatitis E virus; HFV: hepatitis F virus; HGV: hepatitis G virus; IVC: type IV collagen; LN: laminin; PCIII: type III procollagen; TBIL: total bilirubin; TGF- β : transforming growth factor-beta.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cao 2003	Not an appropriate comparison group
Cao 2015a	A duplicate
Cao 2015b	A duplicate

Study	Reason for exclusion
Chang 2004	A duplicate
Chen 2006a	Not a randomised clinical trial
Chen 2006b	Not a randomised clinical trial
Chen 2007	Not an appropriate comparison group
Chen 2008	Not a randomised clinical trial
Chen 2009a	Not an appropriate comparison group
Chen 2009b	Not chronic hepatitis B
Chen 2009c	Not a randomised clinical trial
Chen 2010	A duplicate
Chen 2011	Not a randomised clinical trial
Chen 2014	Not a randomised clinical trial
Ding 2008	Not a randomised clinical trial
Ding 2011a	Not an appropriate comparison group
Ding 2011b	Not a randomised clinical trial
Dong 2006	A duplicate
Duan 2003	A duplicate
Feng 2007	Not an appropriate comparison group
Fu 2012	Not a randomised clinical trial
Fu 2013	We contacted the study author and found he had a wrong interpretation for randomisation. Participants were recruited according to willingness. We judged this not to be a randomised clinical trial
Gao 2006	Study author said this trial was not randomised. Participants were randomised according to their willingness
Gao 2007	Not a randomised clinical trial
Ge 2006	Not an appropriate comparison group
Gu 2010	A duplicate
Guan 2002	Not a randomised clinical trial
Guo 2001	Not a randomised clinical trial
Guo 2005	Not a randomised clinical trial

Study	Reason for exclusion
Han 2010	Number of participants randomised was less than the number analysed. Untrusted data. We could not contact the study author
Hao 2009	Review article
He 2002	We contacted study author on 20 April 2018 by phone; he said this indeed was not a randomised clinical trial
Hong 2011	Not a randomised clinical trial
Hou 2004	We contacted study author on 30 May 2018 by phone; he said this indeed was not a randomised clinical trial
Hu 2002	Participants changed drugs during the study: if drugs were not effective, participants in control group were changed to intervention group, and participants in intervention group, if drug was not substantially effective, continued treatment longer. Participants for whom drug was found to be ineffective were changed to other treatments
Hu 2009	Participants changed drugs during the study: if HBV-DNA level was 1.0×10 copies/mL higher than the last test (every 12 weeks), treatment was regarded as not effective, and participant was changed to other treatments. This design did not allow us to decide if oxymatrine or other drugs may be responsible for the observed effect
Hu 2010	Not a randomised clinical trial
Hu 2014	Not a randomised clinical trial
Huang 2001	Not a randomised clinical trial
Huang 2003	Not a randomised clinical trial
Huang 2004	Not an appropriate comparison group
Huang 2009	We contacted the study author on 20 April 2018 by phone; he said this indeed was not a randomised clinical trial
Jia 2006	Not an appropriate comparison type
Jia 2008	Not an appropriate comparison group
Jia 2011	Not an appropriate comparison group
Jiang 2005	Not a randomised clinical trial
Lei 2012	Not an appropriate comparison group
Li 2001a	Not an appropriate comparison group
Li 2001b	Not an appropriate comparison group
Li 2004a	Not a randomised clinical trial
Li 2004b	Not a randomised clinical trial
Li 2004c	A case series

Study	Reason for exclusion
Li 2005	Co-intervention was not comparable
Li 2008a	Not a randomised clinical trial
Li 2010a	Not an appropriate comparison group
Li 2010b	Not an appropriate comparison group
Li 2010c	Not a randomised clinical trial
Li 2010d	Not a randomised clinical trial
Li 2012	A case series
Li 2015	Co-intervention was not similar in both groups
Lian 2011	Not an appropriate comparison group
Liao 2001	Not a randomised clinical trial
Liao 2003	Review article
Liao 2011	Not a randomised clinical trial
Lin 2002	Not a randomised clinical trial
Lin 2004	Not a randomised clinical trial
Liu 2002	A duplicate
Liu 2006	Not an appropriate comparison group
Liu 2007	A case series
Long 2004	A duplicate - English version of a published Chinese version
Lu 2002	A duplicate
Luo 2004a	Not appropriate participants
Luo 2004b	Not an appropriate comparison group
Luo 2005	Co-intervention was not comparable
Lv 2005	Not an appropriate comparison group
Mao 2013	Not a randomised clinical trial
Mao 2014a	Not a randomised clinical trial
Mo 2009	Co-intervention was not comparable in both groups
Mo 2010	Not an appropriate comparison group
Ni 2006	Not a randomised clinical trial

Study	Reason for exclusion
Ou 2004	Not a randomised clinical trial
Ou 2011	Co-intervention was not comparable
Ou 2012	We contacted study author on 14 May 2018 by phone; he said this indeed was not a randomised clinical trial
Pan 2002a	We contacted study authors; they said this indeed was not a randomised clinical trial
Pan 2002b	Not a randomised clinical trial
Peng 2013	Not an appropriate comparison group
Qin 2005a	Not a randomised clinical trial
Qin 2005b	A duplicate
Qin 2008	A duplicate
Qin 2009	We contacted study author on 24 April 2018 by phone; she said this indeed was not a randomised clinical trial
Qiu 2002	A duplicate
Qu 2005	Not an appropriate comparison group
Ren 2007	We contacted study author on 14 May by phone; study author said this indeed was not a randomised clinical trial
Run 2008	Not a randomised clinical trial
Sha 2007	Not a randomised clinical trial
She 2003	A duplicate
She 2004	A duplicate
Shen 2005	Not a randomised clinical trial
Shen 2008	Not a randomised clinical trial
Shen 2013	Not a randomised clinical trial
Shi 2004	We contacted study author on 25 June 2018 by phone; he said this indeed was not a randomised clinical trial
Shi 2011	Not a randomised clinical trial
Song 2009	We contacted study author on 18 May 2018 by phone; he said this indeed was not a randomised clinical trial
Su 2005a	We contacted study author on 25 June 2018 by phone; he said this indeed was not a randomised clinical trial

Study	Reason for exclusion
Su 2005b	We contacted study author on 25 June 2018 by phone; he said this indeed was not a randomised clinical trial
Sun 2005	Study author said this indeed was not a randomised clinical trial
Sun 2006	We contacted study author on 23 April 2018 by phone; he said this indeed was not a randomised clinical trial
Sun 2006a	Not a randomised clinical trial
Tang 2006	A duplicate
Tang 2007	Not an appropriate comparison group
Tao 2008	We contacted study author on 14 May 2018 by phone; he said this indeed was not a randomised clinical trial
Tian 2005	Not an appropriate comparison group
Tian 2009	Not an appropriate comparison group
Wang 2000	A case report
Wang 2003a	Not an appropriate comparison group
Wang 2003b	A duplicate
Wang 2004a	Review article
Wang 2004b	Not a randomised clinical trial
Wang 2004c	Not a randomised clinical trial
Wang 2005	Study author said this indeed was not a randomised clinical trial
Wang 2006a	Not a randomised clinical trial
Wang 2006b	A duplicate
Wang 2006c	Not an appropriate comparison group
Wang 2009	Not an appropriate comparison group
Wang 2011a	Review article
Wang 2013	Not an appropriate comparison group
Wu 2004	Review article
Wu 2006	Not a randomised clinical trial
Wu 2008	Not an appropriate comparison group
Xiao 2017	We contacted study author on 7 August 2018 by phone: the doctor received our call. Study author said this indeed was not a randomised clinical trial

Study	Reason for exclusion
Xie 2002	Not chronic hepatitis B
Xiong 2011	Not an appropriate comparison group
Xu 2005a	A duplicate
Xu 2005b	Not an appropriate comparison group
Xue 2012	A duplicate
Yang 2004	Not an appropriate comparison group
Yang 2008	Not an appropriate comparison group
Yang 2012	We contacted study author on 16 July by phone; he said this indeed was not a randomised clinical trial
Yang 2014	Not a randomised clinical trial
Yuan 2011	Not a randomised clinical trial
Zhai 2009	Not a randomised clinical trial
Zhan 2006	A duplicate
Zhang 2004	Not a randomised clinical trial
Zhang 2005	Not an appropriate comparison group
Zhang 2006	Not an appropriate comparison group
Zhang 2007	Not a randomised clinical trial
Zhang 2010	Not a randomised clinical trial
Zhang 2011	Not an appropriate comparison group
Zhang 2012a	Not an appropriate comparison group
Zhang 2012b	Not a randomised clinical trial
Zhang 2012c	Not a randomised clinical trial
Zhao 2001a	Not an appropriate comparison group
Zhao 2001b	Not a randomised clinical trial
Zhao 2002	Not a randomised clinical trial
Zhao 2005	Not a randomised clinical trial
Zhao 2009	Not a randomised clinical trial
Zhao 2011	Not an appropriate comparison group

Study	Reason for exclusion
Zhao 2013	We contacted study authors; they said this indeed was not a randomised clinical trial
Zheng 2008	Not a randomised clinical trial
Zhou 2004	Not a randomised clinical trial
Zhou 2005a	Not a randomised clinical trial
Zhou 2005b	We contacted study authors; they said this indeed was not a randomised clinical trial
Zhou 2009	Not a randomised clinical trial

DATA AND ANALYSES

Comparison 1. Radix Sophorae flavescentis versus no intervention or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1	86	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.04, 0.04]
2 Proportion of participants with one or more serious adverse events	10	1140	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
3 Proportion of participants with one or more adverse events considered not to be serious - worst-best	19	2005	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.78, 1.61]
4 Proportion of participants with one or more adverse events considered not to be serious - incomplete data	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 low risk	16	1614	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.69, 1.60]
4.2 unclear or high risk	3	388	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.43, 4.10]
5 Proportion of participants with one or more adverse events considered not to be serious - control group	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 versus placebo	1	144	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.35, 4.47]
5.2 versus no intervention	18	1858	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.72, 1.60]
6 Proportion of participants with one or more adverse events considered	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
not to be serious - forms + administration ways				
6.1 oral capsules	10	1080	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.61]
6.2 intravenous infusion	5	480	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.26, 2.00]
6.3 mixed - injections + capsules/intravenous + intramuscular	4	442	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.05]
7 Proportion of participants with one or more adverse events considered not to be serious - duration	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 less than 6 months	3	311	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.47, 2.42]
7.2 more than 6 months	16	1691	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.65]
8 Proportion of participants with one or more adverse events considered not to be serious - overall	19	2002	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.76, 1.59]
9 Proportion of participants with one or more adverse events considered not to be serious - co-intervention	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 western medicine	12	1242	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.38, 1.50]
9.2 Chinese herbal medicine	3	280	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.27, 3.56]
9.3 liver protective drugs	3	336	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.07, 2.01]
9.4 no co-intervention	1	144	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.35, 4.47]
10 Proportion of participants with detectable HBV-DNA - overall	31	2914	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.55, 0.68]
11 Proportion of participants with detectable HBV-DNA - best-worst	31	2944	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.54, 0.67]
12 Proportion of participants with detectable HBV-DNA - worst-best	31	2944	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.56, 0.70]
13 Proportion of participants with detectable HBV-DNA - blinding of outcome assessors	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 low risk	5	435	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.78]
13.2 unclear or high risk	26	2479	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.53, 0.68]
14 Proportion of participants with detectable HBV-DNA - incomplete data	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 low risk	24	2226	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.51, 0.68]
14.2 unclear or high risk	7	688	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.58, 0.73]
15 Proportion of participants with one or more adverse events considered not to be serious - best-worst	19	2005	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.77, 1.58]
16 Proportion of participants with detectable HBV-DNA - forms + administration way	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 oral capsules	15	1381	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.55, 0.72]
16.2 oral dispersible tablets	1	80	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.90]
16.3 intravenous infusion	10	937	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.56, 0.80]
16.4 acupoint injection	1	74	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.71]
16.5 mixed - injections+capsules/ intravenous+intramuscular	4	442	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.43, 0.67]
17 Proportion of participants with one or more adverse events considered not to be serious - concomitant disease	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 with concomitant diseases	1	96	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 without concomitant diseases	12	1298	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.04, 1.84]
17.3 unclear	6	608	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.28, 2.14]
18 Proportion of participants with detectable HBV-DNA - concomitant diseases	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 with concomitant diseases	2	157	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.52, 0.83]
18.2 some with concomitant diseases	1	80	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.90]
18.3 without concomitant diseases	19	1825	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.74]
18.4 unclear	9	852	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.46, 0.63]
19 Proportion of participants with detectable HBV-DNA - co-intervention	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 western medicine	19	1715	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.51, 0.67]
19.2 Chinese herbal medicine	8	733	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.78]
19.3 liver protective drugs	3	336	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.55, 0.84]
19.4 no co-intervention	1	130	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.74]
20 Proportion of participants with detectable HBeAg - overall	22	2129	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.66, 0.76]
21 Proportion of participants with detectable HBeAg - best-worst	22	2159	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.65, 0.74]
22 Proportion of participants with detectable HBeAg - worst-best	22	2159	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.67, 0.78]
23 Proportion of participants with detectable HBeAg - blinding of outcome assessors	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 low risk	5	435	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.62, 0.80]
23.2 unclear or high risk	17	1694	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.65, 0.77]
24 Proportion of participants with detectable HBeAg - incomplete data	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 low risk	17	1634	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.64, 0.76]
24.2 unclear or high risk	5	495	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.66, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Proportion of participants with detectable HBeAg - control group	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 with no intervention	21	1999	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.66, 0.75]
25.2 with placebo	1	130	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.93]
26 Proportion of participants with detectable HBeAg - forms + administration way	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 oral capsules	10	922	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.65, 0.81]
26.2 intravenous infusion	8	787	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.63, 0.77]
26.3 acupoint injection	1	74	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.38, 0.75]
26.4 mixed - injections+capsules/ intravenous+intramuscular	3	346	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.88]
27 Proportion of participants with detectable HBV-DNA - duration	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 less than 6 months	3	311	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.34, 0.84]
27.2 more than 6 months	28	2603	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.55, 0.69]
28 Proportion of participants with detectable HBeAg - concomitant diseases	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 with concomitant diseases	1	96	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.68, 1.10]
28.2 without concomitant diseases	16	1533	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.67, 0.76]
28.3 unclear	5	500	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.55, 0.78]
29 Proportion of participants with detectable HBeAg - co-intervention	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.1 western medicine	10	930	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.63, 0.77]
29.2 Chinese herbal medicine	8	733	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.60, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.3 liver protective drugs	3	336	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.61, 0.89]
29.4 no co-intervention	1	130	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.93]
30 Proportion of participants with nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
31 Proportion of participants with nausea and vomiting	2	186	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.12, 3.13]
32 Proportion of participants with upper abdomen discomfort	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
33 Proportion of participants with digestive symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
34 Proportion of participants with loss of appetite	3	320	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.30, 2.21]
35 Proportion of participants with detectable HBV-DNA - control group	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
35.1 with no intervention	30	2784	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.55, 0.68]
35.2 with placebo	1	130	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.74]
36 Proportion of participants with diarrhoea	2	192	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.33, 4.92]
37 Proportion of participants with dizziness and headache	3	288	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.27, 1.81]
38 Proportion of participants with dizziness and fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
39 Proportion of participants with fatigue	6	596	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.13, 1.86]
40 Proportion of participants with fever	3	288	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.60, 4.46]
41 Proportion of participants with rash	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
42 Proportion of participants with yellow urine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43 Proportion of participants with detectable HBeAg - duration	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 less than 6 months	2	225	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.50, 0.74]
43.2 more than 6 months	20	1904	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.67, 0.77]
44 Proportion of participants with creatinine increase	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
45 Proportion of participants with phosphorus increase	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
46 Proportion of participants with liver pain	4	400	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.45, 2.19]
47 Proportion of participants with hepatomegaly	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
48 Proportion of participants with jaundice	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
49 Proportion of participants with splenomegaly	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
50 Proportion of participants with muscle pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
51 Proportion of participants with creatinine kinase increase	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
52 Proportion of participants with abdominal distention	2	225	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.14, 0.62]

Analysis 1.1. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 2 Proportion of participants with one or more serious adverse events.

Analysis 1.3. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 3 Proportion of participants with one or more adverse events considered not to be serious - worst-best.

Analysis 1.4. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 4 Proportion of participants with one or more adverse events considered not to be serious - incomplete data.

Analysis 1.5. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 5 Proportion of participants with one or more adverse events considered not to be serious - control group. **Analysis 1.6. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 6 Proportion of participants with one or more adverse events considered not to be serious - forms + administration ways.**

Analysis 1.7. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 7 Proportion of participants with one or more adverse events considered not to be serious - duration.

Analysis 1.8. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 8 Proportion of participants with one or more adverse events considered not to be serious - overall.

Analysis 1.9. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 9 Proportion of participants with one or more adverse events considered not to be serious - co-intervention.

Analysis 1.10. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 10 Proportion of participants with detectable HBV-DNA - overall.

Analysis 1.11. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 11 Proportion of participants with detectable HBV-DNA - best-worst.

Analysis 1.12. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 12 Proportion of participants with detectable HBV-DNA - worst-best.

Study or subgroup	Radix Sophorae flavescentis n/N	No interven- tion/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=8.75(P<0.0001)					
Favours Radix Sophorae flavescentis 0.01 0.1 1 10 100 Favours no intervention/placebo					

Analysis 1.13. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 13 Proportion of participants with detectable HBV-DNA - blinding of outcome assessors.

Study or subgroup	Radix Sophorae flavescentis n/N	No interven- tion/placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 low risk					
Huang 2004a	26/36	35/36		42.76%	0.74[0.6,0.92]
Huang 2004b	16/37	26/37		14.47%	0.62[0.4,0.94]
Huang 2005	31/56	43/51		31.38%	0.66[0.5,0.85]
Wang 2006	13/57	24/55		8.65%	0.52[0.3,0.92]
Wu 2018	4/35	12/35		2.74%	0.33[0.12,0.93]
Subtotal (95% CI)	221	214		100%	0.66[0.56,0.78]
Total events: 90 (Radix Sophorae flavescentis), 140 (No intervention/placebo)					
Heterogeneity: Tau ² =0.01; Chi ² =4.77, df=4(P=0.31); I ² =16.22%					
Test for overall effect: Z=4.72(P<0.0001)					
1.13.2 unclear or high risk					
Chai 2018	8/45	18/45		2.12%	0.44[0.22,0.92]
Duan 2004	22/60	46/60		4.68%	0.48[0.33,0.69]
He 2013	9/54	20/62		2.23%	0.52[0.26,1.04]
Li 2006	20/40	38/40		5.14%	0.53[0.38,0.72]
Li 2008	23/70	38/76		4.26%	0.66[0.44,0.98]
Li 2010	21/61	51/59		4.68%	0.4[0.28,0.57]
Liu 2005	27/50	28/30		5.65%	0.58[0.44,0.76]
Liu 2016	17/40	21/40		3.69%	0.81[0.51,1.29]
Lu 2004	38/65	63/65		6.38%	0.6[0.49,0.74]
Luo 2018	8/48	25/48		2.27%	0.32[0.16,0.64]
Lv 2011	18/54	30/50		3.92%	0.56[0.36,0.86]
Su 2014	1/43	9/43		0.35%	0.11[0.01,0.84]
Sun 2011	14/75	19/70		2.69%	0.69[0.37,1.26]
Wang 2010	2/30	4/30		0.54%	0.5[0.1,2.53]
Wei 2010	11/36	18/32		2.87%	0.54[0.3,0.97]
Xi 2010	22/47	36/48		4.84%	0.62[0.44,0.88]
Xie 2010	16/30	29/31		4.82%	0.57[0.4,0.81]
Xue 2008	16/37	33/37		4.43%	0.48[0.33,0.71]
Yan 2011	28/72	32/60		4.55%	0.73[0.5,1.06]
Yang 2018	13/46	23/46		3.1%	0.57[0.33,0.97]
Ye 2015	32/50	38/50		5.8%	0.84[0.65,1.09]
Zhang 2011a	41/50	47/50		7.03%	0.87[0.75,1.01]
Zhang 2011b	36/50	42/50		6.36%	0.86[0.69,1.06]
Zhang 2015	5/40	14/40		1.45%	0.36[0.14,0.9]
Zhang 2017	27/48	37/48		5.42%	0.73[0.54,0.98]
Zhou 2013	2/14	7/14		0.72%	0.29[0.07,1.14]
Subtotal (95% CI)	1255	1224		100%	0.6[0.53,0.68]
Favours Radix Sophorae flavescentis 0.01 0.1 1 10 100 Favours no intervention/placebo

Analysis 1.14. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 14 Proportion of participants with detectable HBV-DNA - incomplete data.

Analysis 1.15. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 15 Proportion of participants with one or more adverse events considered not to be serious - best-worst.

Analysis 1.16. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 16 Proportion of participants with detectable HBV-DNA - forms + administration way.

**Analysis 1.17. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 17
Proportion of participants with one or more adverse events considered not to be serious - concomitant disease.**

Analysis 1.18. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 18 Proportion of participants with detectable HBV-DNA - concomitant diseases.

Analysis 1.19. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 19 Proportion of participants with detectable HBV-DNA - co-intervention.

Analysis 1.20. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 20 Proportion of participants with detectable HBeAg - overall.

Analysis 1.21. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 21 Proportion of participants with detectable HBeAg - best-worst.

Analysis 1.22. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 22 Proportion of participants with detectable HBeAg - worst-best.

Analysis 1.23. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 23 Proportion of participants with detectable HBeAg - blinding of outcome assessors.

Analysis 1.24. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 24 Proportion of participants with detectable HBeAg - incomplete data.

Analysis 1.25. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 25 Proportion of participants with detectable HBeAg - control group.

Analysis 1.26. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 26 Proportion of participants with detectable HBeAg - forms + administration way.

Analysis 1.27. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 27 Proportion of participants with detectable HBV-DNA - duration.

Analysis 1.28. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 28 Proportion of participants with detectable HBeAg - concomitant diseases.

Analysis 1.29. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 29 Proportion of participants with detectable HBeAg - co-intervention.

Analysis 1.30. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 30 Proportion of participants with nausea.

Analysis 1.31. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 31 Proportion of participants with nausea and vomiting.

Analysis 1.32. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 32 Proportion of participants with upper abdomen discomfort.

Analysis 1.33. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 33 Proportion of participants with digestive symptoms.

Analysis 1.34. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 34 Proportion of participants with loss of appetite.

Analysis 1.35. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 35 Proportion of participants with detectable HBV-DNA - control group.

Analysis 1.36. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 36 Proportion of participants with diarrhoea.

Analysis 1.37. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 37 Proportion of participants with dizziness and headache.

Analysis 1.38. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 38 Proportion of participants with dizziness and fatigue.

Analysis 1.39. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 39 Proportion of participants with fatigue.

Analysis 1.40. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 40 Proportion of participants with fever.

Analysis 1.41. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 41 Proportion of participants with rash.

Analysis 1.42. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 42 Proportion of participants with yellow urine.

Analysis 1.43. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 43 Proportion of participants with detectable HBeAg - duration.

Analysis 1.44. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 44 Proportion of participants with creatinine increase.

Analysis 1.45. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 45 Proportion of participants with phosphorus increase.

Analysis 1.46. Comparison 1 Radix Sophorae flavescentis versus no intervention or placebo, Outcome 46 Proportion of participants with liver pain.

Analysis 1.47. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 47 Proportion of participants with hepatomegaly.

Analysis 1.48. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 48 Proportion of participants with jaundice.

Analysis 1.49. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 49 Proportion of participants with splenomegaly.

Analysis 1.50. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 50 Proportion of participants with muscle pain.

Analysis 1.51. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 51 Proportion of participants with creatinine kinase increase.

Analysis 1.52. Comparison 1 Radix Sophorae flavescens versus no intervention or placebo, Outcome 52 Proportion of participants with abdominal distention.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Controlled Trials Register	13 December 2018	(sophor* or ku shen or kushen or matrine or oxymatrine or kujin) AND ((hepatitis B or hep B or hbv) and chronic)
Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library	13 December 2018	(sophor* or ku shen or kushen or matrine or oxymatrine or kujin) AND CENTRAL:TARGET MESH DESCRIPTOR Hepatitis B, Chronic EXPLODE ALL AND CENTRAL:TARGET ((hepatitis B or hep B or hbv) and chronic) AND CENTRAL:TARGET #2 OR #3 #1 AND #4
MEDLINE Ovid	1946 to 13 December 2018	1. (sophor* or ku shen or kushen or matrine or oxymatrine or kujin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2. exp Hepatitis B, Chronic/

(Continued)

		<p>3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]</p> <p>4. 2 or 3</p> <p>5. 1 and 4</p>
Embase Ovid	1974 to 13 December 2018	<p>1. (sophor* or ku shen or kushen or matrine or oxymatrine or kujin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]</p> <p>2. exp chronic hepatitis B/</p> <p>3. ((hepatitis B or hep B or hbv) and chronic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]</p> <p>4. 2 or 3</p> <p>5. 1 and 4</p>
LILACS (Bireme)	1982 to 13 December 2018	(sophor\$ or ku shen or kushen or matrine or oxymatrine or kujin) [Words] and ((hepatitis B or hep B or hbv) and chronic) [Words]
Science Citation Index Expanded (Web of Science)	1900 to 13 December 2018	<p>#3 #2 AND #1</p> <p>#2 TS=((hepatitis B or hep B or hbv) and chronic)</p> <p>#1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)</p>
Conference Proceedings Citation Index – Science (Web of Science)	1990 to 13 March 2018	<p>#3 #2 AND #1</p> <p>#2 TS=((hepatitis B or hep B or hbv) and chronic)</p> <p>#1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)</p>
China National Knowledge Infrastructure (CNKI)	1994 to 13 December 2018	<p>Search strategy in Chinese.</p> <p>#1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis)</p> <p>#2 Title/Abstract=(chronic hepatitis B)</p> <p>#3 Text word=(random)</p> <p>#4 #1 AND #2 AND #3</p>
Chongqing VIP (CQVIP)	1989 to 13 December 2018	<p>Search strategy in Chinese.</p> <p>#1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis)</p> <p>#2 Title/Abstract=(chronic hepatitis B)</p> <p>#3 Text word=(random)</p> <p>#4 #1 AND #2 AND #3</p>
Wanfang Data	1982 to 13 December 2018	Search strategy in Chinese.

(Continued)

#1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis)

#2 Title/Abstract=(chronic hepatitis B)

#3 Text word=(random)

#4 #1 AND #2 AND #3

SinoMed	1978 to 13 December 2018	Search strategy in Chinese.
		#1 Title/Abstract=(matrine or oxymatrine or kushen or Radix sophorae flavescentis)
		#2 Title/Abstract=(chronic hepatitis B)
		#3 Text word=(random)
		#4 #1 AND #2 AND #3

CONTRIBUTIONS OF AUTHORS

NL wrote the first draft of the protocol. Five authors (DZK, DN, CG, JCJ, JPL) contributed with comments for revisions. All of the above authors reviewed the final version of the protocol and approved its validity for publication.

Eight authors (SSM, CLL, MY, LDF, XYL, LJC, RLD, CS) independently and in pairs assessed all identified articles for inclusion and exclusion, ensuring that an article was assessed by at least two authors. If a trial was identified as relevant by one author, but not by another, the authors discussed the reasons behind their decision. When they still disagreed, JPL served as arbitrator. Eight authors (SSM, CLL, MY, LDF, XYL, LJC, RLD, CS) tried to contact the trial authors for missing information such as randomisation method at least two times either by phone or by email, and in pairs extracted data and validated data. NL and DZK assessed the risk of bias of the included studies. When the authors still disagreed after discussion concerning the extracted data and risk of bias assessment, JPL served as an arbitrator. NL and DZK conducted data synthesis and analyses.

NL wrote the first draft of the review. All remaining authors contributed with comments for revisions. All authors reviewed the final version of the review and approved its validity for publication.

DECLARATIONS OF INTEREST

NL: none known
DZK: none known
SSM: none known
CLL: none known
MY: none known
LDF: none known
XYL: none known
LJC: none known
RLD: none known
CS: none known
DN: none known
JCJ: none known
CG: none known
JPL: none known

SOURCES OF SUPPORT

Internal sources

- Copenhagen Trial Unit, Denmark.

External sources

- China State Scholarship Fund (File No. 201706550015), China.

- Capacity Building in Evidence-based Chinese Medicine and Internationalization Project (1000061020008), China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Almost half of the trials (9/19) had zero events regarding the outcome the proportion of participants with adverse events considered 'not to be serious'. Post hoc, we used risk difference rather than risk ratio to meta-analyse the data from all 19 trials.

In case of one trial providing outcome data, when Fisher's exact test could not be calculated due to the limitation of this algorithm, we performed the χ^2 test instead. Post hoc, we compared the results of Fisher's exact test/ χ^2 test with RevMan Analysis, and we found no differences between them. Therefore, in view of future updates of the review, we kept and presented only the results obtained via the RevMan analysis.

We did not assess harmful effects of *Radix Sophorae flavescens* if such data were reported in the studies, listed in 'Excluded studies', and in the 'On waiting list' studies. This is because we intend to conduct a systematic review on harms of *Sophorae flavescens*, reported in observational studies.

Post hoc, we decided to present the results on our surrogate outcomes: proportion of participants with detectable HBV-DNA; and proportion of participants with detectable HBeAg, in the Summary of findings table, in the Abstract, and in the Plain language summary.

Following Cochrane central requirements, we have now excluded the bias risk domain on 'for-profit funding' from the bias risk domains listed in the protocol part of the review, and instead, we reported the gathered information from the trials in a narrative way. Hence, we post-hoc planned a subgroup analysis on trials with for-profit funding compared to trials without for-profit funding. In addition, following Cochrane central requirements, we assessed imprecision with Trial Sequential Analysis in separate with the assessment of imprecision with GRADE in a sensitivity analysis.

The review title is slightly different from the title of the published protocol "*Radix Sophorae flavescens* for chronic hepatitis B" as it contains the control intervention comparisons 'no intervention or placebo'.

NOTES

Cochrane Reviews can be expected to have a high percentage of overlap in the methods section because of standardised methods, and because of common participants, interventions, comparisons, outcomes, and time (PICOT). In addition, overlap may be observed across several of our protocols and reviews, as they share at least six common authors.

INDEX TERMS

Medical Subject Headings (MeSH)

*Drugs, Chinese Herbal; Hepatitis B, Chronic [*drug therapy]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic; Sophora [*chemistry]; Treatment Outcome

MeSH check words

Humans