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Radix Sophorae flavescens versus other drugs or herbs for chronic hepatitis B (Review)

Liang N, Kong DZ, Lu CL, Ma SS, Li YQ, Nikolova D, Jakobsen JC, Gluud C, Liu JP

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	11
Figure 1.	12
Figure 2.	14
Figure 3.	15
Figure 4.	17
Figure 5.	18
Figure 6.	20
DISCUSSION	21
AUTHORS' CONCLUSIONS	24
ACKNOWLEDGEMENTS	24
REFERENCES	26
CHARACTERISTICS OF STUDIES	35
DATA AND ANALYSES	48
Analysis 1.1. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 1 Proportion of participants with ≥ 1 adverse events considered 'not to be serious'.	52
Analysis 1.2. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 2 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' form and administration route.	52
Analysis 1.3. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 3 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' duration.	52
Analysis 1.4. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 4 Proportion of participants with ≥ 1 adverse events considered 'not to be serious;' control drug.	53
Analysis 1.5. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 5 Proportion of participants with detectable HBV-DNA.	54
Analysis 1.6. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 6 Proportion of participants with detectable HBV-DNA: best-worst scenario.	54
Analysis 1.7. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 7 Proportion of participants with detectable HBV-DNA: worst-best scenario.	54
Analysis 1.8. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 8 Proportion of participants with detectable HBV-DNA: blinding of outcome assessments.	55
Analysis 1.9. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 9 Proportion of participants with detectable HBV-DNA: incomplete outcome data.	56
Analysis 1.10. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 10 Proportion of participants with detectable HBV-DNA: form and administration route.	56
Analysis 1.11. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 11 Proportion of participants with detectable HBV-DNA: duration.	57
Analysis 1.12. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 12 Proportion of participants with detectable HBV-DNA: control drug.	58
Analysis 1.13. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 13 Proportion of participants with detectable HBeAg.	59
Analysis 1.14. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 14 Proportion of participants with detectable HBeAg: best-worst scenario.	59
Analysis 1.15. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 15 Proportion of participants with detectable HBeAg: worst-best scenario.	60
Analysis 1.16. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 16 Proportion of participants with detectable HBeAg: blinding of outcome assessments.	60
Analysis 1.17. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 17 Proportion of participants with detectable HBeAg: incomplete outcome data.	61

Analysis 1.18. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 18 Proportion of participants with detectable HBeAg: form and administration route.	62
Analysis 1.19. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 19 Proportion of participants with detectable HBeAg: duration.	63
Analysis 1.20. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 20 Proportion of participants with detectable HBeAg: control drug.	63
Analysis 1.21. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 21 Proportion of participants with nausea.	64
Analysis 1.22. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 22 Proportion of participants with stomach upset.	64
Analysis 1.23. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 23 Proportion of participants with rash.	65
Analysis 1.24. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 24 Proportion of participants with loss of appetite.	65
Analysis 1.25. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 25 Proportion of participants with fatigue.	65
Analysis 1.26. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 26 Proportion of participants with liver pain.	65
Analysis 1.27. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 27 Proportion of participants with jaundice.	65
APPENDICES	66
CONTRIBUTIONS OF AUTHORS	85
DECLARATIONS OF INTEREST	85
SOURCES OF SUPPORT	86
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	86
NOTES	86
INDEX TERMS	86

[Intervention Review]

Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B

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ABSTRACT

Background

Hepatitis B virus (HBV) infection is a liver disease caused by hepatitis B virus, which may lead to serious complications such as cirrhosis and hepatocellular carcinoma. People with HBV infection may also have coinfections including HIV and other hepatitis viruses (hepatitis C or D), and coinfections may increase the risk of all-cause mortality. Chronic HBV infection increases morbidity, psychological stress, and it is an economic burden on people with chronic hepatitis B and their families. Radix Sophorae flavescentis, a herbal medicine, is administered mostly in combination with other drugs or herbs. It is believed that it decreases discomfort and prevents the replication of the virus in people with chronic hepatitis B. However, the benefits and harms of Radix Sophorae flavescentis on patient-centred outcomes are unknown, and its wide usage has never been established with rigorous review methodology.

Objectives

To assess the benefits and harms of Radix Sophorae flavescentis versus other drugs or herbs in people with chronic hepatitis B.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, and seven other databases to December 2018. We also searched the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry for ongoing or unpublished trials to December 2018.

Selection criteria

We included randomised clinical trials, irrespective of publication status, language, or blinding, comparing Radix Sophorae flavescentis versus other drugs or herbs for people with chronic hepatitis B. In addition to chronic hepatitis B, participants could also have had cirrhosis, hepatocellular carcinoma, or any other concomitant disease. We excluded polyherbal blends containing Radix Sophorae flavescentis. We allowed cointerventions when the cointerventions were administered equally to all intervention groups.

Data collection and analysis

Review authors in pairs individually retrieved data from 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 the meta-analysed results as risk ratios (RR) with 95% confidence intervals (CI). We assessed the risk of bias using domains with predefined definitions. We conducted Trial Sequential Analyses to control the risks 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 10 randomised clinical trials with 898 participants. We judged all trials at high risk of bias. The trials covered oral capsules, intravenous infusion, intramuscular injection, and acupoint (a specifically chosen site of acupuncture) injection of *Radix Sophorae flavescens* with a follow-up period from 1 to 12 months. The drugs being used as a comparator were lamivudine, adefovir, interferon, tiopronin, thymosin, or other Chinese herbs. Two trials included children up to 14 years old. Participants in one trial had cirrhosis in chronic hepatitis B. None of the trials reported all-cause mortality, health-related quality of life, serious adverse events, hepatitis B-related mortality, or morbidity. We are uncertain as to whether *Radix Sophorae flavescens* has a beneficial or harmful effect on adverse events considered 'not to be serious' (RR 0.86, 95% CI 0.42 to 1.75; $I^2 = 0\%$; 2 trials, 163 participants; very low-certainty evidence), as well as if it decreases or increases the proportion of participants with detectable HBV-DNA (RR 1.14, 95% CI 0.81 to 1.63; $I^2 = 92\%$; 8 trials, 719 participants; very low-certainty evidence). *Radix Sophorae flavescens* showed a reduction in the proportion of participants with detectable hepatitis B virus e-antigen (HBeAg) (RR 0.86, 95% CI 0.75 to 0.98; $I^2 = 43\%$; 7 trials, 588 participants; very low-certainty evidence).

Two of the 10 trials were not funded, and one received academic funding. The remaining seven trials provided no information on funding.

The randomisation process in another 109 trials was insufficiently reported to ensure the inclusion of any of these studies in our review.

Authors' conclusions

The included trials lacked data on all-cause mortality, health-related quality of life, serious adverse events, hepatitis-B related mortality, and hepatitis-B related morbidity. The evidence on the effect of *Radix Sophorae flavescens* on the proportion of participants with adverse events considered 'not to be serious' and on the proportion of participants with detectable HBV-DNA is still unclear. We advise caution regarding the results of *Radix Sophorae flavescens* showing a reduction in the proportion of people with detectable HBeAg because the trials were at high risk of bias, because it is a non-validated surrogate outcome, and because of the very low certainty in the evidence. As we were unable to obtain information on a large number of studies regarding their trial design, we were deterred from including them in our review. Undisclosed funding may have influence on trial results and lead to poor design of the trial. In view of the wide usage of *Radix Sophorae flavescens*, we need large, unbiased, high-quality placebo-controlled randomised trials assessing patient-centred outcomes.

PLAIN LANGUAGE SUMMARY

Radix Sophorae flavescens versus other medicines or herbs for chronic hepatitis B

Review question

To assess the benefits and harms of *Radix Sophorae flavescens* versus other medicines or herbs in people with chronic hepatitis B.

Background

Chronic hepatitis B virus (HBV) infection is a common liver disease, associated with high morbidity (illness) and death. It causes psychological stress and is a burden to people with chronic hepatitis B and their families. *Radix Sophorae flavescens* is for treating people with chronic hepatitis B as it is believed that it decreases discomfort and prevents the replication of the virus in people with chronic hepatitis B. However, the benefits and harms are still unclear.

Search date

We searched scientific databases in December 2018.

Study characteristics

We included 10 randomised clinical trials (clinical studies where people are randomly put into one of two or more treatment groups) with 898 participants. All the trials were at high risk of bias. The trials covered oral capsules, intravenous (into a vein) infusion, intramuscular (into a muscle) injection, and acupoint (a specifically chosen site of acupuncture) injection of *Radix Sophorae flavescens* with treatment duration from 1 month to 12 months. *Radix Sophorae flavescens* was compared with lamivudine, adefovir, interferon, tiopronin, thymosin, and other Chinese herbs. Two trials included children up to 14 years old. Participants in one trial had cirrhosis (late stage of scarring of the liver) in chronic hepatitis B.

Study funding sources

Two of the 10 trials were not funded, and one received governmental funding. The remaining seven trials provided no information on funding. Undisclosed funding may have influence on trial results and lead to poor design of the trial.

Key results

None of the trials reported health-related quality of life (a measure of a person's satisfaction with their life and health), or followed people who have died from any reason or died from hepatitis B, or who were at risk of dying because of hepatitis B. Side effects considered 'not to be serious' was an outcome in two trials. We could not say if Radix Sophorae flavescentis versus other medicines or herbs was better or worse regarding the occurrence of side effects considered 'not to be serious'. We were uncertain whether Radix Sophorae flavescentis had a positive, neutral, or negative effect on the proportion of participants with detectable HBV-DNA (the genetic blueprint of the virus). Radix Sophorae flavescentis may have reduced the proportion of participants with detectable hepatitis B virus e-antigen (HBeAg; produced by the immune system). However, caution is needed with these findings as the trials providing data on them were small, at high risk of bias, and these outcomes have not yet been proven relevant to people with HBV infection. We identified 109 trials that not be included 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 the evidence on the use of Radix Sophorae flavescentis in 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 side effects cannot be determined as none of the trials reported patient-relevant outcomes. Our certainty in the evidence that Radix Sophorae flavescentis, when compared with other medicines or herbs, would decrease or increase side effects considered 'not to be serious' and number of people with detectable HBV-DNA is very low. Our certainty in the evidence that Radix Sophorae flavescentis decreases the number 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 flavescens versus other drugs or herbs for chronic hepatitis B

Radix Sophorae flavescens versus other drugs or herbs for chronic hepatitis B

Patient or population: chronic hepatitis B

Setting: hospitalised and outpatients

Intervention: Radix Sophorae flavescens

Comparison: other drugs or herbs (lamivudine, adefovir, interferon, tiopronin, thymosin, or other Chinese herbs)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other drugs or herbs	Risk with Radix Sophorae flavescens				
All-cause mortality	No data					—
Proportion of participants with ≥ 1 serious adverse events	No data					—
Health-related quality of life	No data					—
Hepatitis B-related mortality	No data					—
Hepatitis B-related morbidity	No data					—
Proportion of participants with ≥ 1 adverse events considered 'not to be serious' (at maximum follow-up: 1–12 months; median 6 months)	Study population		RR 0.86 (0.42 to 1.75)	163 (2 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c,d}	Number of events < 300 and the CI overlapped no effect and failed to exclude important benefit (RR < 0.75) and important harm (RR > 1.25).
	159 per 1000	136 per 1000 (67 to 277)				
Exploratory outcome: Proportion of participants with detectable HBV-DNA (at maximum follow-up: 1–12 months; median 6 months)	Study population		RR 1.14 (0.81 to 1.63)	719 (8 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c,d}	I ² = 92%, which could implicate substantial heterogeneity. Number of events < 300 and the CI overlapped no effect and failed to exclude important harm (RR > 1.25).
	646 per 1000	738 per 1000 (523 to 1053)				

Exploratory outcome:	Study population		RR 0.86 (0.75 to 0.98)	588 (7 RCTs)	⊕⊕⊕⊕ Very low ^{a,c,d}	Optimal information size criteria not met and sample size not very large (< 4000 participants).
Proportion of participants with detectable HBeAg	786 per 1000	666 per 1000 (590 to 770)				
(at maximum follow-up: 1–12 months; median 6 months)						

***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; **HBeAg:** hepatitis B virus e-antigen; **HBV-DNA:** hepatitis B virus DNA; **RCT:** randomised clinical trial; **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 two levels because of within-study risk of bias: the trials had inadequate allocation concealment, unblinded assessment of outcome by potentially biased people (e.g. participants) using self-reported scales, and high risk of selective reporting.

^bDowngraded one level because of heterogeneity or inconsistency of results. The trials included heterogeneous participants, covered different forms and routes of administration of Radix Sophorae flavescentis, and used different drugs or herbs in the control group.

^cDowngraded two levels (for the proportion of participants with one or more adverse events considered 'not to be serious' outcome and the proportion of participants with detectable HBeAg outcome) or one level (for the proportion of participants with detectable HBeAg outcome) because of imprecision of the result.

^dDowngraded one level because of risk of publication bias: all included studies were small.

BACKGROUND

Description of the condition

Hepatitis B is a liver disease caused by hepatitis B virus. Hepatitis B virus belongs to the *Hepadnaviridae* family of small, enveloped, primarily hepatotropic DNA viruses and is commonly classified into 10 genotypes (A through to J) (Sunbul 2014; Tong 2016). Hepatitis B virus is spread through percutaneous and mucosal exposure to blood and other body fluids such as semen and saliva of people infected with hepatitis B virus (Hou 2005; WHO 2015). Despite that vaccination against hepatitis B virus has substantially reduced the number of newborns with mother-to-child transmission of hepatitis B infection (Goldstein 2005; Lee 2006; WHO 2015; WHO 2017), in 2015, there were approximately 257 million people around the world, or 3.5% of the world's population, infected with hepatitis B virus (WHO 2017). In 2015, the estimated prevalence of hepatitis B virus infection was highest in Africa and the Western Pacific regions (WHO 2017). About 20% to 30% of chronically infected people can develop complications such as cirrhosis or hepatocellular carcinoma (WHO 2015). In 2015, 887,000 people may have died because of chronic hepatitis B virus infection (WHO 2018). People with hepatitis B infection may also have coinfections including HIV and other hepatitis viruses (hepatitis C and D) (Derikx 2011; Mallet 2017), and the coinfections may increase the risk of all-cause mortality (Puoti 2000; Mallet 2017). Chronic hepatitis B infection is a substantial morbidity, psychological stress, and economic burden for the infected people 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, assessment of liver disease activity and severity (e.g. liver biopsy, abdominal hepatic ultrasound, and alanine transaminase assessments), and markers of hepatitis B virus infection (e.g. HBV-DNA and hepatitis B virus e-antigen (HBeAg)) (Pellicelli 2008; Jones 2009; Shepherd 2009; AASLD 2016; Wang 2016a; EASL 2017). An immunological cure may be defined as HBeAg loss and sustained HBV-DNA suppression, and a virological cure may be defined as eradication of the virus from the blood, including the covalently closed circular DNA (cccDNA) form (EASL 2017). Reducing mortality and hepatitis B-related morbidities such as liver cirrhosis, liver failure, and liver cancer; prolonging survival; and improving quality of life are the main goals of chronic hepatitis B treatment (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 in traditional medicine for centuries 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 and 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 2004; Mao 2004; Zhu 2009; Zou 2009). The treatment period usually ranges from one month to 24 months (Yin 2011; Lu 2012; Zhang 2012; 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 2015). People taking Zhi xue capsule, which consists of *Radix Sophora flavescentis* (ku shen) and *Cortex Dictamnus dasycarpus* (bai xian pi), have reported hepatotoxicity (Chan 2011).

How the intervention might work

The Chinese Pharmacopoeia reads that *Radix Sophorae flavescentis* is used to remove heat and damp from the body, and that it can be used for 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 (C₁₅H₂₄N₂O) and oxymatrine (C₁₅H₂₄N₂O₂) are the main components (Liu 2003a). Animal studies have suggested that matrine may prevent liver fibrogenesis by inhibiting platelet derived growth factor (PDGF) synthesis and the transforming growth factor beta-1 (TGF-β1) proliferation (Zhang 2001a), and matrine may inhibit hepatitis B virus replication by increasing Th1 cytokines and decreasing Th2 cytokines to trigger immune responses (Dong 2002). In cell studies, matrine is associated with an anticancer action by inhibiting telomerase and tumour proliferation, preventing tumour cell invasion, and inducing tumour cell apoptosis (Qin 2009; Li 2017). Oxymatrine may inhibit hepatitis B virus replication in vitro by interfering with the process of packaging pregenomic 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. Previously published reviews may have been limited by focusing only on specific group of chronic hepatitis B population (Qi 2013), or assessing only specific form or treatment duration of *Radix Sophorae flavescentis* (Qi 2013; Song 2016). The reviews are likely not able to give dependable results because of flaws in their methodology, such as lack of a protocol, inadequate technique for risk of bias assessment, or unjustified restriction for literature searching (Liu 2003b; Qi 2013; He 2013; Jiang 2013; Song 2016; Wang 2017). Moreover, the translation of the review results into practice were impossible as the review authors primarily focused on assessing the 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; Fleming 2012; Ciani 2017; Jakobsen 2017; Kemp 2017; Jakobsen 2018). Thus, the clinical benefits and harms of *Radix Sophorae flavescentis* remain vague. As assessing benefits and harms of an intervention versus another requires assessment of the intervention against placebo or no intervention, we have planned two reviews: *Radix Sophorae flavescentis* for chronic hepatitis B (Liang 2018a), and this current one entitled: *Radix Sophorae flavescentis* versus other drugs or herbs for chronic hepatitis B (Liang 2018b). In the Liang 2018a review, we compared *Radix Sophorae flavescentis* with placebo or no intervention, but we could not present any results on all-cause mortality, health-related quality of life, serious adverse events, hepatitis-B related mortality, and hepatitis-B related morbidity as trial data for these outcomes were lacking. We could not find sufficient evidence for the effect of *Radix*

Sophorae flavescens on proportion of participants with adverse events considered 'not to be serious.' We have very low confidence that Radix Sophorae flavescens may decrease the proportion of people with detectable HBV-DNA and detectable HBeAg because the trials were at high risk of bias and because both outcomes were non-validated surrogate outcomes (hypothesis generating) (Liang 2018a).

OBJECTIVES

To assess the benefits and harms of Radix Sophorae flavescens versus other drugs or herbs in people with chronic hepatitis B.

METHODS

Criteria for considering studies for this review

Types of studies

We included 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 with our searches for randomised clinical trials. This is because adverse events are rarely reported in randomised clinical trials (Storebø 2018). Moreover, observational studies may provide information on rare or late-occurring adverse events (Storebø 2018). We were aware that the decision not to search for all observational studies might bias our review towards assessment of benefits and might overlook certain harms such as late or rare harms. If we demonstrate benefits from using Radix Sophorae flavescens or its extractions in people with chronic hepatitis B, then a systematic review of harms of Radix Sophorae flavescens or its extractions in people with chronic hepatitis B in observational studies ought to be launched.

Types of participants

Inclusion criteria

Trial participants of any sex and age, diagnosed with chronic hepatitis B, as defined by trialists or according to guidelines (HBeAg positivity for more than six months, serum HBV-DNA positivity more than 2000 IU/mL (i.e. more than 10⁴ copies/mL), persistent or intermittent elevation in levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), and liver biopsy findings showing chronic hepatitis B with moderate or severe necroinflammation) (AASLD 2016; EASL 2017).

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

Exclusion criteria

None.

Types of interventions

Experimental intervention

Radix Sophorae flavescens or its extractions (e.g. matrine, oxymatrine) at any dose, form, or regimen. We excluded polyherbal blends containing Radix Sophorae flavescens because it was impossible to determine if the observed effect was in association with Radix Sophorae flavescens or with the other herbs.

Control intervention

Drugs or herbs recommended either by guidelines (interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir, and emtricitabine) (EASL 2012; AASLD 2016; EASL 2017), or commonly used in clinical practice (e.g. *Phyllanthus* species) (Xia 2011; Xia 2013), for people with chronic hepatitis B.

We allowed cointerventions in the experimental and control intervention groups when the cointerventions were administered equally to all the 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 resulted in death, was life threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was 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 the 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, hepato-renal syndrome, hepatocellular carcinoma, hepatic encephalopathy, or needed liver transplantation, and who had 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 (hbg.cochrane.org/), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2018, Issue 12), MEDLINE Ovid, Embase Ovid, 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: China Network Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), Wanfang Data, and SinoMed. Our last search was 13 December 2018. Appendix 1 provides the search strategies with the time spans for the searches.

Searching other resources

We searched the reference lists of meta-analyses on this topic. 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 guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary Group Module (hbg.cochrane.org/), and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines (MECIR 2018).

We performed analyses using Review Manager 5 (Review Manager 2014), and Trial Sequential Analysis version 0.9.5.10 Beta software (Thorlund 2011a; TSA 2011).

Selection of studies

Review authors in pairs (SSM, CLL, YQL, NL) independently screened titles and abstracts to identify potentially eligible trials. We intended to list multiple reports of the same trial under their main reference. We listed ineligible studies with reasons for exclusion in the [Characteristics of excluded studies](#) table. We resolved any 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, YQL, NL) independently extracted data using a prepiloted 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 still existed, 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). When data were missing in the reports, we contacted the trial authors for the missing information. We extracted data at maximum follow-up.

Assessment of risk of bias in included studies

Two review authors (NL and DZK) independently assessed the risk of bias in the included trials. We assessed risk of bias according to the Cochrane 'Risk of bias' tool (Higgins 2011), the Cochrane Hepato-Biliary Group Module (hbg.cochrane.org/), 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 number 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 only include such studies 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 only include such studies 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 rarely no blinding or incomplete blinding, but the review authors judged that the outcome was unlikely to be influenced by lack of blinding, such as mortality.
- 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 rarely no blinding of outcome assessment, but the review authors judged that the outcome measurement was unlikely to be influenced by lack of blinding, such as mortality.
- 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 on 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 was available (e.g. on ClinicalTrials.gov or other full-available databases), and all prespecified outcomes of interest in the review (all-cause mortality, serious adverse events, and health-related quality of life) were reported in the prespecified way; or the trial protocol was not available or was registered after the trial began, but all expected outcomes were reported in the trial publication.
- Unclear risk of bias: not all predefined 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 the data on these outcomes were reported or not.
- High risk of bias: one or more outcomes in the trial protocol were not reported as prespecified or expected in the trial publication; or outcomes in the trial publication were missing, 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 could not 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 was classified at overall low risk of bias only if all of the risk of bias sources described above were classified at low risk of bias.
- High risk of bias: the outcome result was classified at overall high risk of bias if any of the risk of bias sources described above were classified at unclear risk of bias or high risk of bias.

We tried to reach consensus through discussion. We contacted JPL to arbitrate when disagreements still existed.

We planned to base our primary conclusions on the results of all 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 (RR) for measuring dichotomous outcomes, and we intended to use mean differences (MD) for continuous data with 95% confidence intervals (CI) for head-to-head comparison meta-analysis. If studies used different instruments to measure the same continuous outcome, we planned to calculate the standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

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

The unit of analysis was the participants randomised into the trial intervention groups. For trials with multiple intervention groups, we included the groups in which our experimental and control interventions were compared. We planned to divide the control group into two or more 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 accounted for the cluster design. We planned to determine the inflated errors, that accounted 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). However, 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). However, we found no cross-over trials.

Dealing with missing data

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

We performed our 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 scenario: we assumed that all participants lost to follow-up in the experimental group had survived, had improvement in clinical symptoms, had no serious adverse events, 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);
- worst- and best-case scenario: 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 events, and had no morbidity (for all dichotomous variables).

For continuous outcomes:

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

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

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the trial participant characteristics and design of included trials. We planned to assess the presence of clinical heterogeneity by comparing effect estimates (see [Subgroup analysis and investigation of heterogeneity](#)) in trial reports in terms of participants with different diagnostic criteria, participants diagnosed with only chronic hepatitis B comparing to participants diagnosed with concomitant diseases, intervention forms and administration ways, duration and dosages of the intervention, cointerventions, different control interventions, and follow-up. Different study designs and risk of bias can contribute to methodological heterogeneity. We assessed statistical heterogeneity by comparing the 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 Chi^2 test with significance threshold set as P less than 0.10, and measured the amount of heterogeneity using the I^2 statistic to assess to what extent heterogeneity was present ([Higgins 2002](#); [Higgins 2003](#); [Higgins 2011](#)). A rough guide of the I^2 statistic was as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may 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 the I^2 statistic used for this purpose might underestimate the required information size ([Wetterslev 2009](#)).

Assessment of reporting biases

We planned to assess reporting bias using funnel plots if we had data from at least 10 trials per comparison. To assess bias risk, we planned to look for symmetry or asymmetry of each funnel plot. For dichotomous outcomes, we planned to assess asymmetry using the Harbord test ([Harbord 2006](#)). For continuous outcomes, we intended to apply the regression asymmetry test ([Egger 1997](#)).

Data synthesis

Meta-analysis

We performed the meta-analyses following the instructions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), and the Cochrane Hepato-Biliary Group Module (hbg.cochrane.org/). We analysed data using Review Manager 5 ([Review Manager 2014](#)).

We assessed our intervention effects with both fixed-effect model and random-effects model meta-analyses, and we planned to report 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, in order to secure a family-wise error rate below 0.05 ([Jakobsen 2014](#)). For the 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 the statistical and clinical heterogeneity of the meta-analysed trial data per comparison.

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

When data were available from only one trial, we used Fisher's exact test for dichotomous data ([Fisher 1922](#)), and planned to use Student's t -test for continuous data ([Student 1908](#)).

Trial Sequential Analysis

As cumulative meta-analysis contains a risk of producing random errors due to sparse data and repetitive testing, we performed Trial Sequential Analysis. To minimise random errors, we calculated the DARIS (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) ([Wetterslev 2008](#); [Thorlund 2011a](#); [TSA 2011](#)). The DARIS 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 of the meta-analysis, a relative risk reduction of 15%, an alpha of 2.5% for primary and secondary outcomes, 5.0% for exploratory outcomes, a beta of 10% ([Castellini 2017](#)), and diversity suggested by the 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 the trials in the meta-analysis ([Wetterslev 2009](#); [Jakobsen 2014](#)).

We tested statistical significance and futility 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, it 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 the trial monitoring boundaries for futility are not crossed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect ([Wetterslev 2008](#); [Thorlund 2011b](#)). In our cases, when 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 regarding blinding of outcome assessment;
- trials at low risk of bias compared to trials at high risk of bias regarding incomplete outcome data;
- trials at low risk of bias compared to trials at high risk of bias regarding selective outcome reporting;
- trials with for-profit funding compared to trials without for-profit funding (Lundh 2017);
- different administration routes of *Radix Sophorae flavescentis*;
- different duration of the intervention stratified according to the medians observed (less than or more than six months);
- different drugs or herbs in the control group;
- participants according to different diagnostic criteria;
- 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 in [Dealing with missing data](#), we also compared our GRADE imprecision assessments to those conducted with Trial Sequential Analysis (Jakobsen 2014). Furthermore, we planned to use sensitivity analyses whenever we wanted to test the robustness of our finding (Jakobsen 2014; Castellini 2018; Gartlehner 2019). We planned to report this in the [Differences between protocol and review](#) section.

'Summary of findings' table

We constructed a 'Summary of findings' table in order to show our results and confidence in the evidence on all [Primary outcomes](#) and [Secondary outcomes](#). The 'Summary of findings' table displayed information of assumed control group risk, corresponding intervention group risk, relative effect, CI, statistical significance of relative effect, number of participants, and certainty of the evidence. The corresponding risk (and its 95% CI) was calculated 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 the study design and implementation that suggest the quality 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 (Balslem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Mustafa 2013; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; [GRADEpro GDT](#); Guyatt 2017).

The certainty of 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 3250 duplicated or clearly irrelevant references, we read 794 full-text references. Of these, 631 references have been discussed in another Cochrane Review which compared *Radix Sophorae flavescentis* versus placebo or no intervention (Liang 2018a). Of the remaining 163 references, we excluded 44 references with reasons listed in the [Characteristics of excluded studies](#) table and displayed the summary information on 109 references which failed to provide clear description of random sequence generation methods ([Appendix 2](#)). We found no ongoing and unpublished trials.

Figure 1. Study flow diagram. Last search 13 December 2018

Figure 1. (Continued)

Included studies

Ten randomised clinical trials fulfilled the inclusion criteria of our review (Xu 2003; Huang 2004; Huang 2005; Liang 2006; Zhang 2007; Deng 2010; Xi 2010; Zhang 2011; Wang 2013; Yan 2017). Eight trials provided data for our meta-analyses (Xu 2003; Huang 2004; Huang 2005; Liang 2006; Zhang 2007; Xi 2010; Zhang 2011; Wang 2013). The remaining two trials did not study the outcomes of interest for our review, and hence, we used the provided information only in a narrative way. All 10 trials were conducted in China and were published as full paper articles. One of the publications was published in English (Yan 2017), while the others were published in Chinese. Yan 2017 was a multi-centre dummy placebo-controlled randomised clinical trial. We found the protocol for only one trial (Yan 2017). All but four trials were two-armed parallel-group trials with two three-armed parallel group trials (Huang 2005; Xi 2010), and two four-armed parallel group trials (Huang 2004; Zhang 2011), for which only the relevant intervention and control arms were included in our review. For further details on included studies, see [Characteristics of included studies](#). Two of the 10 trials were not funded, and one received academic funding. The remaining seven trials provided no information on funding. Undisclosed funding may influence trial results and may lead to poor trial design.

Participants

The 10 randomised clinical trials included 898 participants (Xu 2003; Huang 2004; Huang 2005; Liang 2006; Zhang 2007; Deng 2010; Xi 2010; Zhang 2011; Wang 2013; Yan 2017). The number of participants in the 10 trials ranged from 63 to 131. The mean age of participants of all 10 trials was 32 years. Seven trials reported the sex of the participants, and the rate of male:female was 406:126 (Xu 2003; Huang 2004; Liang 2006; Zhang 2007; Deng 2010; Xi 2010; Yan 2017). Participants in all trials were diagnosed with chronic hepatitis B following diagnostic criteria described in guidelines. In addition to the participants diagnosed with chronic hepatitis B, Xu 2003 included participants with cirrhosis. Two trials included children up to 14 years old (Xi 2010; Zhang 2011).

Interventions and comparisons

The 10 trials assessed various forms of *Radix Sophorae flavescentis*: four trials assessed oral capsules (Huang 2004; Liang 2006; Wang

2013; Yan 2017); three trials assessed intravenous infusion (Huang 2005; Deng 2010; Zhang 2011); one trial used intramuscular injection (Zhang 2007); and two trials used intravenous infusion followed by oral capsules (Xu 2003; Xi 2010).

The comparators were lamivudine in Zhang 2007 and Zhang 2011), adefovir in Wang 2013, interferon in Huang 2004, tiopronin in Liang 2006, thymosin in Huang 2005, and Chinese herbs in four trials (Xu 2003; Deng 2010; Xi 2010; Yan 2017). Eight trials had equally implemented cointerventions: four trials received glycyrrhizin diamine plus vitamin or liver protective drugs as cointerventions (Huang 2005; Zhang 2007; Deng 2010; Zhang 2011); two trials received glucuronolactone plus vitamins as cointerventions (Xu 2003; Liang 2006); one trial used silymarin as cointervention (Huang 2004); and one trial received basic treatment as cointerventions (Wang 2013). The follow-up periods ranged from one month to 12 months.

Outcomes

None of the 10 trials reported data on all-cause mortality, serious adverse events, health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity. Two trials reported data on adverse events considered 'not to be serious' (Liang 2006; Xi 2010); eight trials reported proportion of participants with detectable HBV-DNA (Xu 2003; Huang 2004; Huang 2005; Liang 2006; Zhang 2007; Xi 2010; Zhang 2011; Wang 2013); and seven trials reported proportion of participants with detectable HBeAg (Xu 2003; Huang 2004; Huang 2005; Liang 2006; Zhang 2007; Xi 2010; Zhang 2011).

Two trials also reported other biomarkers such as liver (function) tests (e.g. aspartate transaminase) (Deng 2010; Yan 2017). One trial reported efficacy assessment index which was a composite outcome combining liver (function) tests, HBV-DNA, and HBeAg (Yan 2017).

Excluded studies

We excluded 44 references after reading the full texts of the articles. We explained the reasons for their exclusion in the [Characteristics of excluded studies](#) table. We excluded further 109 references because of insufficient information (Appendix 2).

Risk of bias in included studies

We carried out the risk of bias assessment based on the information retrieved from the publications and some from the trial authors.

We judged many trials to have unclear risk of bias in certain domains because we could not obtain additional information from the authors after we contacted them. See 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3) for detailed information.

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
Deng 2010	+	?	?	?	+	-	?
Huang 2004	+	-	-	+	-	-	+
Huang 2005	+	-	?	+	-	-	+
Liang 2006	+	?	-	?	+	-	+
Wang 2013	+	?	-	?	+	-	?
Xi 2010	+	?	-	?	+	-	+
Xu 2003	+	?	-	?	+	-	+
Yan 2017	+	?	+	?	-	+	+
Zhang 2007	+	?	-	?	+	-	+
Zhang 2011	+	?	-	?	+	-	+

Allocation

All trials used a random number table, computer software, or ball-grabbing method to generate the random sequence.

Two trials did not implement any method to conceal the allocation and were at high risk of bias (Huang 2004; Huang 2005); the remaining eight trials did not report how the allocation concealment was performed, resulting our assessment of unclear risk of bias.

Blinding

Yan 2017 used a dummy placebo-controlled design and was at low risk of bias regarding blinding of participants and personnel; seven trials compared two drugs which had different forms and administration routes, and there was no blinding, so were at high risk of bias (Xu 2003; Huang 2004; Liang 2006; Zhang 2007; Xi 2010; Zhang 2011; Wang 2013); the remaining two trials did not describe blinding method of participants and personnel and thus were at unclear risk of bias.

Two trials blinded outcome assessors, and were at low risk of bias (Huang 2004; Huang 2005); the remaining eight trials did not describe blinding method of outcome assessment, so were at unclear risk of bias.

Incomplete outcome data

Seven trials reported having no missing outcome data and included all participants in data analyses and were at low risk of bias (Xu 2003; Liang 2006; Zhang 2007; Deng 2010; Xi 2010; Zhang 2011; Wang 2013). The remaining three trials had dropouts and did not use adequate methods to deal with missing data, so were at high risk of attrition bias.

Selective reporting

We found the protocol of Yan 2017, and all the predefined outcomes in the protocol were reported in the published paper. So we assessed Yan 2017 at low risk of reporting bias. The remaining nine trials seemed at high risk of bias regarding the selective reporting domain because of lack of prepublished trial protocols and no data

reporting on mortality, serious adverse events, and health-related quality of life.

Other potential sources of bias

Two trials had only one author in the publications, and the author did not mention any acknowledgements (Deng 2010; Wang 2013). If the trial was conducted by a single person in every step, there would be high potential for risks of bias. So we assessed these two trials at unclear risk of other bias before we could obtain further information about the trial conduct. The remaining eight trials appeared free of other factors that could put them at risk of bias, and therefore were at low risk of other biases.

Overall risk of bias

We assessed the 10 randomised clinical trials at overall high risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B](#)

Below, in accordance with our protocol (Liang 2018b), all outcomes were presented with 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

None of the 10 trials provided data on all-cause mortality.

Proportion of participants with one or more serious adverse events

None of the 10 trials provided data on serious adverse events.

Health-related quality of life

None of the 10 trials provided data on health-related quality of life.

Secondary outcomes

Hepatitis B-related mortality

None of the 10 trials provided data on hepatitis B-related mortality.

Hepatitis B-related morbidity

None of the 10 trials provided data on hepatitis B-related morbidity.

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

We were uncertain in the effect of Radix Sophorae flavescentis versus other drugs or herbs on adverse events considered 'not to be serious'; the obtained results were imprecise (RR 0.86, 95% CI 0.42 to 1.75; $I^2 = 0\%$; 2 trials, 163 participants; very low-certainty evidence; Analysis 1.1).

Trial Sequential Analysis

The DARIS was calculated to be 14,661 participants, based on an event proportion in control group of 15.9%, a relative risk reduction of 15%, a two-side alpha of 2.5%; a beta of 10%, and the diversity of 25%. The monitoring boundaries were ignored because only 1.11% (163/14,661) of the information size was accrued (Figure 4).

Figure 4. Trial Sequential Analysis on proportion of participants with one or more adverse events considered 'not to be serious' in two high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 15.9%, relative risk reduction of 15%, type I error 2.5%, type II error 10% (90% power), and diversity 25%. The required information size was 14,661 participants. The monitoring boundaries were ignored because only 1.11% (163/14,661) of the information size was accrued.

Subgroup analysis

We could not perform all of the prespecified subgroup analyses because of insufficient information ([Subgroup analysis and investigation of heterogeneity](#)).

We found no statistically significant differences when comparing trials with different forms and administration routes of Radix Sophorae flavescens (test for subgroup difference: $P = 0.91$, $I^2 = 0\%$; [Analysis 1.2](#)); when comparing trials with different control drugs (test for subgroup difference: $P = 0.91$, $I^2 = 0\%$; [Analysis 1.4](#)); and when comparing trials with follow-up period less than six months to trials with follow-up period more than six months (test for subgroup difference: $P = 0.91$, $I^2 = 0\%$; [Analysis 1.3](#)).

Sensitivity analysis

Both trials that reported data on this outcome included and described all the trial participants as randomised. Hence, performing 'best-worst' and 'worst-best' scenario analyses became irrelevant.

Our GRADE and Trial Sequential Analysis assessments on imprecision for the proportion of participants with adverse

events considered 'not to be serious' outcome did not differ: we downgraded the evidence for imprecision by two levels with GRADE because the number of events was fewer than 300 and the CI overlapped no effect, failing to exclude important benefit (RR less than 0.75) and important harm (RR greater than 1.25) ([GRADE 2013](#); [Schünemann 2016](#)). When the Trial Sequential Analysis was used to assess imprecision, we downgraded the evidence also by two levels because none of the trial sequential boundaries for benefit, harm, or futility were crossed ([Jakobsen 2014](#)).

Exploratory outcomes

Proportion of participants with detectable HBV-DNA

Eight trials with 719 participants reported data on the proportion of participants with detectable HBV-DNA; 262/355 (79%) participants in the Radix Sophorae flavescens group had detectable HBV-DNA versus 235/364 (65%) participants in the group of other drugs or herbs ([Xu 2003](#); [Huang 2004](#); [Huang 2005](#); [Liang 2006](#); [Zhang 2007](#); [Xi 2010](#); [Zhang 2011](#); [Wang 2013](#)). We are uncertain as to whether Radix Sophorae flavescens has an effect on proportion of participants with detectable HBV-DNA because the results were

imprecise and not consistent (RR 1.14, 95% CI 0.81 to 1.63; $I^2 = 92\%$; 8 trials, 719 participants; very low-certainty evidence; [Analysis 1.5](#)).

Visual inspection of the forest plot suggested that the proportion of participants with detectable HBV-DNA in [Zhang 2007](#) and [Wang 2013](#) studies reduced in the group of other drugs or herbs, unlike the proportion of participants with detectable HBV-DNA in the other six trials ([Xu 2003](#); [Huang 2004](#); [Huang 2005](#); [Liang 2006](#); [Xi 2010](#); [Zhang 2011](#); [Analysis 1.5](#)). The high heterogeneity was probably produced by [Zhang 2007](#) and [Wang 2013](#) in which the control arm was lamivudine or adefovir. The subgroup analysis shown below on different comparators showed statistically different ([Analysis 1.12](#)).

However, we should be cautious that there is another trial ([Zhang 2011](#)) showing a different result to [Zhang 2007](#) in which the control arm was also lamivudine and the heterogeneity of this subgroup was high ($I^2 = 96\%$).

Trial Sequential Analysis

The DARIS was calculated to be 15,575 participants, based on an event proportion in control group of 64.6%, a relative risk reduction of 15%, a two-side alpha of 5%; a beta of 10%, and the observed diversity of 93%. The monitoring boundaries were ignored because only 4.62% (719/15,575) of the information size was accrued ([Figure 5](#)).

Figure 5. Trial Sequential Analysis on proportion of participants with detectable hepatitis B virus DNA (HBV-DNA) in eight high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 64.6%, relative risk reduction of 15%, type I error 5%, type II error 10% (90% power), and diversity 93%. The required information size was 15,575 participants. The monitoring boundaries were ignored because only 4.62% (719/15,575) of the information size was accrued.

Subgroup analysis

We could not perform all of the prespecified subgroup analyses because of insufficient data ([Subgroup analysis and investigation of heterogeneity](#)).

We found no statistically significant differences when comparing trials at low risk of bias to trials at high risk of bias regarding the blinding of outcome assessment domain (test for subgroup difference: $P = 0.23$, $I^2 = 30.6\%$; [Analysis 1.8](#)) and incomplete

outcome data domain (test for subgroup difference: $P = 0.23$, $I^2 = 30.6\%$; [Analysis 1.9](#)); and when comparing trials with a period of follow-up of no more than six months to trials with a period of follow-up of more than six months (test for subgroup difference: $P = 0.58$, $I^2 = 0\%$; [Analysis 1.11](#)).

We found a statistically significant subgroup difference when comparing trials with different forms and administration routes of *Radix Sophorae flavescentis* (test for subgroup difference: $P =$

0.002, $I^2 = 79.4\%$; [Analysis 1.10](#)). The subgroup with intramuscular injection of Radix Sophorae flavescentis showed an increase in the proportion of participants with detectable HBV-DNA (RR 11.35, 95% CI 2.91 to 44.27; 1 trial, 63 participants), compared to the subgroup with intravenous infusion (RR 0.94, 95% CI 0.82 to 1.07; 2 trials, 203 participants; $I^2 = 0\%$), as well as to the subgroup with oral capsules (RR 1.45, 95% CI 0.54 to 3.87; 3 trials, 272 participants; $I^2 = 96\%$) and to the subgroup with mixed forms of the drug and administration routes (RR 0.72, 95% CI 0.43 to 1.22; 2 trials, 181 participants; $I^2 = 86\%$). However, we were uncertain whether the effect between the different forms and administration routes of Radix Sophorae flavescentis was truly different or not because the results were imprecise, and the subgroup with oral capsules showed even higher heterogeneity than the overall analysis.

We also found a statistically significant subgroup difference when comparing trials with different comparators (test for subgroup difference: $P < 0.00001$, $I^2 = 89.1\%$; [Analysis 1.12](#)). Radix Sophorae flavescentis may have been associated with a better effect in reducing the proportion of participants with detectable HBV-DNA versus tiopronin (RR 0.74, 95% CI 0.58 to 0.96; 1 trial, 68 participants). However, it may also have had a worse effect than adefovir (RR 4.15, 95% CI 2.64 to 6.55; 1 trial, 131 participants) or may have seen no difference of Radix Sophorae flavescentis versus lamivudine (RR 3.19, 95% CI 0.09 to 114.84; 2 trials, 163 participants; $I^2 = 96\%$), interferon (RR 1.03, 95% CI 0.77 to 1.38; 1 trial, 73 participants), thymosin (RR 0.89, 95% CI 0.73 to 1.08; 1 trial, 103 participants), or other Chinese herbs (RR 0.72, 95% CI 0.43 to 1.22; 2 trials, 181 participants; $I^2 = 86\%$). Based on this subgroup analysis, we must acknowledge the very low certainty in the effect of Radix Sophorae flavescentis for these subgroup comparisons due to imprecision and significant heterogeneity within the subgroups.

Sensitivity analysis

We had to impute data for one trial for the outcome: proportion of participants with detectable HBV-DNA ([Huang 2005](#)). The '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 1.13, 95% CI 0.79 to 1.62; 8 trials, 730

participants; $I^2 = 92\%$; [Analysis 1.6](#); 'worst-best' meta-analysis: RR 1.16, 95% CI 0.82 to 1.65; 8 trials, 730 participants; $I^2 = 92\%$; [Analysis 1.7](#)).

Our GRADE and Trial Sequential Analysis assessments on imprecision for the proportion of participants with detectable HBV-DNA outcome did not differ: we downgraded the certainty of the evidence for imprecision by two levels with GRADE because the number of events was fewer than 300 and the CI overlapped no effect, failing to exclude important benefit (RR less than 0.75) and important harm (RR greater than 1.25) ([GRADE 2013](#); [Schünemann 2016](#)). When the Trial Sequential Analysis was used to assess imprecision, then we downgraded the evidence also by two levels because none of the sequential boundaries for benefit, harm, or futility were crossed ([Jakobsen 2014](#)).

Proportion of participants with detectable HBeAg

Seven trials, with 588 participants, reported data on proportion of participants with detectable HBeAg; 195/293 (67%) participants in the Radix Sophorae flavescentis group had detectable HBeAg versus 232/295 (79%) participants in the control group who received other drugs or herbs ([Xu 2003](#); [Huang 2004](#); [Huang 2005](#); [Liang 2006](#); [Zhang 2007](#); [Xi 2010](#); [Zhang 2011](#)). Radix Sophorae flavescentis showed a better effect in reducing the proportion of participants with detectable HBeAg (RR 0.86, 95% CI 0.75 to 0.98; $I^2 = 43\%$; [Analysis 1.13](#)).

Trial Sequential Analysis

The DARIS was calculated to be 1158 participants, based on an event proportion in control group of 78.6%, a relative risk reduction of 15%, a two-side alpha of 5%; a beta of 10%, and the observed diversity of 48%. The Trial Sequential Analysis showed that the Z-curve did not cross the trial sequential monitoring boundaries for benefit, harm, or futility and the required information size. This indicates that there was insufficient evidence to support or refute a 15% risk reduction of Radix Sophorae flavescentis versus other drugs or herbs in the proportion of participants with detectable HBeAg. The Trial Sequential Analysis-adjusted CI was 0.70 to 1.04 ([Figure 6](#)).

Figure 6. Trial Sequential Analysis on proportion of participants with detectable hepatitis B virus e-antigen (HBeAg) in seven high risk of bias randomised clinical trials. The diversity-adjusted required information size was calculated based on event proportion in control group of 78.6%, relative risk reduction 15%, type I error 5%; type II error 10% (90% power), and diversity 48%. The required information size was 1158 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit, harm, or futility (red inward sloping lines) and the required information size. The green dotted line shows the conventional boundaries (5.0%). The Trial Sequential Analysis-adjusted confidence interval was 0.70 to 1.04.

Subgroup analysis

We could not perform all of the prespecified subgroup analyses because of insufficient information data ([Subgroup analysis and investigation of heterogeneity](#)).

We found no statistically significant differences when comparing trials at low risk of bias to trials at high risk of bias regarding the blinding of outcome assessment domain (test for subgroup difference: $P = 0.20$, $I^2 = 39.9\%$; [Analysis 1.16](#)) and incomplete outcome data domain (test for subgroup difference: $P = 0.20$, $I^2 = 39.9\%$; [Analysis 1.17](#)); when comparing trials with different form and administration routes of Radix Sophorae flavescens (test for subgroup difference: $P = 0.61$, $I^2 = 0\%$; [Analysis 1.18](#)); when comparing trials with a period of follow-up of no more than six months to trials with a period of follow-up of more than six months (test for subgroup difference: $P = 0.58$, $I^2 = 0\%$; [Analysis 1.19](#)); and when comparing trials with different control drugs (test for subgroup difference: $P = 0.42$, $I^2 = 0\%$; [Analysis 1.20](#)).

Sensitivity analysis

We had to impute data for one trial for the outcome: proportion of participants with detectable HBeAg ([Huang 2005](#)). The '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 0.84, 95% CI 0.73 to 0.96; 7 trials, 599 participants; $I^2 = 47\%$; [Analysis 1.14](#); 'worst-best' meta-analysis: RR 0.87, 95% CI 0.79 to 0.96; 7 trials, 599 participants; $I^2 = 51\%$; [Analysis 1.15](#)).

Our GRADE and Trial Sequential Analysis assessments on imprecision for the proportion of participants with detectable HBeAg outcome 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](#); [Schünemann 2016](#)). When the Trial Sequential Analysis was used to assess imprecision, we downgraded the evidence by two levels because none of the sequential boundaries for benefit, harm, or futility were crossed ([Jakobsen 2014](#)).

Separately reported serious adverse events

None of the 10 trials separately reported serious adverse events.

Separately reported hepatitis B-related morbidity

None of the 10 trials separately reported hepatitis B-related morbidity.

Separately reported adverse events considered 'not to be serious'

Following our protocol, we presented the results of dichotomous outcomes from one trial, using Fisher's exact test. As the results between Fisher's exact tests (not shown) and those obtained with Review Manager 5 analysis did not differ, and in view of future updates of the review, we present the analysis result obtained with Review Manager 5 only ([Review Manager 2014](#)).

Based on the reporting of two trials on separately reported adverse events considered 'not to be serious' outcome, our analysis results showed no effect of Radix Sophorae flavescentis on nausea (RR 3.00, 95% CI 0.13 to 71.15; 1 trial, 68 participants; [Analysis 1.21](#); [Liang 2006](#)); stomach upset (RR 0.33, 95% CI 0.01 to 7.91; 1 trial, 68 participants; [Analysis 1.22](#); [Liang 2006](#)); rash (RR 0.33, 95% CI 0.01 to 7.91; 1 trial, 68 participants; [Analysis 1.23](#); [Liang 2006](#)); loss of appetite (RR 0.68, 95% CI 0.31 to 1.51; 1 trial, 95 participants; [Analysis 1.24](#); [Xi 2010](#)); liver pain (RR 0.56, 95% CI 0.22 to 1.38; 1 trial, 95 participants; [Analysis 1.26](#); [Xi 2010](#)); and jaundice (RR 1.13, 95% CI 0.51 to 2.54; 1 trial, 95 participants; [Analysis 1.27](#); [Xi 2010](#)). However, Radix Sophorae flavescentis showed lower risk of fatigue (RR 0.34, 95% CI 0.12 to 0.98; 1 trial, 95 participants; [Analysis 1.25](#); [Xi 2010](#)).

'Summary of findings' tables

We planned to construct a Summary of Finding table on all primary and secondary outcomes ([Primary outcomes](#); [Secondary outcomes](#)). However, because of lack of data, we could present the GRADE assessments with outcome data only for the proportion of participants with one or more adverse events considered 'not to be serious.' Our data ensued from two trials assessing Radix Sophorae flavescentis versus other drugs or herbs (lamivudine, adefovir, interferon, tiopronin, thymosin, or other Chinese herbs) ([Liang 2006](#); [Xi 2010](#)). 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. [Summary of findings for the main comparison](#) presents details on how we assessed the evidence. We defined the certainty of evidence for all outcomes with data as very low.

DISCUSSION

Summary of main results

We identified 10 completed randomised clinical trials with 898 participants. The certainty of the evidence was very low. For our meta-analyses, we could gather quantitative data information from eight of the 10 trials. We could not perform meta-analyses on each of our predefined outcomes. Data on all-cause mortality, serious adverse events, health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity were not reported in any of the included randomised clinical trials. We were uncertain whether Radix Sophorae flavescentis versus other drugs or herbs had significant effect on the proportion of

participants with adverse events considered 'not to be serious' and the proportion of participants with detectable HBV-DNA. Radix Sophorae flavescentis may have decreased the proportion of participants with detectable HBeAg; however, we caution the beneficial effect of Radix Sophorae flavescentis on this non-validated surrogate outcome. We performed Trial Sequential Analysis for all three outcomes, and the monitoring boundaries were not crossed and the required information size was not reached for any of the outcomes. Hence, we could not exclude random errors in the results of the conventional naive meta-analyses. Sensitivity analyses showed that there was no impact of missing data on the results. Regarding the reduction effect on proportion of participants with detectable HBV-DNA, subgroup analyses showed that intramuscular injection of Radix Sophorae flavescentis may have been better than intravenous infusion or oral capsules; Radix Sophorae flavescentis may have been better than tiopronin, but worse than adefovir, and was not significantly different from lamivudine, interferon, thymosin, or other Chinese herbs; however, we were uncertain whether there were truly different in the effect between different forms and administration routes of Radix Sophorae flavescentis; and when compared with different drugs or herbs.

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 the relative reviews for any trials that we might have missed. We found no unpublished or ongoing trials. We identified 109 trials which failed to describe the randomisation methods used. Because it was uncertain if these studies were indeed randomised trials, we were unable to include them in our review; we urged the authors to contact us if the trial indeed was a properly randomised trial. Overall, we included 10 randomised clinical trials in our systematic review.

The participants included in the 10 trials generally reflected the characteristics of the general chronic hepatitis B population. Two trials included children up to 14 years old. One trial recruited participants with cirrhosis. The forms and routes of administration of Radix Sophorae flavescentis varied between trials, as did the duration of treatment and the comparator drugs. The trials assessed Radix Sophorae flavescentis in oral capsules, intravenous infusion, intramuscular injection, and acupoint injection. The follow-up periods were relatively short, with a median of six months and a range of 1 month to 12 months. The comparators used in the 10 trials included lamivudine, adefovir, interferon, tiopronin, thymosin, or other Chinese herbs. We performed meta-analysis only on adverse events considered 'not to be serious' with data from two trials. In contrast, most of the trials reported on exploratory outcomes, the proportion of participants with detectable HBV-DNA and the proportion of participants with detectable HBeAg. The findings in relation to these two outcomes, and whether or not they were clinically meaningful, were inconclusive. We also conducted subgroup analyses and sensitivity analyses in attempts to identify differences in the effects. Based on the scanty evidence, we found no significant differences when comparing trials at low risks of bias to trials at high risks of bias regarding the blinding of outcome assessments domain and the incomplete outcome data domain, when comparing trials with different forms and administration routes of Radix Sophorae flavescentis, when comparing trials with follow-up periods no more

than six months to trials with follow-up periods more than six months, and when comparing trials using different drugs or herbs as comparators.

Quality of the evidence

The lack or insufficiency of clinically relevant data was a serious limitation of our review and findings. Below, we described our assessments of each of the five GRADE factors.

Within-study risk of bias

Risk of bias is known to be responsible for the 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 10 randomised clinical trials, all used adequate generation of randomisation sequence; none (0%) performed adequate allocation concealment; one (10%) was conducted with blinding of participants and two (20%) with binding of outcome assessments; seven (70%) appeared to be uninfluenced by incomplete outcome data; one (10%) appeared free from selective reporting; and eight (80%) appeared free from other bias. All the randomised clinical trials were assessed at overall high risk of bias.

Indirectness of the evidence

All the included trials assessed *Radix Sophorae flavescentis* in people with chronic hepatitis B. We found the 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 considered the outcome, proportion of participants with one or more adverse events considered 'not to be serious', to have appreciable heterogeneity, as the two trials included quite heterogeneous participants (children under 14 years old versus adults). We observed a significant level of heterogeneity regarding the proportion of participants with detectable HBV-DNA outcome ($I^2 = 92\%$), and a moderate level of heterogeneity regarding the proportion of participants with detectable HBeAg outcome ($I^2 = 43\%$). Visual inspection of the forest plot of detectable HBV-DNA outcome indicated that Zhang 2007 and Wang 2013 had extreme opposite results compared to other trials. However, we are unable to prove if the high heterogeneity of 92% was due to the fact that *Radix Sophorae flavescentis* was used as the control drug in two of the trials or not (Zhang 2007; Wang 2013). As shown in our predefined subgroup analyses, the different routes of administration of *Radix Sophorae flavescentis* or the different control drugs being used could be other sources of heterogeneity. Moreover, the small sample sizes of the trials could also be a cause for heterogeneity.

We applied both the fixed-effect and random-effects meta-analysis models, and we found the outcome results of these two models similar.

Imprecision of results

Following the GRADE criteria on 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 fewer than

300 and the CI overlapped no effect, failing to exclude important benefit (RR less than 0.75) and important harm (RR greater than 1.25); for the proportion of participants with detectable HBV-DNA outcomes, we downgraded the evidence by two levels because the optimal information size criteria was not met and the CI overlapped no effect, failing to exclude important harm (RR greater than 1.25); for the proportion of participants with detectable HBeAg outcome, we downgraded the evidence by one level because the optimal information size criteria was not met and the sample size was low (fewer than 4000 participants) (GRADE 2013; Schünemann 2016).

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

Risk of publication bias

We could not construct funnel plots because no more than eight included trials provided data on an outcome. We suspect publication bias because of the small sample sizes and the positive results shown in all trials (GRADEpro GDT; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Guyatt 2017).

Potential biases in the review process

We performed our systematic review in accordance with the recommended methodology (Higgins 2011; Cochrane Hepato-Biliary Group Module; GRADE 2013). We followed our peer-reviewed and prepublished protocol with predefined participants, interventions, comparisons, and outcomes to avoid biased in the review process (Liang 2018b). We performed a comprehensive literature search which covered published and unpublished studies, and combined electronic data searches with manual searches of the reference lists of the identified reviews. We included trials regardless of language of publication and whether they reported data on the outcomes we needed. We contacted relevant authors for additional information. We extracted all available data to perform our predefined analyses, including Trial Sequential Analysis, sensitivity analyses, and several subgroup analyses.

All the trials we identified were carried out in China, which could be because *Radix Sophorae flavescentis* is mostly used in Asian countries. Although we 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, we should search Japanese and Korean medical databases, and contact experts 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 our outcomes of interest. We planned to consider quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms of *Radix Sophorae*

flavescens if retrieved with our searches for randomised clinical trials. One hundred and nine studies, which are on the waiting list due to the lack of details of 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 have biased our reviews towards assessment of benefits and might have overlooked certain harms such as late or rare harms. This decision may currently appear less problematic as we found no beneficial effect of Radix Sophorae flavescens on patient-centred outcomes in this review. Moreover, to conduct a systematic review of observational studies on harms of Radix Sophorae flavescens is desirable.

We identified 109 trials that lacked proper reporting of the randomisation method, and our attempt to receive information from the authors of these 109 trials failed because of reasons listed in [Appendix 2](#). Previous studies have demonstrated misuse of randomisation in Chinese medicine trials which might significantly influence the quality of clinical evidence ([Liu 2002](#); [Wu 2009](#)). Thus, we could not include these 109 trials for analysis until necessary methodology information is received to supplement trial information and data. However, there was a possibility that some true randomised trials were limited by poor reporting, and, therefore, we might have excluded potentially useful trials. Trial authors should realise how important it is to promote their research findings and to reduce research waste ([Chalmers 2009](#); [Al-Shahi Salman 2014](#); [Chalmers 2014](#); [Glasziou 2014](#); [Ioannidis 2014](#); [Macleod 2014](#); [Moher 2016](#)).

A possible limitation of our review could also be that we did not define a minimum duration of treatment with Radix Sophorae flavescens. We did this in order to avoid the 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. The analyses found no difference when comparing trials with Radix Sophorae flavescens interventions for six months or more to trials with interventions administered for less than six months. The subgroups regarding duration of treatment were divided following our predefined definitions using the median as the cut-off value, but this choice of a cut-off value might be questionable.

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

We included several subgroup analyses and numerous outcomes. There could have been problems with multiplicity in terms of the three to five subgroup analyses for each outcome ([Imberger 2011](#)). We did not adjust the threshold for subgroups analyses, as we considered subgroup analyses results as exploratory and only hypothesis-generating.

We conducted Trial Sequential Analyses for the three outcomes: the proportion of participants with adverse events considered 'not to be serious' (secondary outcome); with detectable HBV-DNA (exploratory outcome); and with detectable HBeAg (exploratory outcome) in order to test the robustness of our results ([Wetterslev 2008](#); [Thorlund 2011b](#); [TSA 2011](#); [Wetterslev 2017](#)). We calculated the DARIS on the basis of events proportion in the control group, risk reduction of 15%, type I error 2.5% for secondary outcomes, 5.0% for exploratory outcomes, type II error 10%, and observed diversity ([Wetterslev 2009](#)). The cumulative Z-curves in the three Trial Sequential Analyses did not cross the trial sequential monitoring boundaries neither was the DARIS reached. Therefore, we could not exclude a risk of random errors regarding our results on these three outcomes.

Our search was conducted in December 2018. It is possible that further studies of relevance to our review could have been published since then. This must be dealt with in review updates.

This review was inconclusive as the evidence of any effect, benefit or harm, remained uncertain. This result was 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

Three non-Cochrane meta-analyses on Radix Sophorae flavescens compared with other drugs or herbs have been published ([Liu 2003b](#); [Wu 2011a](#); [Wang 2016b](#)). [Liu 2003b](#) and [Wu 2011a](#) also included trials in which Radix Sophorae flavescens plus a cointervention was compared to a cointervention, or Radix Sophorae flavescens as an adjuvant to an intervention was compared to another intervention. [Wang 2016b](#) assessed the benefits and harms of Radix Sophorae flavescens versus lamivudine. Compared with the three meta-analyses, we dealt more extensively with risk of bias and risk of random errors in the randomised clinical trials included in our review. We performed subgroup and sensitivity analyses in an attempt to identify causes of heterogeneity, explore the impact of missing data on the results, performed Trial Sequential Analyses for all outcomes to control random errors, and used GRADE assessments to define the certainty of the evidence.

[Liu 2003b](#) showed that matrine, when compared with other drugs or herbs (interferon, tiopronin, Chinese herbs), reduced the proportion of participants with detectable HBV-DNA, detectable HBeAg, and the hepatitis B virus surface antigen (HBsAg) level. [Wu 2011a](#) showed that the Radix Sophorae flavescens was not significantly different from interferon and lamivudine in reducing detectable HBeAg; Radix Sophorae flavescens had a better effect than lamivudine, but not than interferon, on reduction of detectable HBV-DNA; compared with other drugs other than interferon and lamivudine (e.g. Chinese herbs), Radix Sophorae flavescens had better effect on reduction of detectable HBeAg and detectable HBV-DNA. [Wang 2016b](#) showed Radix Sophorae flavescens reduced the proportion of participants with detectable HBV-DNA when compared with lamivudine, but there was no evidence of a difference on proportion of participants with detectable HBeAg, ALT levels, and the YMDD mutation. In our review, we found only uncertainties regarding beneficial or harmful

effect of Radix Sophorae flavescentis on adverse events considered 'not to be serious,' proportion of participants with detectable HBV-DNA. The proportion of participants with detectable HBeAg may have been reduced; however, this was based on very low-quality evidence.

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

In view of the wide usage of Radix Sophorae flavescentis, we need more placebo-controlled, blinded randomised clinical trials, which assess patient-centred outcomes. We suggest the following implications for research ([Brown 2006](#)).

Evidence (what is the current state of the evidence?): this review included 10 randomised clinical trials with 898 participants. All trials were at high risk of bias, and the certainty of the evidence was very low. Totally 109 studies failed to provide the method of randomisation in sufficient detail; supplementary methodology information is needed before these studies can be considered for inclusion in future review updates. All-cause mortality, serious adverse events, health-related quality of life, hepatitis B-related mortality, and hepatitis B-related morbidity were not reported in any of the included trials. We found no evidence of a difference of Radix Sophorae flavescentis versus other drugs or herbs on adverse events considered 'not to be serious' and also on detectable HBV-DNA. The analysis on the proportion of participants with detectable HBeAg showed a beneficial decrease in the Radix Sophorae flavescentis group. The DARIS having not been reached indicated more randomised clinical trials were needed. However, we still cannot determine the true effect of Radix Sophorae flavescentis because data on patient-centred outcomes are missing or data regarding other outcomes are insufficient for meaningful analyses.

Participants (what is the population of interest?): we focused on people with chronic hepatitis B, with, or without other concomitant diseases. We could only obtain some information about concomitant diseases from one trial. Since there were only a very few trials providing data for a very few outcomes, further trials with detailed information on concomitant diseases and strictly defined diagnostic criteria are needed. When concomitant disease are present, stratified randomisation should be employed.

Interventions (what are the interventions of interest?): our review covered oral capsules, intravenous infusion, and intramuscular injection of Radix Sophorae flavescentis. Regarding

the reduction effect of detectable HBV-DNA, subgroup analyses showed that intramuscular injection of Radix Sophorae flavescentis may be better than intravenous infusion or oral capsules, but this is based on the limited evidence. The follow-up periods were relatively short with a range from 1 month to 12 months. Therefore, future randomised clinical trials should be designed to look for the differences in the different forms of Radix Sophorae flavescentis, and participants should be followed up for a longer period allowing to observe the long-term effect on outcomes, such as mortality.

Comparisons (what are the comparisons of interest?): future randomised clinical trials should select their comparators among drugs or herbs used for chronic hepatitis B and assessed in systematic reviews. The double placebo-controlled trials are recommended when the intervention drugs and the comparators are different (e.g. intravenous infusion of Radix Sophorae flavescentis versus oral administration of lamivudine), in order to obtain blinding of the participants, the practitioners, and the outcome assessors. The comparison with no intervention and placebo has been discussed 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 health-related quality of life) should be included as primary outcomes in all future trials. The trials also need to validate the relationship between surrogate outcomes and patient-centred outcomes. Moreover, we suggest conducting pharmacovigilance studies to gather serious adverse effects and to stratify the severity.

Time stamp (date of recommendation): September 2018.

Further randomised clinical trials ought to be designed according to the SPIRIT standards (Standard Protocol Items: Recommendations for Interventional Trials; [Chan 2013](#)), and reported according to the CONSORT standards ([Moher 2001](#)).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Deng 2010

Methods	Randomised clinical trial, China Parallel group design
Participants	68 participants diagnosed with moderate or severe chronic hepatitis B according to Chinese guidelines 2000 (CMA 2001). Serum TBIL > 34.2 µmol/L. Male:female: 55:13 Mean age: 40.2 years (experimental group), 47.5 years (control group) Exclusion criteria: with obvious heart, brain, kidney, or nervous system diseases; extrahepatic obstructive jaundice verified by colour ultrasound or CT tests.
Interventions	Experimental intervention: matrine glucose solution, 250 mL, once daily, intravenous infusion, 1 month (n = 36) Control intervention: yin zhi huang injection, 30 mL, with 5% glucose solution 250 mL, once daily, intravenous infusion, 1 month (n = 32) Cointervention: diammonium glycyrrhizinate injection, 150 mg, once a day, intravenous injection; and reduced glutathione, 250 mL, once daily, intravenous infusion, 1 month Post-treatment follow-up: no follow-up
Outcomes	Clinical symptoms; liver (function) tests (ALT, AST, TBIL)
Notes	Study dates: May 2007 to May 2008 Funding information: author did not provide any information on clinical study support or sponsorship. Notes: we contacted the authors on 29 June 2018 by telephone and received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number table to generate random sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B (Review)

Deng 2010 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of participants included in the analysis was equal to the number of participants randomised; no missing data.
Selective reporting (reporting bias)	High risk	We could not obtain the protocol, and author did not report any data on the primary outcomes.
Other bias	Unclear risk	Paper only had 1 author, and author did not mention any acknowledgements. If the trial was conducted by a single person, there would be potential risks of bias in every step.

Huang 2004

Methods	Randomised clinical trial, China Parallel group design (four-arms)
Participants	73 participants diagnosed with chronic hepatitis B according to Chinese guidelines 2000 (CMA 2001), with HBeAg positive, HBV-DNA positive, and ALT > 100 U. Male:female: 58:15 Mean age: 35.7 years (experimental group), 41.2 years (control group) Exclusion criteria: concomitant jaundice and other viral infections such as hepatitis virus A, C, D, E, or F infections
Interventions	Experimental intervention: kushensu capsules, 200 mg, 3 times daily, oral administration, 6 months (n = 36) Control intervention: interferon-a 2b, 5 MU, intramuscular injection, every other day, 6 months (n = 37) Cointervention: liver protective drugs (e.g. silymarin and vitamin C), oral administration, 6 months Post-treatment follow-up: 6 months In addition to the two groups mentioned above, there were two more groups: - 37 participants (mean age 37.4 years, 5 females) receiving kushensu capsules plus interferon-a 2b plus liver protective drugs. - 36 participants (mean age 39.5 years, 6 females) receiving liver protective drugs. The dose and treatment duration were same as with the mentioned two groups above, of interest to our review.
Outcomes	HBV-DNA; HBeAg; liver (function) tests (ALT level); TGF- β , serum liver fibrosis biomarkers (HA, LN, IVC, PCIII); liver histology tests
Notes	Study dates: June 2001 to May 2003 Funding information: study received no funding.

Huang 2004 (Continued)

Notes: we contacted the authors on 28 June 2018 by telephone and received the reply on missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number table to generate random sequence
Allocation concealment (selection bias)	High risk	Author reported they did not conceal the allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Author did not report that they blinded participants and personnel, and the administration route was different between groups, 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	There were dropouts, but author did not remember the number and did not include those people in the analysis.
Selective reporting (reporting bias)	High risk	We could not find protocol of this study, and author did not report any data on the primary outcomes.
Other bias	Low risk	No other potential sources of bias

Huang 2005

Methods	Randomised clinical trial, China Parallel group design (three arms)
Participants	118 participants diagnosed with chronic hepatitis B according to Chinese guidelines 2000 (CMA 2001), with HBeAg positive and HBV-DNA positive Male:female: not reported Mean age: 36.8 years (experimental group), 35.7 years (control group) Exclusion criteria: concomitant other viral infections such as hepatitis A, C, D, E, or F virus infection; used antiviral drug or other immunomodulators in past 6 months
Interventions	Experimental intervention: kushensu, 600 mg, with glucose solution, intravenous infusion, once daily, 3 months (n = 58) Control intervention: thymosin injection, 80 mg, with 10% glucose solution 250 mL, intravenous infusion, once daily, 3 months (n = 56) Cointervention: liver protective drugs (e.g. diammonium glycyrrhizinate and vitamin C), 3 months Post-treatment follow-up: 6 months

Huang 2005 (Continued)

In addition to the two groups mentioned above, there is another group of 64 participants (mean age 35.3 years) receiving kushensu plus thymosin injection plus liver protective drugs. The dose and treatment duration were the same as in the above two groups.

Outcomes	HBV-DNA; HBeAg; clinical effective rate; liver (function) tests (ALT level); serum TGF- β
Notes	<p>Study dates: October 2001 to January 2004</p> <p>Funding information: study received no funding.</p> <p>Notes: we contacted the authors on 28 June 2018 by telephone and received author's reply on missing information.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number table to generate random sequence.
Allocation concealment (selection bias)	High risk	Author reported they did not conceal the allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 6 dropouts in intervention group and 5 dropouts in control group. Although author reported all dropouts were owing to economic reasons, we assessed it as high risk considering the overall dropouts rate was 9%.
Selective reporting (reporting bias)	High risk	We could not find protocol, and author did not report any data on the primary outcomes.
Other bias	Low risk	No other potential sources of bias

Liang 2006

Methods	<p>Randomised clinical trial, China</p> <p>Parallel group design</p>
Participants	<p>68 participants diagnosed as chronic hepatitis B according to Chinese guidelines 2000 (CMA 2001), with HBeAg positive and HBsAg positive for > 6 months, HBV-DNA positive twice in succession, serum ALT level > 2 times upper normal limit but < 10 times upper normal limit</p> <p>Male:female: 56:12</p> <p>Mean age: 34.5 years</p> <p>Exclusion criteria: hepatitis A, C, D, or E virus infection, or HIV coinfection; decompensated cirrhosis; obvious heart, brain, or kidney diseases history; psychological diseases and diabetes history; exces-</p>

Liang 2006 (Continued)

sive drinking and drug abuse history; pregnant or lactating women; used antiviral drug and other immunomodulators during past 1 year.

Interventions	<p>Experimental intervention: kushensu capsules, 200 mg, 3 times daily, 3 months (n = 34)</p> <p>Control intervention: tiopronin tablets, 200 mg, 3 times daily, 3 months (n = 34)</p> <p>Cointervention: glucuronolactone, 400 mg, once daily; plus vitamin B and vitamin C</p> <p>Post-treatment follow-up: 6 months</p>
Outcomes	Adverse events considered 'not to be serious;' HBV-DNA; liver (function) tests (ALT level); HBeAg sero-conversion
Notes	<p>Study dates: not reported</p> <p>Funding information: author did not report this information.</p> <p>Notes: we contacted the authors on 26 September 2018 by telephone and received no reply.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer software to generate random sequence.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but experimental drug was in capsule form while the control drug was in tablet form, which can easily unseal the blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants included in the analysis was equal to the number of participants randomised; no missing data.
Selective reporting (reporting bias)	High risk	We could not find protocol of this study. Author did not report any data on the 3 primary outcomes.
Other bias	Low risk	No other potential sources of bias

Wang 2013

Methods	Randomised clinical trial, China
Participants	<p>131 participants diagnosed with chronic hepatitis B according to Chinese guidelines 2005 (CMA 2005), with HBsAg positive for > 6 months, HBeAg positive, serum HBV-DNA > 10⁵ copies/ mL, elevated ALT level in serum at least once during the past 6 months (1.5–8 upper limit)</p> <p>Male:female: not reported</p>

Wang 2013 (Continued)

Mean age: 32.8 years

Exclusion criteria: B-mode ultrasound or imaging test found suspicious lesion; continuously elevated serum AFP or AFP > 100 µg/L; clinical manifestation of decompensated liver diseases, and blood creatinine > 130 µmol/L; transient hepatic decompensation induced by severe and acute liver diseases; serum amylase > 2 times the normal upper limit; hepatitis C or D virus infection, HIV coinfection, autoimmune hepatitis, or other active liver diseases; other severe or active diseases which may have interfered with the participants' adherence and evaluation; excessive drinking or drug abuse history; used immunosuppressants, immunomodulators, cytotoxic drugs, or antiviral drug in past 6 months; used transaminase drugs during the past month; used other research drugs; allergic to nucleoside drugs or nucleoside analogues

Interventions	<p>Experimental intervention: kushensu capsules, 200 mg, 3 times daily, 12 months (n = 62)</p> <p>Control intervention: adefovir capsules, 10 mg, once daily, 12 months (n = 69)</p> <p>Cointervention: basic treatment</p> <p>Post-treatment follow-up: none</p>
Outcomes	HBV-DNA; liver (function) tests (ALT, AST, TBIL); HBeAg seroconversion
Notes	<p>Study dates: May 2009 to March 2011</p> <p>Funding information: author did not report this information.</p> <p>Notes: we contacted the author on 29 June 2018 by telephone, but author said he could not remember the details as it was long time ago and provided us with an email address. We sent email again on 3 August but have not received a reply.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants in experimental group and 5 in control group dropped out due to loss of follow-up, violation of protocol, or safety problems. The overall the dropout rate was 6.1%. Author used both intention-to-treat and per-protocol analysis methods to analyse the data.
Selective reporting (reporting bias)	High risk	We could not find the protocol of the study, and author did not report any data on the primary outcomes.
Other bias	Unclear risk	This paper only had 1 author, and author did not mention any acknowledgements. If the trial was conducted by a single person, there would be potential risks of bias in every step.

Xi 2010

Methods	Randomised clinical trial, China Parallel group design (three arms)
Participants	95 children (aged 5–14 years) diagnosed with chronic hepatitis B according to Chinese guidelines 2000 (CMA 2001), with HBV-DNA, HBeAg, and HBsAg positive for ≥ 6 months, ALT > 2 times normal upper limit Male:female: 68:27 Mean age: 10.69 years (experimental group); 10.51 years (control group) Exclusion criteria: other diseases that may have affected liver function; used oxymatrine injections and liver protective drugs during past 6 months, and had adverse events when taking these drugs.
Interventions	Experimental intervention: matrine, 50–100 mg (for children aged 5–10 years), 100–150 mg (for children aged 11–14 years), intravenous infusion with 10% glucose solution, once daily, 2 months; then matrine capsules, 3 times daily, 4 months (n = 47) Control intervention: Chinese formula: Chai Hu (<i>Bupleuri Radix</i> , <i>Bupleurum falcatum</i> Linne, 250 g), Yin Chen (<i>Artemisiae Capillaris Flos</i> , <i>Artemisia capillaris</i> Thunberg, 250 g), Ban Lan Gen (<i>Indigowoad root</i> , <i>Isatis tinctoria</i> L, 250 g), Wu Wei Zi (<i>Schisandrae Fructus</i> , <i>Schisandra chinensis</i> Baillon, 300 g), Zhu Dan Fen (biliary power of pig, 20 g), Lv Dou (green beans, 128 g), 1–2 tablets (for children aged 1–8 years), 2–3 tablets (for children aged 9–14 years), oral administration, 6 months (n = 48) Cointervention: none Post-treatment follow-up: none In addition to the two groups mentioned above, there is another group of 47 participants (mean age 10.23 years, 15 females) receiving matrine plus Chinese formula. The dose and treatment duration were same as in the other two groups.
Outcomes	Adverse events considered 'not to be serious,' HBV-DNA; HBeAg; liver (function) tests (ALT, AST level)
Notes	Study dates: February 2007 to May 2009 Funding information: author did not report this information. Notes: we contacted the authors on 9 November 2018 by email but received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number table to generate random sequence.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but the experimental drug was in injection form while the control drug was in tablets, which could easily unseal the blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Xi 2010 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; the number of participants analysed was equal to number randomised.
Selective reporting (reporting bias)	High risk	We could not find the protocol of the study, and author did not report any of the primary outcomes.
Other bias	Low risk	No other potential sources of bias

Xu 2003

Methods	Randomised clinical trial, China Parallel group design
Participants	86 participants diagnosed with chronic hepatitis B according to Chinese guidelines 1995 (no reference), with HBV-DNA positive for ≥ 6 months, abnormal ALT level (< 10 times normal upper limit), serum bilirubin < 5 times normal upper limit, no obvious ascites, and stable disease condition Male:female: 72:14 Mean age: 35.7 years (experimental group); 36.8 years (control group) Exclusion criteria: fatty liver, drug-induced liver injury, alcohol-induced injury, or other severe diseases (except cirrhosis); aged under 16 years or over 65 years; pregnant women; used biphenyl diester, schisandra preparation, hormone which may have affected the results.
Interventions	Experimental intervention: matrine glucose solution (matrine 600 mg), 100 mL, once daily, intravenous infusion, 2 months; then matrine capsules, 200 mg, 3 times daily, 1 month (n = 43) Control intervention: ganlixin, inosine, etc, 3 months (n = 43) Cointervention: basic treatment (gantaile, vitamin C, vitamin E, etc), oral administration (n = 43) Post-treatment follow-up: none
Outcomes	HBV-DNA; HBeAg; liver (function) tests (ALT, TBIL, albumin); liver fibrosis serum indexes (HA, PCIII)
Notes	Study dates: January 2002 to September 2002 Funding information: author did not report this information. Notes: we contacted the authors on 2 August 2018 by telephone but received no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random number table to generate the random sequence.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but the form and administration route of drugs were different which could easily unseal the blinding.

Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B (Review)

Xu 2003 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	High risk	We could not find the protocol of the study, and author did not report any data on the primary outcomes.
Other bias	Low risk	No other potential sources of bias

Yan 2017

Methods	Randomised, double-blind, placebo-controlled trial with 2 parallel groups, China
Participants	<p>100 participants aged 18–65 years diagnosed with chronic hepatitis B according to guidelines 2010 (CMA 2011), conforming to the TCM standard of "zheng" differentiation for chronic hepatitis B</p> <p>Male:female: 49:33 (excluding 18 dropouts)</p> <p>Mean age: 38.45 years (excluding 18 dropouts)</p> <p>Exclusion criteria: used related medicine for treating chronic hepatitis B within half a month; coinfect-ed with other type hepatitis virus; had autoimmune hepatitis or hepatitis caused by drug intoxication and alcohol; severe hepatitis, hepatic failure, cirrhosis, hepatocellular carcinoma; serious primary dis-ease in cardiovascular, cerebrovascular, kidney, lung, endocrine system, haematopoietic system or mental disease; pregnant or lactating women; allergic physique or allergic to multiple drugs</p>
Interventions	<p>Experimental intervention: matrine capsules, 200 mg, 3 times daily; plus mimetic Longchai formula used for placebo control, twice daily, half dose a time, infused with water, 3 months (n = 50)</p> <p>Control intervention: mimetic matrine capsules, 200 mg, 3 times daily; plus Longchai formula (con-sisting of 6 medicinal herbs: Solanum nigrum L, Bupleurum chinense DC., Hedyotis diffusa Willd, Se-dum sarmentosum Bunge, Gardenia jasminoides Ellis and Scutellaria baicalensis Georgi), twice daily, half dose a time, infused with water; 3 months (n = 50)</p> <p>Cointervention: none</p> <p>Post-treatment follow-up: none</p>
Outcomes	Clinical symptom; HBV-DNA; HBeAg; HBsAg; liver (function) tests (ALT, AST); damage assessment (com-posite outcome involving clinical symptom, liver (function) tests, etc); efficacy assessment (composite outcome involving liver (function) tests, HBV-DNA, HBeAg, HBsAg)
Notes	<p>Study dates: December 2010 to December 2012</p> <p>Funding information: supported by governmental funds: Scientific and Technological Innovation and Achievements Transformation Special Projects of Jiangsu Province (BM2009903).</p> <p>Notes: we contacted the authors on 2 August and 13 August 2018 by telephone but received no reply.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Yan 2017 (Continued)

Random sequence generation (selection bias)	Low risk	Used software SAS 9.1 to generate random sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo-controlled design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	18 dropouts and withdrawals, containing 10 cases in experimental group and 8 cases in control group. The overall dropouts rate was 18%.
Selective reporting (reporting bias)	Low risk	We obtained the trial registration information (www.chictr.org.cn/showproj.aspx?proj=9976). Author reported all outcomes predefined in protocol.
Other bias	Low risk	No other potential sources of bias

Zhang 2007

Methods	Randomised clinical trial, China
Participants	<p>63 participants aged 12–60 years diagnosed with chronic hepatitis B according to guidelines 2000 (CMA 2001), with ALT level > 1 upper limit of normal, TBIL < 5 times upper limit of normal, HBeAg positive, HBV-DNA positive or HBV-DNA quantitative level > 10³ copies/mL</p> <p>Male:female: 48:12</p> <p>Mean age: 34.5 years (experimental group), 30.5 years (control group)</p> <p>Exclusion criteria: used antiviral drugs or immunomodulators during the past 6 months; decompensated cirrhosis, HCV coinfection, or autoimmune hepatitis</p>
Interventions	<p>Experimental intervention: kushensu, 400 mg, once daily, intramuscular injection, 6 months (n = 31)</p> <p>Control intervention: lamivudine, 100 mg, once daily, oral administration, 6 months (n = 32)</p> <p>Cointervention: either diammonium glycyrrhizinate, 150 mg, 3 times daily; or diammonium glycyrrhizinate enteric-coated capsule, 150 mg, 3 times daily, for participants with elevated ALT level (> 5 times the upper limit of the normal)</p> <p>Post-treatment follow-up: none</p>
Outcomes	HBV-DNA; HBeAg; HBsAg; liver (function) tests (ALT, AST level)
Notes	<p>Study dates: June 2005 to January 2006</p> <p>Funding information: author did not report this information.</p> <p>Notes: we contacted the authors on 2 August and 13 August 2018 by telephone but received no reply.</p>

Zhang 2007 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated through selecting balls
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Forms and administration routes of drugs were different in 2 groups, which can easily unseal the blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in experimental group changed to receive control drug and 1 participant was lost of follow-up, while there was no dropouts in control group. Author used intention-to-treat analysis to analyse the data.
Selective reporting (reporting bias)	High risk	We could not find the protocol of the study, and author did not report any data on the three primary outcomes.
Other bias	Low risk	No other potential sources of bias

Zhang 2011

Methods	Randomised clinical trial, China Parallel group design (four arms)
Participants	100 children diagnosed with chronic hepatitis B according to guidelines 2000 (CMA 2001), with HBsAg, HBeAg, HBV-DNA positive for ≥ 6 months, ALT or AST > 2 upper limit of normal Male:female: not reported Mean age: 11.59 years Exclusion criteria: used antiviral drugs such as matrine and lamivudine; coinfectd with other type hepatitis virus
Interventions	Experimental intervention: matrine injections, 50–100 mg (aged 5–10 years), 100–150 mg (aged 11–14 years), intravenous infusion with 10% glucose solution, once daily, 6 months (n = 50) Control intervention: lamivudine, 3 mg/kg/day, 100 mg (maximum dose), once daily, oral administration, 6 months (n = 50) Cointervention: routine liver protective treatment (diammonium glycyrrhizinate capsules, 3 mg/kg/day, twice daily; inosine tablets, 100–400 mg, 3 times daily) Post-treatment follow-up: none In addition to the two groups mentioned above, there were two more groups with 100 children:

Zhang 2011 (Continued)

- Participants in the combination group received matriline injections plus lamivudine plus routine liver protective treatment.

- Participants in baseline treatment group received routine liver protective treatment only.

The dose and treatment duration are same as in the mentioned two groups.

Totally, there were 200 children enrolled in this trial. And the ratio of female to male was 88:112.

Outcomes	HBV-DNA; HBeAg; HBeAg seroconversion; liver (function) tests (ALT level)
Notes	<p>Study dates: not stated</p> <p>Funding information: author did not report such information.</p> <p>Notes: we contacted the authors on 9 November 2018 by email but received no reply.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author used random number table to allocate the participants.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but the forms and administration routes of drugs were different which could easily unseal the blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
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 of the study, and author did not report any data on the 3 primary outcomes.
Other bias	Low risk	No other potential sources of bias

AFP: alpha fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computer tomography; HA: hyaluronic acid; HBV-DNA: hepatitis B virus DNA; HBeAg: hepatitis B virus e-antigen; HBsAg: hepatitis B virus surface antigen; IVC: type IV collagen; LN: laminin; n: number of participants; PCIII: type III procollagen; TBIL: total bilirubin; TGF- β : serum transforming growth factor beta.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cao 2007	Not a randomised trial
Chen 2000	Duplicate

Study	Reason for exclusion
Chen 2001	Not a randomised trial
Chen 2004	Not a randomised trial
Chen 2008	Not a randomised trial
Cui 2006	Not a randomised trial
Gong 2010	Not a randomised trial
Hu 2006	Not appropriate comparison group
Jiang 2013	Similar method and data as Zhang 2007 but with different author team
Jiao 2003	Not a randomised trial
Jin 2008	Not a randomised trial
Li 2004	Not a randomised trial
Li 2006a	Not a randomised trial
Li 2006b	Not a randomised trial
Li 2006c	Not a randomised trial
Li 2013	Not a randomised trial
Liu 2001a	Not a randomised trial
Liu 2001b	Not a randomised trial
Liu 2002	Not a randomised trial
Pan 2005	Not a randomised trial
Qin 2003	Not a randomised trial
She 2000	Not a randomised trial
Song 2008	Not a randomised trial
Su 2006	Not a randomised trial
Sui 2006	Not a randomised trial
Sun 2002	Not a randomised trial
Sun 2006	Not a randomised trial
Tang 2005	Not a randomised trial
Wang 2001	Not a randomised trial
Wang 2003	Not a randomised trial

Study	Reason for exclusion
Wang 2006a	Not a randomised trial
Wang 2006b	Not a randomised trial
Wang 2007	Not a randomised trial
Wang 2009	Not a randomised trial
Wu 2009	Not a randomised trial
Xia 2003	Not a randomised trial
Xiao 2013	Not a randomised trial
Xie 2003	Not a randomised trial
Xue 2016	Not a randomised trial
Yang 2005	Not a randomised trial
Yu 2002	Not a randomised trial
Zhang 2001b	Not a randomised trial
Zhong 2008	Not a randomised trial
Zhou 2014	Not a randomised trial

DATA AND ANALYSES

Comparison 1. Radix Sophorae flavescentis versus other drugs or herbs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with ≥ 1 adverse events considered 'not to be serious'	2	163	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.75]
2 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' form and administration route	2	163	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.75]
2.1 Oral capsule	1	68	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.34]
2.2 Mixed route	1	95	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' duration	2	163	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.75]
3.1 No more than 6 months	1	95	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.78]
3.2 More than 6 months	1	68	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.34]
4 Proportion of participants with ≥ 1 adverse events considered 'not to be serious;' control drug	2	163	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.42, 1.75]
4.1 Chinese herbs	1	95	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.78]
4.2 Tiopronin	1	68	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.34]
5 Proportion of participants with detectable HBV-DNA	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
6 Proportion of participants with detectable HBV-DNA: best-worst scenario	8	730	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.79, 1.62]
7 Proportion of participants with detectable HBV-DNA: worst-best scenario	8	730	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.82, 1.65]
8 Proportion of participants with detectable HBV-DNA: blinding of outcome assessments	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
8.1 Low risk of bias	2	176	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.10]
8.2 Unclear or high risk of bias	6	543	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.77, 2.21]
9 Proportion of participants with detectable HBV-DNA: incomplete outcome data	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
9.1 Low risk of bias	6	543	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.77, 2.21]
9.2 Unclear or high risk of bias	2	176	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.10]
10 Proportion of participants with detectable HBV-DNA: form and administration route	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
10.1 Intravenous infusion	2	203	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
10.2 Oral capsule	3	272	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.54, 3.87]
10.3 Intramuscular injection	1	63	Risk Ratio (M-H, Random, 95% CI)	11.35 [2.91, 44.27]
10.4 Mixed route	2	181	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Proportion of participants with detectable HBV-DNA: duration	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
11.1 No more than 6 months	4	344	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.63, 1.62]
11.2 More than 6 months	4	375	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.68, 2.34]
12 Proportion of participants with detectable HBV-DNA: control drug	8	719	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.63]
12.1 Lamivudine	2	163	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.09, 114.84]
12.2 Adefovir	1	131	Risk Ratio (M-H, Random, 95% CI)	4.15 [2.64, 6.55]
12.3 Interferon	1	73	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.38]
12.4 Thymosin	1	103	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
12.5 Tiopronin	1	68	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.96]
12.6 Chinese herbs	2	181	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.22]
13 Proportion of participants with detectable HBeAg	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
14 Proportion of participants with detectable HBeAg: best-worst scenario	7	599	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.96]
15 Proportion of participants with detectable HBeAg: worst-best scenario	7	599	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.96]
16 Proportion of participants with detectable HBeAg: blinding of outcome assessments	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
16.1 Low risk of bias	2	176	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
16.2 Unclear or high risk of bias	5	412	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
17 Proportion of participants with detectable HBeAg: incomplete outcome data	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
17.1 Low risk of bias	5	412	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
17.2 Unclear or high risk of bias	2	176	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
18 Proportion of participants with detectable HBeAg: form and administration route	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Intravenous infusion	2	203	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
18.2 Oral capsule	2	141	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.62, 1.27]
18.3 Intramuscular injection	1	63	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.51, 1.01]
18.4 Mixed route	2	181	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.37]
19 Proportion of participants with detectable HBeAg: duration	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
19.1 No more than 6 months	4	344	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.02]
19.2 More than 6 months	3	244	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.73, 1.06]
20 Proportion of participants with detectable HBeAg: control drug	7	588	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.98]
20.1 Lamivudine	2	163	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.64, 1.10]
20.2 Interferon	1	73	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.81, 1.41]
20.3 Thymosin	1	103	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
20.4 Tiopronin	1	68	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.96]
20.5 Chinese herbs	2	181	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.37]
21 Proportion of participants with nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22 Proportion of participants with stomach upset	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23 Proportion of participants with rash	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24 Proportion of participants with loss of appetite	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25 Proportion of participants with fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26 Proportion of participants with liver pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27 Proportion of participants with jaundice	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 1 Proportion of participants with ≥ 1 adverse events considered 'not to be serious'.

Analysis 1.2. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 2 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' form and administration route.

Analysis 1.3. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 3 Proportion of participants with ≥ 1 adverse events considered 'not to be serious:' duration.

Analysis 1.4. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 4 Proportion of participants with ≥ 1 adverse events considered 'not to be serious;' control drug.

Analysis 1.5. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 5 Proportion of participants with detectable HBV-DNA.

Analysis 1.6. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 6 Proportion of participants with detectable HBV-DNA: best-worst scenario.

Analysis 1.7. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 7 Proportion of participants with detectable HBV-DNA: worst-best scenario.

Analysis 1.8. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 8 Proportion of participants with detectable HBV-DNA: blinding of outcome assessments.

**Analysis 1.9. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs,
Outcome 9 Proportion of participants with detectable HBV-DNA: incomplete outcome data.** **Analysis 1.10. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome
10 Proportion of participants with detectable HBV-DNA: form and administration route.**

Analysis 1.11. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 11 Proportion of participants with detectable HBV-DNA: duration.

Analysis 1.12. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 12 Proportion of participants with detectable HBV-DNA: control drug.

Analysis 1.13. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 13 Proportion of participants with detectable HBeAg.

Analysis 1.14. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 14 Proportion of participants with detectable HBeAg: best-worst scenario.

Analysis 1.15. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 15 Proportion of participants with detectable HBeAg: worst-best scenario.

Analysis 1.16. Comparison 1 Radix Sophorae flavescens versus other drugs or herbs, Outcome 16 Proportion of participants with detectable HBeAg: blinding of outcome assessments.

Analysis 1.17. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 17 Proportion of participants with detectable HBsAg: incomplete outcome data.

Analysis 1.18. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 18 Proportion of participants with detectable HBeAg: form and administration route.

Analysis 1.19. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 19 Proportion of participants with detectable HBeAg: duration.

Analysis 1.20. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 20 Proportion of participants with detectable HBeAg: control drug.

Analysis 1.21. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 21 Proportion of participants with nausea.

Analysis 1.22. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 22 Proportion of participants with stomach upset.

Analysis 1.23. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 23 Proportion of participants with rash.

Analysis 1.24. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 24 Proportion of participants with loss of appetite.

Analysis 1.25. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 25 Proportion of participants with fatigue.

Analysis 1.26. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 26 Proportion of participants with liver pain.

Analysis 1.27. Comparison 1 Radix Sophorae flavescentis versus other drugs or herbs, Outcome 27 Proportion of participants with jaundice.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Controlled Trials Register	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	December 2018	#1 (sophor* or ku shen or kushen or matrine or oxymatrine or kujin) AND CENTRAL:TARGET #2 MESH DESCRIPTOR Hepatitis B, Chronic EXPLODE ALL AND CENTRAL:TARGET #3 ((hepatitis B or hep B or hbv) and chronic) AND CENTRAL:TARGET #4 #2 OR #3 #5 #1 AND #4
MEDLINE Ovid	1946 to 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/ 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] 4. 2 or 3 5. 1 and 4
Embase Ovid	1974 to December 2018	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] 2. exp chronic hepatitis B/ 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] 4. 2 or 3 5. 1 and 4
LILACS (Bireme)	1982 to 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 December 2018	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic)

(Continued)

		#1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to December 2018	#3 #2 AND #1 #2 TS=((hepatitis B or hep B or hbv) and chronic) #1 TS=(sophor* or ku shen or kushen or matrine or oxymatrine or kujin)
China Network Knowledge Infrastructure (CNKI)	1994 to 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
Chongqing VIP (CQVIP)	1989 to 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
Wanfang	1982 to 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
SinoMed	1978 to 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

Appendix 2. Characteristics of 109 trials, claiming to be randomised clinical trials

ID	Author	Title	Journal	Year; volume (Issue); pages	Contact date in 2018 and results	Contact person
Bai 2003	Bai H, Zhao W	Clinical study of oxymatrine in treatment of hepatic fibrosis	Chinese Journal of Primary Medicine and Pharmacy	2003;10(8):711-715	Contacted author 28 June by telephone: author	YQL

(Continued)

					no longer worked at hospital.	
Cao 2004	Cao L, Zhang YW, Zhang YJ, Fu J	[Clinical efficacy of matriline injection in the treatment of chronic hepatitis B]	China Journal of Clinical Medicine Hygiene	2004;2(5):59-60	Contact-ed author 28 June by telephone: Dr Cao was away and Dr Zhang was unable to answer ques-tions. Con-tacted 18 Oc-tober: Dr Cao did not re-member the details.	YQL
Chen 2005	Chen CJ, Guo CL, Wang YQ	[Efficacy of chemotherapy α -1b interfer-on combined with lamivudine to treat 30 cases with chronic hepatitis B]	Journal of Bao-tou Medical Col-lege	2005;21(3):255-6	Contact-ed author 29 June by telephone: Dr Chen no longer worked at hospital. Dr Wang and Dr Chen were not avail-able.	YQL
Chen 2000	Chen CX, Guo SM	[A clinical randomized study of matriline and interferon to treat patients with chronic hepatitis B]	Chinese Hepatol-ogy	2000;5(3):176-7	Contact-ed author's work depart-ment on 29 June and 18 October, but no reply.	YQL
Chen 2006	Chen HY	[Therapeutic effect of oxymatrine on 48 patients with hepatitis B]	International Journal of Epi-demiology and Infectious Dis-eases	2006;33(2):148-51	Contact-ed author's work depart-ment on 29 June and 18 October, but no reply.	YQL
Chen 2005	Chen X, Li CX, Shi YZ, Cao TG, Li JN	[Treatment of 110 cases of chronic he-patitis B with oxymatrine combined with fermented Cordyceps powder]	Journal of Zhe-jiang College of Traditional Chi-nese Medicine	2005;29(5):423-6	Contact-ed author's work depart-ment on 29 June and 18 October, but no reply.	YQL
Chen 2006	Chen XR, Lu YF,	[Clinical observation of sequential thera-py for chronic hepatitis B with dampness and heat resistance]	Chinese Hepatol-ogy	2006;11(5):342-6	Contact-ed author's work depart-	YQL

(Continued)

Wang JR,
Chen JJ

ment on 29
June and 18
October: au-
thors were
not avail-
able.

Chen 2001	Chen YX, Yang YQ, Mao BY, Shi JH	[Observation of the relationship between serum HBV DNA content and the efficacy of oxymatrine injection]	Infectious Phar- macy	2001;11(4):235	Contact- ed author's work depart- ment on 29 June and 18 October, but no reply.	YQL
Chen 2002	Chen YX, Tian YY	[Observation and nursing of oxymatrine complex (Bo'er tai li) in treating chronic hepatitis B]	Shandong Medi- cine Journal	2002;42(29):40	Contacted author on 29 June: author no longer worked at hospital. New contact information not avail- able.	YQL
Deng 2004	Deng HP, Tang JW	[Therapeutic effect of kushen injection on chronic hepatitis B]	Journal of Liaon- ing College of TCM	2004;6(4):311	Contact- ed author's work depart- ment on 29 June and 18 October, but no reply.	YQL
Ding 2010	Ding YL	[Clinical observation of 52 cases of chron- ic hepatitis B with matrine]	Chinese and For- eign Medical Re- search	2010;8(12):735	Contacted author on 29 June: but he no longer worked at hospital. New contact information not avail- able.	YQL
Dong 2005	Dong GF	[Therapeutic effect of matrine and glu- cose injection on chronic hepatitis B]	Modern Jour- nal of Integrated Traditional Chi- nese and West- ern Medicine	2005;14(20):260	Contact- ed author's work depart- ment on 29 June and 18 October, but no reply.	YQL
Fan 2005	Fan XW, Li YF, Zhang XF	[Clinical observation on the treatment of chronic hepatitis B with matrine]	Shandong Medi- cine Journal	2005;45(25):72	Contact- ed author's work depart- ment on 29 June: Dr Fan no longer worked in	YQL

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					department. Attempted contact on 27 September and 18 October: Dr Li was not available.	
Feng 2003	Feng YH	[Therapeutic effect of matrine on chronic hepatitis B]	Medical Forum Magazine	2003;24(13):456	Contacted author's work department on 29 June and 18 October, but author was not available.	YQL
Gai 2003	Gai XD, Wang LR, Yang YJ	[Therapeutic effect of oxymatrine on liver fibrosis]	Chinese Medicine of Factory and Mine	2003;16(6):456	Contacted author's work department on 26 September, but the responder refused to transfer the line.	YQL
Gong 2009	Gong DL	[Effect of adefovir dipivoxil on chronic hepatitis B]	Journal of Clinical Rational Drug Use	2009;2(21):145	Contacted author on 26 September by email, but no reply. Contacted author's work department on 18 October, but author was not available. Contacted on 29 October, but no answer.	YQL
Guo 2008	Guo Y	[Therapeutic effect of matrine capsule on 67 cases of chronic hepatitis B]	Shanxi Medical Journal	2008;37(2):120	Contacted author on 11 October, but he was not available. Attempted contact on 18 October, but no reply.	YQL
Hong 2005	Hong YL, Wei YH	Clinical observation on sophorcarpidine treating chronic hepatitis B	Modern Diagnosis and Treatment	2005;16(6):340	Contacted author's work department	YQL

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					ment on 27 September and 18 October, but no reply.	
Hou 2005	Hou ZH, Tan DM, Xie YT, Lu MH, Xie JP, Liu GZ, et al	Therapeutic effect of kurarinone in patients with chronic hepatitis B	Practical Preventive Medicine	2005;12(4):824-6	Contact-ed author's work department on 27 September and 18 October, but no reply.	YQL
Hua 2013	Hua Z	[Effects and significance of thymocyte α -1 on T cell subsets and cytotoxic T lymphocytes in patients with chronic hepatitis B]	16th National Conference on Viral Hepatitis and Liver Diseases of the Chinese Medical Association	—	Contact-ed author's work department on 26 September and 18 October, but no reply.	YQL
Huang 2004	Huang P	[Observation of curative effect of oxymatrine complex (Bo'er tai li) injection on 20 cases of chronic hepatitis B]	Journal of Medical Theory and Practice	2004;17(5):530-40	Contact-ed author's work department on 26 September and 18 October, but no reply.	YQL
Cao 2005	Huang WF, Xie ZJ, Huang CB, Xu QL, Wang XM	[Comparative observation of the clinical efficacy between Radix Sophora flavescens and α -2b interferon for chronic hepatitis B]	Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine	2005;5(6):9	Contact-ed author's work department on 26 September, 27 September, and 18 October, but no reply.	YQL
Huang 2004	Huang Y	Clinical observation and nursing on hyperbilirubinemia of chronic hepatitis B treated by oxymatrine injection	Hunan Guiding Journal of TCM	2004;10(3):167	Contact-ed author's work department on 27 September, but he did not work there.	YQL
Huang 2004	Huang YQ, Lin ZH, Ji SM, Wang CG	Effect of expression of Fas/FasL of chronic hepatitis B undergoing treatment with kurorinone	Physician's Training Magazine (Internal Science Edition)	2004;27(6):1920	Contact-ed author's work department on 27 September, but he did	YQL

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					not work there.	
Huang 2004	Huang YQ, Lin ZH, Ji SM, Wang CG	The effect of kurorinone on the serum level of TNF-a and IL-6 in patients with chronic hepatitis B	Journal of Chinese Physician	2004;6(10):1328	Contacted author's work department on 27 September, but he did not work there.	YQL
Huang 2005	Huang YQ, Lin ZH, Xu ZJ, Chen XL, Wang CG	Clinical effects of kurorinone in the treatment of sixty patients with chronic hepatitis B	Acta Academiae Medicinae Jiangxi	2005;45(1):768	Contacted author's work department on 27 September, but he did not work there.	YQL
Jiang 2004	Jiang B, Li YP	[Clinical observation of tianqing fuxin in the treatment of chronic hepatitis B]	Guide of China Medicine	2004;2(12):966	Contacted author on 27 September, but author was not available. Contacted on 28 September, but no reply.	YQL
Kang 2012	Kang DQ, Xiao SJ, Wang P	[Curative effect of matrine in treating 20 cases of chronic hepatitis B]	Chinese Journal of Aesthetic Medicine	2012;21(12):3828	Contacted author's work department on 28 June and 28 September, but he no longer worked there.	YQL
Kang 2003	Kang YH, Suo ZM	[Therapeutic effect of matrine on 78 cases of chronic viral hepatitis B]	Modern Journal of Integrated Traditional Chinese and Western Medicine	2003;12(10):1044	Contacted author's work department on 27 September and 18 October, but he was not available.	YQL
Li 2005	Li AB, Jin S, Liu WG	Therapeutic efficacy of oxymatrine combined with thymotide in the treatment of chronic hepatitis B	Journal of Lanzhou Medical College	2005;28(4):332-336	Contacted author 28 September, but the author refused	YQL

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					to answer questions.	
Li 2008	Li AC	[Clinical observation on treatment of HBeAg positive chronic hepatitis B with matrine capsule combined with α interferon]	Chinese Journal of Misdiagnosis	2008;8(7):1588-9	Contact- ed author's work depart- ment on 28 September and 18 Octo- ber, but no reply.	YQL
Li 2002	Li J	[Therapeutic effect of matrine injection combined with thymic factor D on chronic hepatitis B]	Shandong Medi- cine Journal	2002;42(21):4560	Contact- ed author 26 Septem- ber, but no reply. Con- tacted on 27 September, but had diffi- culty in com- munication with respon- der.	YQL
Li 2005	Li LM, Li FL	[Report of 42 cases of chronic hepatitis B treated with matrine]	Shandong Medi- cine Journal	2005;45(9):767	Contact- ed author's work depart- ment on 27 September and 18 Octo- ber, but no reply.	YQL
Li 2005	Li SW	[45 patients with chronic hepatitis B treated by matrine injection]	China Pharma- ceuticals	2005;14(1):69-70	Contact- ed author 28 Septem- ber and 18 Oc- tober: au- thor was not available.	YQL
Lin 2004	Lin CS, Chong YT, Lin BL	[Therapeutic effect of matrine injection on 150 cases of chronic hepatitis B]	New Medical Journal	2004;35(1):223	Contact- ed author 27 September, but no reply. Contacted on 18 Octo- ber: author was too busy to reply.	YQL
Lin 2008	Lin D, Yin DH	[Comparison of clinical efficacy between patients with lamivudine resistance and rebound after withdrawal with dicyclol and matrine]	Lishizhen Medi- cine and Materia Medica Research	2008;19(9):2258-61	Contact- ed author's work depart- ment on 28 August, but no reply. Contacted on 18 Octo-	YQL

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					ber, but author was not available.	
Lin 2001	Lin JB	[Matrine in the treatment of 20 cases of chronic hepatitis B]	Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases	2001;11(Suppl):60	Contact-ed author's work department on 28 August and 18 October, but no reply.	YQL
Liu 2003	Liu CK	[Matrine treat on 39 cases with chronic hepatitis B]	Jiangxi Medicine	2003;38(4):283	No efficient contact information available.	YQL
Liu 2006	Liu CL	[Therapeutic effect of matrine injection on chronic viral hepatitis B]	Practical Clinical Medicine	2006;7(5):42-3	Contact-ed author's work department on 27 August and 18 October, but no reply.	YQL
Liu 2006	Liu JS, Deng FY, He DH, Cui QY, Xu NM	[Therapeutic effect of matrine and glucose injection on chronic hepatitis B]	Chinese Clinical New Medicine	2006;6(6):517-8	Contact-ed author's work department on 11 October, but no reply.	YQL
Liu 2003	Liu LZ	[Clinical observation of 26 cases of chronic hepatitis B with matrine]	Central Plains Medical Journal	2003;30(24):48-9	Contact-ed author on 28 September and 18 October, but author was not available.	YQL
Liu 2000	Liu M, Zhang SL	[Oxymatrine complex (Bo'er tai li) injection for the treatment of chronic hepatitis B]	Infect Dis Info	2000;13(1):42-3	Contact-ed author's work department on 28 September and 18 October, but no reply.	YQL
Lu 2002	Lu BL, Zhong LH, Fan Y	[Therapeutic effect of matrine on chronic hepatitis B]	Hei Long Jiang Medical Journal	2002;26(1):46	Contact-ed author 27 August, but he refused to answer questions.	YQL
Lu 2009	Lu MW	[Therapeutic effect of matrine capsule combined with interferon α - 1b on HBeAg positive chronic hepatitis B]	Chinese Journal of Clinical Rational Drug Use	2009;2(10):40	Contact-ed author 29 June, but no reply. Con-	SSM

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					tacted on 1 August, but he refused to answer the questions.	
Luan 2003	Luan L, Zhang JL	Treatment of cases of chronic hepatitis B with oxymatrine	Herald Medicine	2003;22(10):623-628	Contact- ed author's work hospi- tal, but he has retired.	SSM
Ma 2005	Ma L, Zhang JL	Comparison of oxymatrine and adefovir in the treatment of chronic hepatitis B	Chinese Journal of Natural Medi- cines	2005;7(1):28-9	Contacted author 29 June: author was busy and offered us the email address. We sent emails on 29 June and 1 August but have not received a reply.	SSM
Ma 2001	Ma XY	[Clinical observation of the curative ef- fect of matrine and α -1b interferon in the treatment of chronic hepatitis B]	Qinghai Medicine Magazine	2001;31(7):189	Contact- ed author's work hos- pital on 29 June, but he did not work there.	SSM
Meng 2006	Meng BL	[Clinical observation of 78 cases of chronic hepatitis B with recurrence after lamivudine withdrawal]	9th National Conference of In- fectious Diseases of the Chinese Medical Associa- tion	—	Contacted author 29 June by tele- phone: the author re- fused to an- swer ques- tions.	SSM
Pan 2006	Pan XH, Li ZP, Chu F	Clinical observation on treatment of 84 cases of chronic hepatitis B with combi- nation of matrine and diammonium gly- cyrrhizinate	World Journal of Infection	2006;6(3):216-9	Contacted author 29 June: author confirmed it was a ran- domised tri- al but could not remem- ber the de- tailed infor- mation.	SSM
Qiao 2008	Qiao WL, Li H, Li MJ	[Therapeutic effect of matrine on 29 cas- es of chronic hepatitis B]	Journal of Tais- han Medical Col- lege	2008;29(2):146-7	Contacted author 29 June by tele- phone: the author re-	SSM

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					fused to answer questions.	
Qin 2008	Qin H, Du-an HY	[Clinical management of YMDD variation in hepatitis B]	Chinese Physician Training Magazine	2008;31(Suppl):71-2	Attempted contact with author through the author's work hospital on 29 June and 3 August, but no reply.	SSM
Qiu 2009	Qiu ZQ, Xie LM, Zheng WQ	[Cost-effectiveness analysis of four options for treating chronic hepatitis B]	Journal of Huai-hai Medicine	2009;27(4):358-60	Contacted authors' work hospital on 29 June and 15 August, but Dr Qiu and Dr Xie no longer work there, and Dr Zheng was not available.	SSM
Quan 2008	Quan B	[Therapeutic effect of matrine on chronic hepatitis B]	Chinese Journal of Primary Medicine and Pharmacy	2008;15(2):308-9	Contacted author's work department on 29 June and 3 August, but he did not work there.	SSM
Ren 2010	Ren WX, Wang JH, Cui J	[The sequential treatment of chronic hepatitis B with matrine and glucosamine injection]	Jilin Medicine Journal	2010;31(25):4201-2	Attempted contact through the author's work department on 29 June, but no reply. Contacted on 15 August: he was not available. Contacted on 16 August, but no reply.	SSM
She 2005	She HY, Wu XH, Zhang JM, Feng ZZ	[Changes of liver fibrosis indexes in the treatment of chronic hepatitis B with matrine]	Chinese Journal of Infectious Diseases	2005;23(5):358-60	Contacted author's work department on 29 June and 3	SSM

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					August, but Dr She did not work there and Dr Wu had retired.	
She 2004	She HY, Wu XH, Zhang JM, Feng ZZ, Huang MY, Chen YZ, et al	[Matrine injection was used to treat 98 cases of chronic hepatitis B]	Chinese Journal of Infectious Diseases	2004;22(3):212-26	Contact-ed author's work department on 29 June and 3 August, but Dr She did not work there and Dr Wu had retired.	SSM
Shen 2004	Shen GH	[Clinical observation of 27 cases of chronic hepatitis B treated by tianqing fuxin]	Chinese Journal of Modern Practical Medicine	2004;3(19/20):85	Contact-ed author's work department on 29 June, but no reply. Contacted on 15 August: author was not available. They requested author to contact us.	SSM
Qin 2010	Qin WH, Tu YY, Huang B, Deng JG	[Clinical observation on the treatment of chronic hepatitis B with compound rhizome solution]	Lishizhen Medicine and Materia Medica Research	2010;21(10):2618-20	Contact-ed author's work hospital on 29 June and 14 September, but no reply.	SSM
Tang 2007	Tang GL	Comparison off cost-effectiveness between matrine and interferon in treatment of chronic hepatitis B	China Tropical Medicine	2007;7(1):6-7	Contact-ed author's work hospital on 3rd August and 15 August, but no reply.	SSM
Tang 2000	Tang HF, Qiao M, Wang XG, Ren HL	[Clinical observation of the curative effect of chronic hepatitis B treated with the matrine on combined with α -2b interferon]	6th National Symposium on Clinical Application of Interferon and Cytokines	—	Contact-ed author's work hospital on 3 August and 15 August, but no reply.	SSM

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Tang 2007	Tang ZQ, Guo Y	[Clinical observation of interferon and matrine in the treatment of chronic hepatitis B]	Inner Mongolia Medical Journal	2007;39(8):952-6	Contacted author's work hospital on 3 August and 15 August, but no reply.	SSM
Wang 2008	Wang Z	[Clinical observation of post hepatitis B fibrosis treated with matrine]	Practical Chinese and Western Medicine Combined Clinical	2008;8(5):58	Contacted author 3 August: on author's request we sent questions through Wechat on 3 August and 15 August, but received no reply.	SSM
Wang 2010	Wang J	Clinical evaluation on the treatment effect of hepatitis B in HBeAg-positive patients with adefovir dipivoxil	Chinese Journal of Hepatology	2010;2(2):18-21	Contacted author 29 June: author could not remember details and preferred communication through emails. Sent emails on 29 June and 3 August, received no reply.	SSM
Wang 2002	Wang TD, Yang H, Gu JJ	Clinical observation of bicyclol in treating chronic hepatitis B with 60 cases	Chinese Journal of Clinical Pharmacy	2002;11(5):273-4	Contacted author 29 June: author could not remember details and refused to provide email addresses for further contact.	SSM
Wang 2005	Wang XG	The interferon symphysis kurarinone treat chronic hepatitis B clinic observation	Chinese Journal of the Practical Chinese with Modern Medicine	2005;18(12):1739-40	Contacted author's work hospital on 3 August and 14 September: author had possibly re-	SSM

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					tried from hospital.	
Wang 2010	Wang X, She JJ, Qiao J, He XL	Clinical effect of marine tablets in the treatment of chronic hepatitis B patients with low level of HBV	Journal of Tropical Medicine	2010;10(8):961-963	Contacted author's hospital on 29 June: author had retired. No other contact information available.	SSM
Wang 2010	Wang Y	[Observation of curative effect of matrine injection combined with diammonium glycyrrhizinate in the treatment of 1200 cases of chronic hepatitis B]	Medical Information	2010;23(11):500-501	Contacted author's hospital on 29 June, but he did not work there.	SSM
Wang 2003	Wang YZ	[Cost-effectiveness analysis of three treatment options for chronic hepatitis B]	Chinese Journal of Integrated Traditional and Western Medicine	2003;13(5):307-309	Contacted author's hospital on 29 June and 15 August: author had retired. No other contact information available.	SSM
Wei 2007	Wei YH	[Clinical observation on the treatment of chronic hepatitis B with matrine combined with glycyxin]	Strait Pharmaceutical Journal	2007;19(10):890-891	Contacted author's work department on 29 June and 14 September: author was not available.	SSM
Wu 2009	Wu DL	[Effect of compound glycyrrhizin on 52 cases of chronic hepatitis B]	China Modern Medicine	2009;16(10):845-846	Contacted author's work department on 29 June and 14 September, but no reply.	SSM
Wu 2004	Wu LF	Comparison of therapeutic effects and cost-effectiveness analysis of matrine and α -interferon for chronic hepatitis B	Anhui Medical and Pharmaceutical Journal	2004;8(5):370-371	Contacted author's work department on 4 August and 14 September, but no reply.	SSM

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Wu 2004	Wu YL	[Clinical study on anti - liver fibrosis with matrine]	Chinese Herbal Medicine	2004;27(2):153-4	Contact- ed author's work depart- ment on 4 August and 14 Septem- ber: author had retired.	SSM
Wu 2002	Wu CQ	[Therapeutic effect of matrine on chronic hepatitis B]	Shanxi Medical Journal	2002;31(2):125-6	Contact- ed author 29 June and 5 August: we obtained the author's person tele- phone num- ber and Wechat number. Contacted author on 14 September, but number was incor- rect.	SSM
Xiao 2006	Xiao Q	[The curative effect of matrine injection on HBeAg negative chronic hepatitis B and its relationship with gene mutation site]	Shaanxi Journal of Traditional Chinese Medicine	2006;27(1):3-4	Contact- ed author's work depart- ment on 29 June, but no reply. Con- tacted on 14 Septem- ber, but au- thor was not available.	SSM
Huang 2008	Huang T, Yang L, Zhao LF	[Therapeutic effect of matrine on 102 cases of chronic hepatitis B]	Chinese Remedies & Clinics	2008;8(6):490-1	Contact- ed author's work depart- ment on 2 August and 13 August, but no reply.	CLL
Xie 2006	Xie R	[Clinical observation of matrine in treating patients with lamivudine resistance to chronic hepatitis B]	15th National Conference on Integrative Medicine for Liver Diseases	—	Contact- ed author's work hospi- tal on 2 Au- gust, but he did not work there.	CLL
Xiong 2005	Xiong Y, Shen NS, Chen B, Wu YN,	Clinical observation on retreating chronic hepatitis B after lamivudine withdrawing	Chinese Journal of Modern Chinese and Western Medicine	2005;3(1):	Contact- ed author's work depart- ment on 2 August, but	CLL

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	Huang YH, Yang H				he did not work there.	
Xu 2008	Xu DX	Effect of oxymatrine capsule on chronic hepatitis B	Occupation and Health	2008;24(15):1674	Contact- ed author's work depart- ment on 7 August, but he did not work there.	CLL
Xu 2005	Xu HF, Wang YB	[Retreatment of patients with chronic he- patitis B after lamivudine treatment fail- ure]	Journal of Clinical Hepatology	2005;8(5):2945	Contact- ed author's work depart- ment on 8 August, but he did not work there.	CLL
Xu 2004	Xu J, Yao YC	[Fifty patients with positive HBV deoxyri- bonucleic acid treated with matrine]	Modern Jour- nal of Integrated Traditional Chi- nese and West- ern Medicine	2004;13(14):1846	Contact- ed author's work depart- ment on 2 August and 8 August, but no reply.	CLL
Xu 2013	Xu LH	[Clinical observation on treatment of HBeAg positive chronic hepatitis B with matrine capsule combined with interfer- on- α]	Medical Informa- tion	2013;26(5):609-10	Contact- ed author on 2 August, but author re- fused to an- swer ques- tions.	CLL
Xu 2005	Xu HQ, Wang QT, Wu RT, Dai SL, Wang X	[Treatment of 38 cases with chronic he- patitis B with oxymatrine]	Modern Medicine & Health	2005;21(1):49	Contact- ed author's work depart- ment on 2 August and 9 August, but no reply.	CLL
Yan 2009	Yan HB	[Clinical efficacy of matrine in the treat- ment of hepatic fibrosis of chronic hepati- tis B]	Jilin Medicine	2009;30(15):1676	Contact- ed author's work depart- ment on 2 August and 9 August, but no reply.	CLL
Yang 2005	Yang JG, Xin JL, He XF	[Treatment of 36 cases with chronic he- patitis B with matrine]	Chinese Jour- nal of Integrated Traditional and Western Medi- cine	2005;15(5):305-6	Efficient contact in- formation available.	CLL
Yao 2007	Yao MW	[Clinical observation of 52 cases of chron- ic hepatitis B with matrine]	Journal of Clin- ical Medicine in Practice	2007;11(1):74	Contact- ed author's work depart-	CLL

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					ment on 2 August and 9 August, but no reply.	
Yin 2005	Yin MS, Cui XY, Piao HX, Zhou ZX	[Preliminary study on the treatment of chronic viral hepatitis B with matrine]	Chinese Journal of Clinical Hepatology	2005;21(4):237-8	Contact-ed author's work hospital on 2 August, but he did not work there.	CLL
Yin 2002	Yin YK, Zhang JM, Lu Q, Zhang WQ, Zhang QB, Wu XH, et al	[Therapeutic effect of matrine capsule on 29 cases of chronic hepatitis B]	Chinese Hepatology	2002;7(2):134-6	Contact-ed author's work hospital on 2 August, but he did not work there.	CLL
Yin 2002	Yin YM	[36 cases of HBsAg negative chronic hepatitis B were treated by ganlixin combined with matrine]	Jilin Traditional Chinese Medicine	2002;22(5):14	Contact-ed author's work hospital on 2 August, but he did not work there.	CLL
Yu 2001	Yu YY, Si CW, Zeng Z, Wang QH, Zhou XQ, Zhang QB, et al	A clinical trial of oxymatrine in treating chronic viral hepatitis type B	Chinese Journal of Internal Medicine	2001;40(12):843-6	Contact-ed authors' work department on 2 August, but author was not available. Contacted on 9 August, but no reply.	CLL
Yu 2005	Yu FQ	[Therapeutic effect of matrine on chronic hepatitis B]	Central Plains Medical Journal	2005;32(8):40	Contact-ed authors' work hospital on 2 August and 9 August, but no reply.	CLL
Yu 2005	Yu LL, Wen XF	[Therapeutic effect of matrine injection on 42 cases of chronic hepatitis B]	Acta Academiae Medicinae Zunyi	2005;28(4):363-4	Contact-ed author's work department on 2 August and 9 August, but no reply.	CLL
Zhan 2006	Zhan DA	[Matrine in the treatment of HBeAg positive hepatitis B fibrosis]	First National Conference on	—	Contact-ed author's	CLL

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			Integrative Medicine		work department on 2 August and 9 August, but no reply.	
Zhang 2004	Zhang DH, Liu H	Clinical observation on the changes of T subsets in the treatment of chronic hepatitis B with alkaloids sophora	Modern Medical and Health	2004;20(16):1588-9	Contact author's hospital on 2 August, but telephone number was incorrect.	CLL
Zhang 2002	Zhang HL, Shan TH, Liu XX	[Matrine in the treatment of HBeAg negative chronic hepatitis B]	Qingdao Medical Journal	2002;34(1):26	Contacted author's work hospital on 2 August, but he did not work there.	CLL
Zhang 2012	Zhang JH	[Analysis of curative effect of matrine capsule on chronic hepatitis B]	Medical Frontier	2012;2(35):157-8	Contacted author's work hospital on 2 August, but the responder refused to transfer the call. Contacted on 13 August, but he did not work there.	CLL
Zhang 2002	Zhang LC, Mao JZ, Song Z	[Short-term efficacy of matrine injection in the treatment of chronic hepatitis B]	Ningxia Medical Journal	2002;24(12):780-1	Contacted author's work department on 2 August, but no reply. Contacted on 13 August: the responder said the author did not work here.	CLL
Zhang 2006	Zhang WD, Li JY, Ye XB, Yang JX	[Clinical efficacy of matrine in the treatment of chronic hepatitis B]	Journal of Clinical and Experimental Medicine	2006;5(6):737	Contacted author's work department on 2 August and 13 August, but no reply.	CLL
Zhang 2006	Zhang XY	[Therapeutic effect of kushen capsule on chronic hepatitis B]	10th National Conference on	—	Contacted author's	CLL

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			Liver Diseases and the 10th Anniversary of the Chinese Journal of Liver Diseases		work department on 2 August and 13 August, but no reply.	
Zhang 2005	Zhang X, Qu J	[Analysis of therapeutic effect of drug combination on chronic hepatitis B]	China Health Statistics Year-book	2005;22(3):182-90	Contact-ed author's work department on 2 August and 13 August, but no reply.	CLL
Zhang 2005	Zhang YT, Lan LP	[Effect of adenosine monophosphate combined with lentinan polysaccharide on 56 cases of unresponsive chronic hepatitis B]	Proceeding of the Clinical Medicine Journal	2005;14(9):684-5	Contact-ed author's work department on 2 August and 13 August, but no reply.	CLL
Zhang 2001	Zhang YJ	[Clinical efficacy of matrine injection in the treatment of chronic hepatitis B]	7th National Conference on Infectious Diseases of the Chinese Medical Association	—	Contact-ed author's work hospital on 2 August, but he did not work there.	CLL
Zhao 2001	Zhao SK, Zhao JH, Zhao QX	[Clinical observation on the curative effect of matrine combined with thymosin in the treatment of chronic hepatitis B]	Worldwide Medicine	2001;19(2):189	Contact-ed author's hospital on 2 August, but telephone number was incorrect.	CLL
Zhou 2003	Zhou DM, Kang DQ, Liu AP, Chen B, Ju LX	A clinical study of kurorinone in the treatment of hepatic fibrosis for chronic hepatitis B	Chinese Journal of Medical Writing	2003;10(13):1097-100	Contact-ed author's work hospital on 2 August, but he did not work there.	CLL
Zhou 2004	Zhou GH	[30 cases of chronic hepatitis B were treated by matrine and glucose sequence]	World Chinese Journal of Digestology	2004;12(10):1097-100	Contact-ed author's hospital on 2 August, but telephone number was incorrect.	CLL
Zeng 2003	Zeng XQ, Xu WD	[Clinical observation of matrine injection in treating chronic hepatitis B]	Zhong Hua Lin Chuang Yi Yao Za Zhi	—	Contact-ed author 28 September, but ne was not available. Con-	YQL

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					tacted 18 October, but no reply.	
Wan 2009	Wan NY, Su ZW	United adefovir dipivoxil and matriner treatment efficacy and analysis of hepatitis B	Sichuan Medical Journal	2009;30(6):930-2	Contacted author 21 December and 24 December, but no reply.	YQL
Long 2006	Long X, Lu TH, Luo X	Efficacy of oxymatrine in the treatment of patients with chronic hepatitis B	Medical Journal of West China	2006;18(4):425-30	Contacted author 21 December and 24 December, but no reply.	YQL
Luo 2010	Luo DD, Qiu ZW	Benefit evaluation of matriner injection and diammonium glycyrrhizinate injection in treatment of chronic hepatitis	China Modern Medicine	2010;17(11):1051-5	Contacted author 21 December and 24 December, but no reply.	YQL
Li 2013	Li XH	[Clinical observation on treatment of chronic hepatitis B with combination of traditional Chinese medicine and western medicine](Abstract)	Health Horizon	2013;(19)	Contacted author 21 December and 24 December, but no reply.	YQL

Notes: — exact information could not be provided (presented at a conference).

CONTRIBUTIONS OF AUTHORS

NL: developed and drafted the protocol; selected trials to include; extracted data from trials; interpreted data; drafted the final review.

DZK: developed and co-ordinated the protocol; interpreted data; commented on the final review.

CLL: selected trials to include; extracted data from trials; contacted the authors for missing data; commented on the final review.

SSM: selected trials to include; extracted data from trials; contacted the authors for missing data; commented on the final review.

YQL: selected trials to include; extracted data from trials; contacted the authors for missing data; commented on the final review.

DN: developed, co-ordinated, and advised on the protocol; advised on the interpretation of data; commented on the final review.

JCJ: developed, co-ordinated, and advised on the protocol; advised on the interpretation of data; commented on the final review.

CG: developed, co-ordinated, and advised on the protocol; advised on the interpretation of data; commented on the final review.

JPL: initiated the review; and advised and commented on the protocol and final review.

All authors approved of the publication of the review.

DECLARATIONS OF INTEREST

NL: none known.

DZK: none known.

CLL: none known.

SSM: none known.

YQL: none known.

DN: none known.

JCJ: none known.

CG: none known.

JPL: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the protocol ([Liang 2018](#)).

To increase the clarity of the control interventions, we changed the title from "Radix Sophorae flavescentis versus antiviral drugs for chronic hepatitis B" to "Radix Sophorae flavescentis versus other drugs or herbs for chronic hepatitis B."

For the calculation of the DARIS regarding adverse events considered 'not to be serious,' we used a diversity of 25% rather than the observed diversity of 0% ([Jakobsen 2014](#)).

We did not assess harmful effects of Radix Sophorae flavescentis 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 Radix Sophorae flavescentis, reported in observational studies.

Post-hoc, we decided to present the results of our surrogate outcomes, proportion of participants with detectable HBV-DNA, and proportion of participants with detectable HBeAg in the 'Summary of findings' table, Abstract, and 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 separately from with the assessment of imprecision with GRADE in a sensitivity analysis.

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, time (PICOT). In addition, there may be overlap across several of our protocols and full reviews as they share at least six common authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects] [*therapeutic use]; DNA, Viral [analysis]; Hepatitis B e Antigens [blood]; Hepatitis B virus [genetics]; Hepatitis B, Chronic [*drug therapy] [virology]; Plants, Medicinal [adverse effects] [*chemistry]; Randomized Controlled Trials as Topic [statistics & numerical data]; Sophora [adverse effects] [*chemistry]

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male