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[Intervention Review]

Medicinal herbs for hepatitis C virus infection

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ABSTRACT

Background

Hepatitis C virus (HCV) infection is a serious health problem world-wide. Medicinal herbs are increasingly being used for hepatitis C.

Objectives

To assess the efficacy and safety of medicinal herbs for hepatitis C virus infection.

Search methods

Searches were applied to *The Controlled Trial Registers of The Cochrane Hepato-Biliary Group*, *The Cochrane Complementary Medicine Field*, and *The Cochrane Library* as well as MEDLINE, EMBASE, BIOSIS, Chinese and Japanese databases (February 2001). Five Chinese and one Japanese journals were handsearched. No language restriction was used.

Selection criteria

Randomised clinical trials comparing medicinal herbs versus placebo, no intervention, general non-specific treatment, other herbal medicine, or interferon and/or ribavirin treatment. Trials of medicinal herbs plus interferon and/or ribavirin versus interferon and/or ribavirin alone were also included.

Data collection and analysis

Two authors extracted data independently. The methodological quality of the trials was evaluated using the generation of allocation sequence, allocation concealment, double blinding, and the Jadad-scale. The outcomes were presented as relative risk or weighted mean difference, both with 95% confidence interval.

Main results

Ten randomised trials, including 517 patients with mainly chronic hepatitis C, evaluated ten different medicinal herbs versus various control interventions (four placebo, four interferon, two other herbs). The methodological quality was considered adequate in four trials and inadequate in six trials. Compared with placebo in four trials, none of the medicinal herbs showed positive effects on clearance of serum HCV RNA or anti-HCV antibody or on serum liver enzymes, except one short-term trial in which a silybin preparation showed a significant effect on reducing serum aspartate aminotransferase and gamma-glutamyltranspeptidase activities. The herbal compound Bing Gan Tang combined with interferon-alpha showed significantly better effects on clearance of serum HCV RNA (relative risk 2.54; 95% confidence interval 1.43 to 4.49) and on normalisation of serum alanine aminotransferase activity (relative risk 2.54; 95% confidence interval 1.43 to 4.49) than interferon-alpha monotherapy. The herbal compound Yi Zhu decoction showed a significant effect on clearance

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of serum HCV RNA and normalisation of ALT levels compared to glycyrrhizin plus ribavirin. Yi Er Gan Tang showed a significant effect on normalising serum alanine aminotransferase compared to silymarin plus glucuro lactone. There was no significant efficacy of the other examined herbs. The herbs were associated with adverse events.

Authors' conclusions

There is no firm evidence of efficacy of any medicinal herbs for HCV infection. Medicinal herbs for HCV infection should not be used outside randomised clinical trials.

PLAIN LANGUAGE SUMMARY

Still awaiting evidence on efficacy of medicinal herbs for viral hepatitis C

Hepatitis C is an infectious disease of the liver caused by hepatitis C virus. Around 170 million people world-wide are chronically infected with this virus. The infection is associated with severe sequelae such as liver cirrhosis, liver cancer, or liver failure. Herbal medicines have been used for treating hepatitis C. This systematic review evaluates the effects of herbal medicines for treating acute and chronic hepatitis C infection.

Ten different herbal medicines were tested in ten randomised trials in patients with chronic hepatitis C. The present systematic review found no significant antiviral effect of the herbal medicines when compared with placebo, but the data suggest that some herbal medicines in combination with interferon may have effects on the clearance of HCV RNA and on normalisation of liver enzymes. However, there is no strong evidence for any efficacy of these medicinal herbs for chronic hepatitis C due to the fact that most positive effects came from clinical trials with low methodological quality. Medicinal herbs for hepatitis C virus infection should not be used outside well-designed, randomised clinical trials.

BACKGROUND

Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV) (Choo 1989). Currently, an estimated 170 million persons world-wide are chronically infected with HCV (WHO 1997). HCV infection may be self-limited (viral clearance) or persist (Farci 1991; Alter 1992; Villano 1999). Viral clearance occurs in approximately 15% of persons and is assumed to have occurred when HCV RNA is undetectable in multiple blood samples from someone with HCV-specific antibodies (anti-HCV) or in whom acute infection was observed (Alter 1992; Barrera 1995; Villano 1999). About 85% develop persistent HCV infection in which the virus continues to replicate and remains in their blood lifelong (Alter 1997). Some studies suggest that cirrhosis of the liver develops in about 20% of patients with chronic hepatitis C within 20 years (Tremolada 1992; Poynard 1997) and once cirrhosis is established, one-fourth of them will ultimately suffer from liver cancer or liver failure (Hoofnagle 1997; Poynard 1997). However, other studies suggest that chronic HCV infection may have a much better prognosis (Thomas 2000; Seeff 2000; Brok 2005).

HCV is a small (40-60 nm in diameter), enveloped, single-stranded RNA virus of the family Flaviviridae. Because the virus mutates rapidly, changes in the envelope protein may help it evade the immune system. The virus is spread primarily by contact with infected blood and blood products. It is also transmitted by sexual contact and from mother to infant. The transmission from HCV infected mother to new-born may occur in five per cent of at risk deliveries. With the implementation of anti-HCV screening in blood donors, the risk of post-transfusion hepatitis C has been dramatically reduced, but the infection continues to occur via other modes of apparent or unapparent parenteral transmission.

Presently, the most effective therapy for chronic hepatitis C is combination therapy with alpha interferon (IFN) and ribavirin (Brok 2005). However, this intervention has only been demonstrated to have an effect on virological, biochemical, and histological responses. We do not yet know whether the effects on these surrogate outcome measures can be turned into patient relevant outcomes such as cirrhosis morbidity, quality-of-life, and increased survival (Brok 2005). Furthermore, IFN and ribavirin are connected with a plethora of adverse events such as anorexia, nausea, dry skin, and leukopenia and are costly (Brok 2005). Therefore, new medications and approaches to treatment are needed. Complementary therapies are being used increasingly (Eisenberg 1998; Vickers 2000). The number of randomised trials of complementary treatments has doubled every five years, and the Cochrane Library now includes nearly 50 systematic reviews of complementary medicine interventions (Vickers 2000). Many people turn to this therapy when conventional medicine fails them or they believe strongly in the effectiveness of complementary medicine.

Medicinal herbs are defined in this review as products derived from plants or parts of plants used for treatment of diseases. Some clinical trials have shown that medicinal herbs might have therapeutic potential for chronic liver diseases, including chronic hepatitis C (Zuin 1987; Ferenci 1989; Arase 1997; O'Hara 1998; Rossum 1998; Philipp 1999; Wang 2000). On the other hand, there is an increasing number of reports in the medical literature about liver toxicity and other adverse events from some herbal products (Melchart 1999; Ishizaki 1996; Gottlieb 2000). Accordingly,

this is another area that needs further research and systematic evaluation.

OBJECTIVES

The objective of this review was to assess the efficacy and safety of treating HCV infection with medicinal herbs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials were included irrespective of blinding, publication status, and language. Quasi-randomised trials and historically controlled clinical trials were excluded.

Types of participants

Male or female patients, of any age or ethnic origin, who had HCV infection (including acute and chronic HCV infection). Acute hepatitis C is diagnosed on the basis of symptoms such as jaundice, fatigue, and nausea, along with marked increases in serum alanine aminotransferase (ALT) and presence of anti-HCV or de novo development of anti-HCV. The diagnosis is confirmed by the finding of HCV RNA in serum. Chronic hepatitis C is diagnosed by elevated or recurrent fluctuating serum ALT levels and HCV RNA positivity lasting more than six months with or without symptoms, and with or without liver biopsy confirmation. Trials in populations with coinfection of HCV with human immune deficiency virus were excluded, but patients co infected with hepatitis B were included.

Types of interventions

Medicinal herbs were compared with no intervention, placebo, non-specific interventions like vitamins, other medicinal herbs, or IFN (no limitation regarding IFN type or treatment regimen) and/or ribavirin. Trials of medicinal herbs plus IFN and/or ribavirin versus IFN and/or ribavirin alone were also included. Co-interventions were allowed as long as both arms of the randomised allocation received the same co-intervention(s).

Types of outcome measures

The primary outcome measures sought at the end of treatment and at maximal follow-up after completion of the treatment were:

- mortality (total and liver related);
- liver fibrosis, liver cirrhosis, and/or liver cancer;
- viral response, defined as loss of detectable HCV RNA (and/or serum anti-HCV) measured by validated methods such as polymerase chain reaction assay and second- or third-generation enzyme immunosorbent assay or recombinant immunoblot assay (Farrell 2000).

The secondary outcome measures were:

- biochemical response, defined as decrease or normalisation of serum ALT or aspartate aminotransferase (AST) levels;
- histological response, improvement of histology assessed by histological activity index and fibrosis score (Ishak 1995);
- number and type of adverse events. Two types of adverse events were analysed, serious adverse events and adverse events not considered serious. The serious adverse events were any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of

hospitalisation, resulted in persistent or significant disability, was a congenital anomaly/birth defect or was an event that may jeopardise the patient or required intervention to prevent one of the former serious adverse events (ICH-GCP 1997). All other adverse events were considered non-serious;

- quality-of-life;
- health economics.

Search methods for identification of studies

Electronic searches

The trials registers of The Cochrane Hepato-Biliary Group, The Cochrane Complementary Medicine Field, and The CENTRAL database of The Cochrane Library as well as MEDLINE (March 1966 to February 2001), EMBASE (January 1980 to February 2001), BIOSIS (January 1969 to February 2001) and Chinese Biomedical CD Database (January 1979 to February 2001) were searched from their date of inception onwards. The search terms included hepatitis-C, medicine-traditional, herbal-medicine, medicine-Chinese, plants-medicinal, drugs-herbal, plants extracts, herbs, herbs-medicinal, medicinal-herbs, drugs-non-prescription, alternative-medicine, complementary-medicine, traditional-medicine, and medicine-traditional-oriental.

Handsearches

The journals *Chinese Journal of Infectious Diseases*, *Chinese Journal of Hepatology*, *Chinese Journal of Clinical Hepatology*, *Chinese Journal of Integrated Traditional and Western Medicine*, *Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases* were searched by JL and *Japanese Journal of Oriental Medicine* was searched by KT from the first publication date onwards to 2001. Conference proceedings in Chinese were also handsearched. The results of the handsearches were submitted to the Cochrane Hepato-Biliary Group. The reference lists of identified randomised clinical trials and review articles were checked in order to find randomised trials not identified by the electronic searches or handsearches.

Data collection and analysis

Selection of trials for inclusion

Two authors independently selected the trials to be included in the review according to the prespecified selection criteria. Any disagreement was resolved by discussion.

Assessment of methodological quality

Concealment of the allocation was scored A (adequate), B (unclear), or C (inadequate), following criteria adopted from The Cochrane Handbook and Schulz et al. (Schulz 1995) as follows:

A - Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment.

B - Unclearly concealed trials, in which the authors either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A).

C - Inadequately concealed trials, in which method of allocation was not concealed, such as alternation methods or use of case record numbers. Such trials were excluded.

The double blinding method was described and assessed as adequate or inadequate.

Further, we registered whether the randomised clinical trials reported to have used intention-to-treat analysis or not (Gluud 2001).

In addition, the randomised clinical trials were assessed by the Jadad scale (Jadad 1996). The scale awards one to five points. Trials with one or two points were considered low methodological quality and trials with three to five points were considered high methodological quality (Moher 1998; Kjaergard 2001b).

Data extraction

Data were extracted independently by two authors using a self-developed data extraction form. Papers not in Chinese, Danish, English, Japanese, German, and French were translated with the help of the Cochrane Hepato-Biliary Group. The following characteristics and data were extracted from each included trial: primary author, quality assessment, mean age, gender, and ethnic of patients, number of randomised patients and number lost during follow-up, patient inclusion and exclusion criteria, dosage and duration of intervention, outcome measures, and number and type of adverse events.

Data on the number of patients with each outcome, by allocated treatment group, irrespective of compliance or follow-up, were sought to allow an intention-to-treat analysis. If the above data were not available in the trial reports, further information was sought by correspondence with the principal investigator.

Data synthesis

Dichotomous data were presented as relative risk (RR) and continuous outcomes as weighted mean difference (WMD), both with 95% confidence intervals (CI). Analyses were performed by intention-to-treat where possible. For dichotomous outcomes, patients with incomplete or missing data were included in a sensitivity analysis by counting them as treatment failures to explore the possible effect of loss to follow-up on the findings ('worst-case' scenario). Meta-analysis was performed within comparisons where individual trials compared the same medicinal herb versus the same control intervention.

We intended to display trials as comparisons of medicinal herbs versus:

- no intervention or placebo;
- non-specific intervention;
- other medicinal herbs;
- IFN monotherapy;
- ribavirin monotherapy;
- IFN/ribavirin combination therapy.

Trials of medicinal herbs plus IFN/ribavirin versus IFN/ribavirin alone were presented as a separate comparison.

If a sufficient number of randomised clinical trials were identified, we planned to perform subgroup analyses according to their methodological quality:

- trials with adequate versus inadequate concealment of allocation;
- trials with adequate versus inadequate double-blinding;
- trials with versus without use of intention-to-treat analysis;
- trials with high versus low Jadad scores ($\geq$ or $<$ three versus $<$ or $=$ two points).

Furthermore, if a sufficient number of randomised clinical trials were identified, we planned to perform the following subgroup analyses:

- ethnic origin;
- acute or chronic HCV infection;
- chronic hepatitis C with or without cirrhosis;
- treatment response. The desired treatment response indicator is viral clearance, as indicated by non-detectability of HCV RNA in serum by the most sensitive test available. An end-of-treatment viral response is defined as non-detectability of HCV RNA at the end of treatment. A sustained viral response is defined as non-detectability of HCV RNA at six months after completion of treatment (Farrell 2000);
- excluding those trials in which chronic hepatitis C was not histologically confirmed.

Potential biases (Vickers 1998) were investigated according to Egger et al. (Egger 1997).

RESULTS

Description of studies

Our initial searches identified 104 references, 89 from the electronic searches and 15 from the handsearches. After reading titles and abstracts, 59 of these articles were excluded because they were duplicates, non-clinical studies, or had study objectives different from this review. A total of 45 references published in three languages (Chinese, English, and Japanese) were retrieved for further assessment. Of these, 35 references were excluded because they did not meet our inclusion criteria. The reasons for exclusion were listed under 'Characteristics of excluded studies'.

The remaining ten randomised clinical trials reported random allocation of patients ($n = 517$) with mainly ($> 75\%$) chronic hepatitis C to medicinal herbs versus control (placebo in four trials, IFN treatment in four trials, herb plus non-specific treatment in one trial, and herb plus ribavirin in one trial). One of these trials included an extra intervention arm, so that the medicinal herb could be compared with IFN and with the combination of IFN and the medicinal herb (Xiao 1999). These ten randomised clinical trials met all our pre-specified inclusion criteria listed under 'Characteristics of included studies', of which four trials were published in English and six in Chinese. One of the trials (Raymond 1998), however, evaluated Complete Thymic Formula versus placebo. Complete Thymic Formula contains various herbs, but in addition vitamins, enzymes, minerals as well as bovine glandular extracts of thymosin, thymopoietin, and thymic humoral factor (Raymond 1998). It is therefore not a pure herb and it may be argued that this trial should be excluded.

Patients

A total of 517 patients were randomised in the ten trials. Two trials included inpatients, three trials included outpatients, and one trial included both out- and inpatients. The remaining four trials did not specify the origin of the patients. All ten randomised clinical trials included adults. The mean age was 32 years in nine trials providing data. One trial did not describe the sex or age of 25 participants from the control arm (Chen 1998), and the rest reported a male to female ratio of 1.9:1 (322:170). The average size of the trials was 53 patients, ranging from 20 to 78 patients.

Diagnosis

The inclusion criteria were explicit HCV infection diagnosed by clinical manifestations, biochemical responses, and virological markers. Three trials confirmed the diagnosis by liver biopsy (Batey 1998; Buzzelli 1993; van Rossum 1999). Seven trials included only patients with chronic hepatitis C, one trial included patients with acute and chronic hepatitis C (Chen 1998), and another two trials included patients with hepatitis C, but did not report the clinical type of hepatitis C (Yu 1995; Jiang 1999). At least 75% of the 517 patients had chronic hepatitis C.

Interventions

Ten different herbs were tested in ten randomised trials. No medicinal herb was tested twice among the ten included trials. According to the category of medicinal herbs, two trials studied a single herb or ingredient of a single herb (silymarin preparation and glycyrrhizin), seven trials studied compounds of herbs (CH-100, Bing Gan Ling, Bing Gan capsule, Bing Gan Tang, Gan Su capsule, Yi Er Gan Tang, and Yi Zhu decoction) and one trial studied various herbs combined with other alternative medicines (Complete Thymic Formula). The constituents and dosage of medicinal herbs varied (see Additional table 01: Preparations and compositions of the medicinal herbs) (Table 1). The median duration of treatment was 14 weeks (range one to 24 weeks). The control interventions included placebo (Batey 1998; Buzzelli 1993; Raymond 1998; van Rossum 1999), IFNs (Chen 1998; Han 1997; Pei 1996; Xiao 1999), other herb plus non-specific treatment (Yu 1995), and glycyrrhizin plus ribavirin (Jiang 1999).

Outcomes

None of the ten trials reported mortality, incidence of liver cirrhosis and/or hepatocellular carcinoma, liver histology, quality-of-life, or health economics. The common outcomes reported were viral responses (including serum HCV RNA and anti-HCV antibody), biochemical responses, symptoms and signs, as well as adverse effects. Six trials reported follow-up after the end of intervention with medicinal herbs. Duration of follow-up after the end of interventions was six to 12 months.

Risk of bias in included studies

Of the ten included randomised clinical trials, two used adequate allocation concealment (Batey 1998; van Rossum 1999), four had high methodological quality (a Jadad-score of five points for van Rossum 1999; four points for Batey 1998; and three points for Buzzelli 1993 and Raymond 1998), and the remaining trials had unclear allocation concealment and low methodological quality (a Jadad-score of one point for Chen 1998; Han 1997; Jiang 1999; Pei 1996; Xiao 1999, and Yu 1995). Four of the ten trials reported using the double-blind design, which was assessed as adequate (Batey 1998; Buzzelli 1993; Raymond 1998; van Rossum 1999).

None of the trials reported a sample size calculation or stated that intention-to-treat analysis was used. Three randomised clinical trials reported the numbers of patients withdrawn and the reasons for withdrawal (Batey 1998; Raymond 1998; van Rossum 1999).

Effects of interventions

Mortality

No trial reported the outcome mortality.

Liver fibrosis, cirrhosis, and/or liver cancer

No trial reported the outcomes of liver fibrosis, liver cirrhosis, and/or liver cancer.

Viral and biochemical responses

- CH-100 versus placebo

The herbal medicine CH-100 showed no significant effect on clearance of serum HCV RNA compared with placebo (Batey 1998). None of the 22 patients with positive HCV RNA in both arms of the trial lost serum HCV RNA or normalised serum ALT activity at the end of six months of treatment. There was no significant difference on serum ALT activity between the herb and the placebo arm after the intervention.

- Glycyrrhizin versus placebo

Glycyrrhizin did not show any effect on clearance of serum HCV compared with placebo (van Rossum 1999). No patient in the two arms cleared serum HCV within four weeks treatment. Glycyrrhizin had no significant effect on serum ALT activity.

- Complete Thymic Formula versus placebo

Complete Thymic Formula showed no significant effects on the clearance of serum HCV RNA or on the level of HCV RNA compared with placebo (Raymond 1998). None of the 32 patients from both arms lost serum HCV RNA within three to six months of treatment. There were no significant differences in mean HCV RNA titers or serum ALT activity between the herbal medicine and placebo. Complete Thymic Formula showed no significant effect on serum AST activity compared with placebo.

- Silybin versus placebo

Silybin showed a significantly better effect compared with placebo on serum AST activity (WMD -24.60 units (U)/l, 95% CI -34.28 to -14.92 U/l, $P < 0.00001$) and serum gamma-glutamyltranspeptidase activity (WMD -18.40 U/l, 95% CI -23.78 to -13.02 U/l, $P < 0.0001$), but was without significant effects on serum ALT activities and total bilirubin levels (Buzzelli 1993). It is noteworthy that these effects were reported after only treating the patients for seven days.

- Bing Gan Ling versus IFN-alpha

Bing Gan Ling versus IFN-alpha showed no significant difference on the clearance of serum HCV RNA at the end of three months treatment (RR 1.31, 95% CI 0.65 to 2.65, $P = 0.5$) (Chen 1998). Serum HCV RNA became negative in 13/31 (42%) patients treated with Bing Gan Ling and in 8/25 (32%) patients treated with IFN-alpha. Bing Gan Ling did not differ significantly from IFN-alpha regarding normalisation of serum ALT activity.

- Bing Gan capsules plus IFN versus IFN

Bing Gan capsules plus IFN (no indication of IFN type) showed a trend towards a better effect of the combination than IFN monotherapy, both on clearance of serum HCV RNA (RR 1.73, 95% CI 0.89 to 3.38, $P = 0.11$) and anti-HCV antibody positivity (RR 1.73, 95% CI 0.89 to 3.38, $P = 0.11$) (Han 1997). Bing Gan capsule plus IFN also showed a trend towards a better effect on ALT normalisation than IFN monotherapy (RR 1.73, 95% CI 0.89 to 3.38, $P = 0.11$).

- Bing Gan Tang plus IFN-alpha versus IFN-alpha

Bing Gan Tang plus IFN-alpha showed a significant effect on the clearance of serum HCV RNA compared with IFN-alpha monotherapy (RR 2.54, 95% CI 1.43 to 4.49, $P = 0.001$) (Pei 1996). For the outcomes of clearance of serum anti-HCV antibody and normalisation of ALT activities, the combination therapy also

showed a significant effect compared with IFN-alpha monotherapy (RR 2.54, 95% CI 1.43 to 4.49, $P = 0.001$).

- Gan Su capsules alone or plus IFN-alpha versus IFN-alpha

Compared to IFN-alpha, Gan Su capsule showed no significant effect on the normalisation either of serum HCV RNA or on ALT activity. Gan Su capsule plus IFN-alpha versus IFN-alpha showed no significant difference on the clearance of serum HCV RNA at the end of four months treatment (RR 1.58, 95% CI 0.52 to 4.77, $P = 0.4$) (Xiao 1999). The serum HCV RNA became negative in 6/20 (30%) patients in the combination group and in 4/21 (19%) patients of the IFN-alpha group. The combination of Gan Su capsule and IFN-alpha showed a trend toward better effect on ALT normalisation compared with IFN-alpha (RR 1.65, 95% CI 0.80 to 3.40, $P = 0.17$).

- Yi Zhu decoction versus glycyrrhizin plus ribavirin

Compared with glycyrrhizin plus ribavirin, Yi Zhu decoction showed a significant effect on the clearance of serum HCV RNA at the end of three months treatment (RR 1.64, 95% CI 1.07 to 2.50, $P = 0.02$) (Jiang 1999). The same effect was observed on the normalisation of serum ALT levels (RR 1.64, 95% CI 1.07 to 2.50, $P = 0.02$). We caution about the interpretation of these results because the herbal treatment varied among the patients depending on the interpretation of the 'symptoms' by the Chinese investigator.

- Yi Er Gan Tang versus silymarin plus glucolactone

The herbal compound Yi Er Gan Tang was significantly better than silymarin plus glucolactone on normalisation of ALT activity (RR 2.09, 95% CI 1.37 to 3.18, $P = 0.0006$) and in shortening the time to serum ALT normalisation (WMD -20.20 days, 95% CI -22.66 to -17.74 days, $P < 0.00001$) (Yu 1995). Viral markers were not analysed.

'Worst-case scenario' analyses

Based on the number of withdrawals and drop-outs reported in three trials (Batey 1998; Raymond 1998; van Rossum 1999), 'worst-case scenario' analyses for the outcome of clearance of HCV RNA including all patients lost as treatment failures were performed. The size and direction of treatment effect were the same as reported above (data not shown).

Duration of follow-up

Six randomised clinical trials reported follow-up of one to 12 months after the end of treatment. However, the analysis of end of treatment response and sustained response could not be performed due to inadequate reporting in these trials. The trials reported the data from the end of treatment, and only stated that the efficacy was unchanged during follow-up.

Symptoms and signs

Five Chinese trials reported improvement of symptoms in patients with hepatitis C after the herbal treatment. However, we were unable to obtain data about individual symptoms and the numbers of patients with improvement of the symptoms after the interventions.

Adverse events

Adverse events were monitored and reported in six trials (Batey 1998; Buzzelli 1993; Chen 1998; Han 1997; Raymond 1998; van Rossum 1999).

Four patients experienced adverse events during herbal therapy with CH-100, in which one patient developed palpitations, two diarrhoea, and one abdominal discomfort (Batey 1998).

In another trial, 13/25 patients receiving IFN-alpha injection developed fever, some developed chill, fatigue, myalgia, poor appetite, nausea, and a few patients lost their hair or experienced a decrease of white blood cells and platelet count (Chen 1998). There was no significant adverse effect found in 31 patients who took the herbal compound Bing Gan Ling (Chen 1998).

During IFN treatment (3 MU, thrice a week), 15/26 patients in the control group developed fever, headache, and myalgia; 9/26 patients developed loss of hair while in the herb group none of these adverse effects happened (Han 1997).

Headache, increased fatigue, pain in the region of the liver, and dizziness were mentioned by patients of the placebo and glycyrrhizin intervention (van Rossum 1999). However, no significant differences between the groups were observed. In this trial, cold or 'flu-like' symptoms, diarrhoea, rash or itching, and nausea were only observed in patients treated with the glycyrrhizin intervention.

One patient developed a serious adverse event, severe thrombocytopenia, during the fifth month of therapy with Complete Thymic Formula (Raymond 1998).

Funnel plot analysis

The outcome measure normalisation of serum ALT levels in seven included trials was used for a funnel plot analysis. A linear regression analysis, in which the standard normal deviate, defined as the RR divided by its standard error, was regressed against the estimate's precision, defined as the inverse of the standard error, showed no significant funnel plot asymmetry (intercept 0.41, standard error 0.67; $t = 0.60$; $P = 0.57$).

DISCUSSION

Twelve different herbal medicines have been evaluated in ten randomised clinical trials including patients with HCV infection, mainly chronic hepatitis C. The present systematic review could not demonstrate any significant efficacy of any of the medicinal herbs (CH-100, glycyrrhizin, silybin, Complete Thymic Formula) when tested against placebo on HCV markers. However, Bing Gan Tang combined with IFN-alpha had positive effects on the clearance of HCV RNA and on normalisation of serum ALT levels compared with IFN-alpha monotherapy. However, at present there is no strong evidence for an efficacy of any of these medicinal herbs for HCV infection due to the fact that most positive effects were observed in single, small trials with low methodological quality. Due to the limited number of trials identified, we were prohibited to perform any of the planned sensitivity analyses and the lack of significant funnel plot asymmetry should be interpreted conservatively.

Strength of evidence

Six of the ten randomised clinical trials included in this review had low methodological quality. They provided only limited descriptions of study design, randomisation, and allocation concealment. Most trials stated only that random assignment was used, but did not give sufficient information to allow a judgement of whether or not it was conducted properly. Methodologically less rigorous trials show larger treatment effects than those conducted with better rigor (Schulz 1995; Moher 1998; Kjaergard 2001b). The insufficient number of trials prohibited us from performing meaningful sensitivity analysis to illuminate how robust the results

of the review are to the exclusion of the trials with inadequate methodology. No large randomised clinical trials were identified.

Populations

Six trials were tested in Chinese patients and one each in Australians, Italians, Americans, and Europeans. They examined different herbal medicines. Therefore, it is not possible to infer anything on the applicability of these herbs in different populations.

Medicinal herbs

The included trials tested different herbs against different control interventions (placebo, IFN, or combination of herbal medicines). The preparations of the herbal medicines were given in different formulations (tablet, capsule, injection, or decoction). Ideally, we should evaluate well defined herbal constituents, dosage, duration, and control intervention in two or more independently conducted randomised trials when evaluating the efficacy of medicinal herbs. We were limited in this respect by the small number of identified trials.

When dealing with the efficacy and adverse events of medical herbs, one should apply just as rigorous criteria in the evaluation of these interventions as internationally required for pharmaceutical products (ICH-GCP 1997). Many factors may affect the effect of herbs, including the species, the geographical origin, harvest season, preparation, storage, and extraction methods as well as dosage and duration of therapy (Blumberg 1998; Schuppan 1999). In clinical trials evaluating herbs it is, therefore, important to mention the specific botanical identification of the plant material, its geographical source, and the condition under which the plant substances were obtained. When the plant preparation is described in a monograph of a national or international Pharmacopoeia, all the quality control requirements should be fulfilled (EEC 1977). If a monograph concerning the plant preparations does not exist, the manufacturer should write a protocol dealing with the above quality control requirements (Geerts 1999).

Potential efficacy

Four trials with high methodological quality did not show any significant efficacy on viral response and/or on liver biochemistry, except one small, short-term trial in which silybin (a milk thistle preparation) appears to have liver protecting effect based on improvement of two out of four biochemical measures (Buzzelli 1993). One should be aware of the fact that this beneficial effect of silybin came from a trial with only 20 patients treated for one week and the trial did not examine if the efficacy was sustained. Further, another herb, Yi Er Gan Tang, seemed to be better than silymarin (another milk thistle preparation) plus glucurrolactone in normalising serum ALT levels. Yi Zhu decoction seemed to be better than glycyrrhizin plus ribavirin in clearing HCV RNA and normalising ALT levels.

One herbal medicine Bing Gan Tang plus IFN may have positive effects on the clearance of HCV RNA and on normalisation of serum ALT levels compared to IFN monotherapy. The potential benefit of the herb Bing Gan Tang combined with IFN for treatment of chronic hepatitis C could encourage further trials. The currently recommended treatment for chronic hepatitis C is the combination therapy of IFN and ribavirin (Brok 2005). Therefore, to explore possible combinations of IFN and ribavirin therapy with some potential herbal therapy may be an attractive option. Further, potential medicinal herbs can be tested against placebo in chronic

hepatitis C patients who do not respond to the IFN and ribavirin treatment or who have contraindications to the standard treatment (Brok 2005).

The goal of treatment of chronic hepatitis C is to prevent progression to hepatic fibrosis, cirrhosis, and primary liver cancer. Available outcomes from the included trials were mainly laboratory tests, i.e., surrogate outcomes. There is lack of data from randomised clinical trials on clinically relevant outcomes from long-term follow-up such as the incidence of liver fibrosis, cirrhosis, cancer, and mortality and, therefore, we are not able to draw conclusions about these important outcomes. The same problem, however, also applies to what is considered standard therapy of chronic hepatitis C today (Brok 2005).

Adverse events

Due to the limited number of trials identified and the limited number of patients included in each of the trials it is not possible to evaluate the full extent of the risk of adverse events connected with intervention with the examined herbs. However, some of the herbs gave rise to adverse events and one of the medications, Complete Thymic Formula, gave rise to a serious adverse event. There have been recent reports of liver toxicity and cancer associated with herbal medicines (Melchart 1999; Gottlieb 2000; Tomlinson 2000). Further, Fleig et al. (Fleig 1997) observed significantly higher mortality among patients with alcoholic cirrhosis treated with LIV.52 (an extract of several plants (Schuppan 1999)) compared with placebo treated patients. These observations were done in spite of studies in rats and uncontrolled observations in patients pointing to a beneficial effect of LIV.52 on liver biochemistry (Schuppan 1999). Monitoring safety of medicinal herbs in hepatitis C is important through adequate recording and reporting of adverse events in clinical trials. Rare and severe adverse events should be identified from large scale epidemiological studies.

Medicinal herbs and hepatitis C infection in the future

It is likely that certain medicinal herbs contain substances that may interact with viral load and/or prevent further liver injury. It is a difficult question, however, to point to which trials we need to conduct in the future. The field of medicinal herbs is more difficult than the traditional development of pharmaceutical interventions. First, we are dealing with a vast plethora of substances that have been brought to us from ancient times. Second, even focusing on one single medicinal herb raises the problems of its components and how they work in consort. Third, in spite of the fact that we may not have plausible biological reason for using some of the herbs, the use of these herbs are widespread in the East as well as in the West (Schuppan 1999). In order to find medicinal herbs that works and to prevent patients from taking herbs, which do not have any efficacy and which may cause significant detrimental effects (see above), we may have to conduct randomised trials which can reveal the true benefits and harms these herbs may cause. In deciding which herbs

to test in the future, we should use the combination of biological experiences as well as the results from randomised clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence for treating HCV infections with any of the examined medicinal herbs due to the small number of randomised trials conducted, the paucity of patients having entered these trials, and the low methodological quality of the trials.

Implications for research

It is necessary to have a much better description of the medicinal herbs being tested, including among others information on plant species, geographical origin, harvest season, preparation procedures, and quality control measures.

The methodological quality of clinical trials on medicinal herbs needs to be improved. The following aspects concerning methodological quality are important: (i) reporting of the generation of the allocation sequence and of allocation concealment, (ii) application of double blinding, (iii) clear description of withdrawals/dropouts during the trial, (iv) reporting of clinically important outcome measures from long-term follow-up.

In patients with HCV infection, it is necessary to have information on clinical and/or histological stage of the liver disease, the presence or absence of cirrhosis, the genotype of HCV, and other well proven prognostic indicators also when assessing the efficacy of medicinal herbs.

Rigorously designed, randomised, multicentre clinical trials are required to evaluate medicinal herbs with potential efficacy for hepatitis C. Besides the standard evaluation of virological and biochemical responses (which should be assessed at the end of treatment and at least at six months of follow-up after the end of treatment), outcome measures should include liver-related outcomes like incidence of hepatic fibrosis, cirrhosis, and liver cancer as well as quality-of-life and health economics. Standardised monitoring or an effective self-report system should critically estimate adverse events.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Batey 1998

Methods	Generation of the allocation sequence: the hospital pharmacy department (inadequate). Allocation concealment: the tablets coded by the manufacturer. Blinding: double-blind. Sample size estimation: no information. Withdrawal: four patients due to incomplete therapy. Intention-to-treat analysis: not used. Jadad score = 4.
Participants	Ethnic: Australians; 40 patients (20 in treatment group, male/female (M/F): 12/8, mean age 40.4 years (29 to 67); 20 in control group, M/F 12/8, mean age 40.9 years (16 to 71)). Setting: outpatients. Inclusion criteria: chronic hepatitis C, diagnosed by anti-HCV antibody positive and elevation of ALT over six months or more. In 24 patients, the diagnosis was confirmed by liver biopsy. Exclusion criteria: other forms of liver disease; patients receiving any other antiviral drugs prior to entry.
Interventions	Herbal intervention: Chinese herbal medicine (CH-100, a compound of 19 herbs) tablets, five tablets orally, three times a day, for six months. Control intervention: placebo, five tablets orally three times a day, for six months.
Outcomes	Hemoglobin concentration, white cell count, platelet count, serum ALT level, alkaline phosphatase, albumin, gamma-glutamyl transpeptidase, bilirubin, HCV RNA, and adverse events. The outcomes were assessed at the end of six months of treatment.
Notes	No information was given about the treatment arm of the four withdrawn patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Buzzelli 1993

Methods	Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: double-blind. Sample size estimation: no information. Withdrawal/drop-out: unstated.
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Medicinal herbs for hepatitis C virus infection (Review)

Buzzelli 1993 (Continued)

Jadad score = 3.

Participants	<p>Ethnic: Italians; 20 patients (M/F 6/14, mean age 53 years (31 to 70); 10 in treatment group, and 10 in control group). Setting: inpatients. Inclusion criteria: histologically proven chronic hepatitis (C coinfectd with B), increased AST and/or ALT levels for more than 12 months, and age from 30 to 70 years. Exclusion criteria: portal hypertension, hepatic encephalopathy, ascites, hepatocellular carcinoma, clinical signs and biochemical parameters of cholestasis, drug addiction, positive antinuclear, antimitochondrial, and antismooth muscle antibodies; ethanol intake > 30 g/day; malabsorption syndrome; cardiovascular, renal or endocrine disorders; pregnancy; and any pharmacological treatment three months before the beginning of the trial.</p>	
Interventions	<p>Herbal intervention: silybinphosphatidylcholine complex (IdB1016, an extract silybin preparation from the herb milk this- tle), two capsules (240 mg silybin) orally, twice a day, for seven days.</p> <p>Control intervention: identical placebo, two capsules orally twice a day, for seven days.</p>	
Outcomes	<p>Liver function tests, haematological and renal tests. The outcomes were measured at the end of treatment.</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chen 1998

Methods	<p>Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: no blinding. Sample size estimation: no information. Loss to follow-up: unstated. Jadad score = 1.</p>	
Participants	<p>Ethnic: Chinese; 56 patients (31 in treatment group, M/F 21/10, age from 15 to 56 years, including 18 acute hepatitis C and 13 chronic hepatitis C; 25 in control group, no details on age, gender, and stage of hepatitis, but stating comparable to treatment group). Setting: unstated. Inclusion criteria: acute and chronic hepatitis C, diagnosed according to the criteria of the national viral hepatitis convention (CMA 1990). Exclusion criteria: unstated.</p>	
Interventions	<p>Herbal intervention: Bing Gan Ling (a herbal compound of 17 herbs) decoction, 300 ml/day, divided into three doses orally, for three months; then the compound was taken as a capsule, 6 g orally, three times a day, for another two months.</p> <p>Control intervention: IFN-alfa 3 million unit (MU) intramuscularly, daily, for two consecutive weeks; then changed to every other day; for a total of three months.</p>	

Chen 1998 (Continued)

The same co-interventions of hypoxanthosine and vitamin C were applied to both groups.

Outcomes	Symptoms, serum ALT level, HCV RNA, and adverse events. The follow-up duration lasted for one year after the end of treatment.	
Notes	No data on symptoms were available.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Han 1997

Methods	Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: no blinding. Sample size estimation: no information. Loss to follow-up: unstated. Jadad score = 1.	
Participants	Ethnic: Chinese; 56 patients (30 in treatment group, M/F 22/8, mean age 35 years, 5/30 complicated with hepatitis B virus (HBV) infection; 26 in control group, M/F 20/6, mean age 35 years, 4/26 complicated with HBV infection). Setting: unstated. Inclusion criteria: chronic hepatitis C, diagnosed by serological tests. Exclusion criteria: unstated.	
Interventions	Herbal intervention: Bing Gan capsule (a herbal compound of 15 herbs), 3 g orally three times a day; plus IFN 3 MU intramuscularly thrice a week, for six months. Control intervention: IFN 3 MU intramuscularly thrice a week, for six months. Alcohol drinking was prohibited during treatment.	
Outcomes	Symptoms and signs, serum ALT level, HCV RNA, anti-HCV, and adverse events. The follow-up duration lasted for one year after the end of treatment.	
Notes	No data on symptoms were available.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jiang 1999

Methods	Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: no blinding.	
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Medicinal herbs for hepatitis C virus infection (Review)

Jiang 1999 (Continued)

Sample size estimation: no information.
Loss to follow-up: unstated.
Jadad score = 1.

Participants	Ethnic: Chinese; 40 patients (20 in treatment group, M/F 12/8, age 14 - 52 years; 20 in control group, M/F 11/9, age 12 - 54 years). Setting: unstated. Inclusion criteria: hepatitis C virus infection, diagnosed by virological tests (both HCV RNA and anti-HCV positive). Exclusion criteria: unstated.
Interventions	Herbal intervention: Yi Zhu decoction (a herbal compound of 10 herbs), decocted oral liquid from one dosage, daily; for three months. Control intervention: glycyrrhizin 50 ml in 250 ml of 10% glucose, intravenous infusion, daily; plus ribavirin 0.7 g in 250 ml of 10% glucose intravenous infusion daily; both for three months.
Outcomes	Symptoms and signs, serum ALT level, and HCV RNA. The outcome was measured at the end of treatment.
Notes	No data on symptoms were available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pei 1996

Methods	Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: no blinding. Sample size estimation: no information. Loss to follow-up: unstated. Jadad score = 1.
Participants	Ethnic: Chinese; 76 patients (46 in treatment group, M/F 30/16, mean age 37 years (19~68); 30 in control group, M/F 21/9, mean age 38 years (17~65)). Setting: outpatients. Inclusion criteria: chronic hepatitis C, diagnosed by positive anti-HCV IgM and HCV RNA, and elevated serum ALT. Exclusion criteria: unstated.
Interventions	Herbal intervention: Bing Gan decoction (a self-formulated compound of 12 herbs), one dose daily orally; plus IFN-alfa 400 IU (two tablets) orally, daily; both for six months. Control intervention: IFN-alfa 400 IU (two tablets) orally, daily, for six months.
Outcomes	Symptoms, serum ALT level, anti-HCV IgM, and HCV RNA. The follow-up duration lasted for one year after the end of treatment.

Pei 1996 (Continued)

Notes No data on symptoms were available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Raymond 1998

Methods	Generation of allocation sequence: not stated. Allocation concealment: no information. Blinding: double-blind. Sample size estimation: no information. Withdrawal: 32 out of 38 patients completed treatment (five patients in the placebo arm and one patient in the drug arm were withdrawn). Jadad score = 3.
Participants	Ethnic: Americans; 38 patients (20 in treatment group, M/F 17/3, mean age 49 years (35~67); 18 in placebo group, M/F 13/5, mean age 46 years (26~68)). Setting: tertiary referral centre. Inclusion criteria: chronic hepatitis C, diagnosed by elevated aminotransferase and positive HCV RNA after at least three months of IFN therapy, or patients did not tolerate IFN. In 13 patients with cirrhosis, the diagnosis was confirmed by liver biopsy. Exclusion criteria: pregnancy, currently abusing drugs or alcohol, hepatoma, serum HIV positive, or co-existent other liver disease.
Interventions	Herbal intervention: Complete Thymic Formula (including herbs), six tablets orally, twice a day, for 12 weeks. Control intervention: Placebo identical in shape, colour, and packaging to the active drug, six tablets orally twice a day, for 12 weeks. After the end of the trial period patients in both arms of the trial were offered open label treatment with Complete Thymic Formula for six months.
Outcomes	Serum HCV RNA levels, ALT and AST levels, and adverse effects. The outcomes were assessed after the three months treatment.
Notes	Complete Thymic Formula consists of various herbs but in addition vitamins, enzymes, minerals and bovine glandular extracts of thymosin, thymopoietin, and thymic humoral factor (Raymond 1998)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Rossum 1999

Methods Generation of allocation sequence: computer-generated.
Allocation concealment: pharmacy controlled code.

Medicinal herbs for hepatitis C virus infection (Review)

van Rossum 1999 (Continued)

Blinding: double-blind.
Sample size estimation: no information.
Withdrawal/drop-out: one patient dropped out due to social problems; two patients randomised were not meeting the inclusion criteria.
Jadad score = 5.

Participants	Ethnic: Europeans; 54 patients (13 in herb group I, M/F 11/2, mean age 45 years (32-66); 14 in herb group II, M/F 10/4, mean age 52 years (35-69); 14 in herb group III, M/F 11/3, mean age 44 years (34-61); 13 in placebo group, M/F 13/0, mean age 47 years (37-60)). Setting: outpatients. Inclusion criteria: chronic hepatitis C, diagnosed by anti-HCV antibody and HCV RNA positive, and elevated ALT levels over two months, confirmed by liver biopsy. Exclusion criteria: other causes of liver disease; significant cardiovascular or pulmonary dysfunction; malignancy; any other antiviral treatment; HIV infection, pregnancy or breast-feeding.	
Interventions	Herbal intervention: glycyrrhizin (an extract from liquorice root, Stronger Neo-Minophagen C), 80 mg for group I, 160 mg for group II, 240 mg for group III; intravenously, thrice weekly for four weeks. Control intervention: placebo, intravenously, thrice weekly for four weeks.	
Outcomes	Serum ALT levels, gamma-GT, HCV RNA, and side effects. The outcomes were assessed at the end of four-week treatment and at the follow-up of four weeks.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Xiao 1999

Methods	<p>Generation of allocation sequence: no information. Allocation concealment: no information. Blinding: no blinding. Sample size estimation: no information. Loss to follow-up: unstated. Jadad score = 1.</p>	
Participants	<p>Ethnic: Chinese; 59 patients (20 in treatment group I, including M/F 9/11, mean age 43 years (25~65); 21 in treatment group II, M/F 10/11, mean age 47 years (24~67); 18 in treatment group III, M/F 10/8, mean age 46 years (27~64)). Setting: out- and inpatients. Inclusion criteria: chronic hepatitis C, diagnosed by positive anti-HCV and HCV RNA and elevated serum ALT. Exclusion criteria: complicated with hepatitis A, B, D, E, and G viruses infection, hepatitis induced by drugs, alcohol, or allergic or auto-immune hepatitis.</p>	
Interventions	<p>Herbal intervention:</p>	

Xiao 1999 (Continued)

group I: Gan Su capsule (a self-formulated compound composed of more than 10 herbs), six capsules orally, thrice daily; plus IFN-alfa 3 MU intramuscularly, daily for the first month, from second month changed to thrice a week; both for another three months.

Control interventions:

Group II: IFN-alfa 3 MU intramuscularly, daily for the first month, and then from second month changed to thrice a week; for another three months.

Group III: Gan Su, six capsules orally, thrice daily, for four months.

Outcomes	Symptoms, serum ALT level, and HCV RNA. The outcomes were assessed at the end of treatment and at the follow-up of six months after the end of treatment.	
Notes	No data on symptoms were available.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yu 1995

Methods	Generation of allocation sequence: no information. Allocation concealment: no information. Blinding: no blinding. Sample size estimation: no information. Loss to follow-up: unstated. Jadad score = 1.	
Participants	Ethnic: Chinese; 78 patients (40 in treatment group I, M/F 27/13, mean age 26 years (9~66); 38 in treatment group II, M/F 24/14, mean age 26 years (11~63)). Setting: inpatients. Inclusion criteria: hepatitis C (stage not specified), diagnosed according to the criteria of the National Viral Hepatitis Convention (CMA 1990). Exclusion criteria: unstated.	
Interventions	Herbal intervention: Yi Er Gan Tang (a self-formulated compound composed of 10 herbs), one dose decoction orally, two times daily for 15 days. Control intervention: Gantaile (glucuro lactone) plus Yiganling (silymarin preparation) orally, usage and dosage unstated; plus potassium magnesium, aspartate intravenous infusion, daily for 15 days.	
Outcomes	Symptoms and signs, serum ALT level, hospital time. The follow-up duration lasted for six to 12 months after the end of treatment.	
Notes	No data on symptoms and signs were available.	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Yu 1995 (Continued)

Allocation concealment? Unclear risk B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abe 1994	Non-randomised, controlled study comparing IFN plus glycyrrhizin (herbal extract) versus IFN alone in 28 patients with chronic hepatitis C who did not respond to previous IFN therapy. Normalisation of serum ALT level was observed in 33% of IFN alone group and in 64% of the combination group, while disappearance of serum HCV RNA was 13% in IFN alone group and 38% in the combination group.
Akbar 1998	The study reported an observational study and a randomised trial. The participants in the randomised trial comparing a herbal extract HpPro versus placebo were 20 cases of chronic hepatitis, but no virological diagnosis was reported.
Arase 1997	A retrospective study on long-term efficacy of glycyrrhizin (a herbal extract named Stronger Neominophagen C) in 193 patients with chronic hepatitis C. The study claimed that long-term administration of glycyrrhizin in the treatment of chronic hepatitis C was effective in preventing liver carcinogenesis, but no comparison group was provided.
Cheng 1997	Randomised clinical trial comparing Bing Gan Ling (a herbal compound) versus control interventions which included adenosine triphosphate, coenzyme A, vitamin C, hypoxanthosine, hepatocyte growth-promoting factors, and IFN in 26 patients with hepatitis C (stage not specified). The confounding of the control intervention with hepatocyte growth-promoting factors led to the exclusion of the trial.
Deng 1997	Case series of 30 patients with hepatitis C (stage not specified) treated by a herbal compound.
Fujiwara 1994	Observational study comparing two different dosages of a combination therapy of two herbal compound (Xiao Chai Hu Tang plus Gui Zhi Fu Ling pill) in patients with chronic hepatitis B and C.
He 1999	Case series of 30 patients with hepatitis C (stage not specified) treated by a herbal compound formulated by the investigator.
Hirayama 1989	A randomised, multicenter, double-blind clinical trial comparing herbal medicine Shosaiko-to versus placebo in chronic active hepatitis. Patients had mainly chronic hepatitis B, and no testing on hepatitis C virus was performed.
Hirayama 1992	A randomised, multicenter, double-blind clinical trial comparing herbal medicine Shosaiko-to versus placebo in chronic active hepatitis. A total of 231 patients with chronic hepatitis was included; 99 patients had chronic hepatitis B and 123 had non-B chronic active hepatitis, but they were not tested for hepatitis C virus makers.
Liang 1996	Case series of 26 patients with hepatitis C (stage not specified) treated by a herbal compound of 12 herbs. This compound was formulated by the investigator.
Lin 1998	Case series of 51 patients with chronic hepatitis C treated by a herbal transdermal therapeutic system.
Liu 1996	Case series of 139 patients with hepatitis C (stage not specified) treated by a herbal compound. This compound was formulated by the investigator.

Study	Reason for exclusion
Ma 1995	Case series of 32 patients with hepatitis C (stage not specified) treated by a herbal compound (Xiao Chai Hu Tang) plus other herbs according to different symptoms diagnosed by traditional Chinese medicine.
Murray-Lyon 1999	A registered trial comparing IFN and ribavirin in conjunction with a Chinese herbal medicine in chronic hepatitis C was not started due to lack of funding.
Murray-Lyon 2000	A registered placebo controlled trial testing a Chinese herbal medicine in chronic hepatitis C was not started due to lack of funding.
Nagao 1996	A quasi-randomised trial comparing glycyrrhizin versus non-specific treatment for patients with chronic HCV infection complicated with oral lichen planus. The intervention aimed at the treatment of complications of chronic HCV infection.
Niu 1999	Case series of 50 patients with post-transfusion hepatitis C (stage not specified) treated by a herbal compound.
Okuno 1994	Case series of eight patients with chronic hepatitis C who were resistant to IFN therapy treated by IFN combined with glycyrrhizin (herbal extract). After six months treatment, their ALT levels decreased about 70% (one became normal), serum HCV RNA became negative in two of eight patients and the hepatic activity index (HAI) scores did not change significantly.
Qiu 1997	Case series of 60 patients with hepatitis C (stage not specified) treated by a herbal compound of seven herbs.
Sun 1996	Case series of 48 patients with chronic hepatitis C treated by a herbal compound composed of 21 herbs (Bing Gan Jian).
Sun 1998	Non-randomised, controlled study comparing Bing Gan Ning decoction (a herbal compound of 19 herbs) versus ribavirin in 52 patients with chronic hepatitis C.
Tian 1998	Case series of 37 patients with hepatitis C (stage not specified) treated by a herbal compound. This compound was formulated by the investigator.
Tsubota 1999	A randomised clinical trial comparing ursodeoxycholic acid plus glycyrrhizin (extract from liquorice root) versus glycyrrhizin alone in 170 patients with chronic hepatitis C virus infection. The result showed that the combined therapy was safe and effective in improving liver-specific enzyme abnormalities. This comparison did not fulfil our inclusion criteria.
Wang 1999	Non-randomised, controlled study comparing Ting Gan granula (herbal compound) versus no treatment in 48 patients with chronic hepatitis C.
Wang 2000a	Non-randomised, controlled study comparing compound Qing Gan granula (herbal compound) versus no treatment in 48 patients with chronic hepatitis C.
Wu 1994	Case series of 33 patients with hepatitis C (stage not specified) treated by a herbal compound.
Xu 1998	Case series of 30 patients with chronic hepatitis C treated by a herbal compound of 15 herbs. This compound was formulated by the investigator.
Yamamura 1997	Case series of eight patients with chronic hepatitis treated with glycyrrhizin.
Yamashiki 1999	An observational study examined the in vitro production of IL-12 by circulating mononuclear cells from liver cirrhosis patients and the effects of TJ-9 (herbal medicine) on IL-12 production.

Study	Reason for exclusion
Yan 2000	Quasi-randomised trial comparing herbal compound Qi Zhi granule versus IFN in 90 patients with chronic hepatitis C.
Yao 1995	An observational study comparing herbal compound '911 Granule' versus non-specific drug treatment in 330 patients with chronic hepatitis B and/or chronic hepatitis C. A long-term follow-up (more than four years) showed a significant difference in the incidence of liver cirrhosis and hepatocellular carcinoma between those treated with '911 granule' group and the control group (Liver cirrhosis: 3.2% versus 10.7%; $P < 0.01$. Hepatocellular carcinoma: 1.3% versus 5.7%; $P < 0.05$)
Yin 1996	Case series of 31 patients with hepatitis C (stage not specified) treated by a compound of 10 herbs.
You 1996	Non-randomised, controlled study comparing Bing Gan Ling (a herbal formulation) versus Ganbi-fu (herbal medicine) and Krestin (a herbal extract) in patients with hepatitis C. Serum HCV RNA in 38/60 patients became negative in the Bing Gan Ling group and 11/40 in the control group after three months treatment.
Zhang 1998	Case series of 40 patients with hepatitis C (stage not specified) treated by a compound composed of more than 15 herbs.
Zhao 1999	Case series of 50 patients with hepatitis C (stage not specified) treated by a compound of 10 herbs.

DATA AND ANALYSES

Comparison 1. Antiviral response

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance of serum HCV RNA	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CH-100 versus placebo	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Glycyrrhizin versus placebo	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Complete Thymic Formula versus placebo	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Bing Gan Ling versus IFN-alpha	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.65, 2.65]
1.5 Bing Gan capsules plus IFN versus IFN	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.89, 3.38]
1.6 Bing Gan Tang plus IFN-alpha versus IFN-alpha	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.43, 4.49]
1.7 Gan Su capsules versus IFN-alpha	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.52, 4.77]
1.8 Gan Su capsules plus IFN-alpha versus IFN-alpha	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.52, 4.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Yi Zhu decoction versus glycyrrhizin plus ribavirin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.07, 2.50]
2 Clearance of serum anti-HCV antibody	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Bing Gan capsules plus IFN versus IFN	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.89, 3.38]
2.2 Bing Gan Tang plus IFN-alpha versus IFN-alpha	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.43, 4.49]
3 Serum HCV RNA levels	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Complete Thymic Formula versus placebo	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.78, 0.62]

Analysis 1.1. Comparison 1 Antiviral response, Outcome 1 Clearance of serum HCV RNA.

Analysis 1.2. Comparison 1 Antiviral response, Outcome 2 Clearance of serum anti-HCV antibody.

Analysis 1.3. Comparison 1 Antiviral response, Outcome 3 Serum HCV RNA levels.

Comparison 2. Liver biochemical response

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Normalisation of serum ALT activity	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 CH-100 versus placebo	1	40	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.52, 156.91]
1.2 Glycyrrhizin versus placebo	1	57	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.18, 53.70]
1.3 Bing Gan Ling versus IFN-alpha	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.65, 2.65]
1.4 Bing Gan capsules plus IFN versus IFN	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.89, 3.38]
1.5 Bing Gan Tang plus IFN-alpha versus IFN-alpha	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.43, 4.49]
1.6 Gan Su capsules plus IFN-alpha versus IFN-alpha	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.80, 3.40]
1.7 Yi Er Gan Tang versus silymarin plus glucuro lactone	1	78	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.37, 3.18]
1.8 Yi Zhu decoction versus glycyrrhizin plus ribavirin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.07, 2.50]
2 Time to serum ALT normalisation (days)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Bing Gan Ling versus IFN-alpha	1	56	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Yi Er Gan Tang versus silymarin plus glucuro lactone	1	78	Mean Difference (IV, Fixed, 95% CI)	-20.2 [-22.66, -17.74]
3 Decrease of serum ALT levels	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Herbal medicine CH-100 versus placebo	1	40	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-54.73, 14.73]
3.2 Gan Su capsules plus IFN-alpha versus IFN-alpha	1	41	Mean Difference (IV, Fixed, 95% CI)	-18.35 [-44.00, 7.30]
3.3 Silybin preparation versus placebo	1	20	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-17.51, 1.51]
3.4 Complete Thymic Formula versus placebo	1	32	Mean Difference (IV, Fixed, 95% CI)	-26.0 [-87.91, 35.91]
4 Decrease of serum AST levels	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Silybin preparation versus placebo	1	20	Mean Difference (IV, Fixed, 95% CI)	-24.60 [-34.28, -14.92]
4.2 Complete Thymic Formula versus placebo	1	32	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-51.21, 41.21]
5 Decrease of serum total bilirubin	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Silybin preparation versus placebo	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.30, -0.14]
6 Decrease of serum alkaline phosphatase	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Herbal medicine CH-100 versus placebo	1	40	Mean Difference (IV, Fixed, 95% CI)	-8.90 [-34.80, 17.00]
6.2 Silybin preparation versus placebo	1	20	Mean Difference (IV, Fixed, 95% CI)	-10.60 [-17.70, -3.50]
7 Decrease of serum gamma-glutamyltranspeptidase	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Silybin preparation versus placebo	1	20	Mean Difference (IV, Fixed, 95% CI)	-18.40 [-23.78, -13.02]

Analysis 2.1. Comparison 2 Liver biochemical response, Outcome 1 Normalisation of serum ALT activity.

Analysis 2.2. Comparison 2 Liver biochemical response, Outcome 2 Time to serum ALT normalisation (days).

Analysis 2.3. Comparison 2 Liver biochemical response, Outcome 3 Decrease of serum ALT levels.

Analysis 2.4. Comparison 2 Liver biochemical response, Outcome 4 Decrease of serum AST levels.

Analysis 2.5. Comparison 2 Liver biochemical response, Outcome 5 Decrease of serum total bilirubin.

Analysis 2.6. Comparison 2 Liver biochemical response, Outcome 6 Decrease of serum alkaline phosphatase.

Analysis 2.7. Comparison 2 Liver biochemical response, Outcome 7 Decrease of serum gamma-glutamyltranspeptidase.

ADDITIONAL TABLES

Table 1. The preparation and composition of the herbal medicines of the included trials

Trial	Name of herb	Preparation	Composition
Batey 1998	CH-100	tablet (360 mg/tab)	Artemisia capillaris thunb (8%), Astragalus membranaceus root (6%), Bupleurem falcatium root (4%), Codonopsis pilosula root (5%), Crataegus pinnatifida fruit (4%), Curcumae longa tuber (3%), Gentiana manshurica plant (5%), Glechoma longituba plant (5%), Glycyrrhiza uralensis root (3%), Loranthus parasiticus stem (6%), Lycium barbarum fruit (4%), Paeonia lactiflora root (6%), Panax pseudoginseng root (2%), Polygonum cuspidatum root (5%), Polyporus umbellatus root (9%), Poria cocos root (7%), Salvia miltiorrhiza root (8%), Taraxacum mongolicum plant (7%), Zizyphus jujuba fruit (4%).
Buzzelli 1993	IdB1016	capsule (120 mg silybin)	Silybinphosphatidylcholine complex (one capsule equivalent to 120 mg of silybin).
Chen 1998	Bing Gan Ling	decoction, capsule	Alisma plantago-aquatica, Angelica sinensis, Arnebiae seu lithospermi, Artemisia capillaris, Astragalus membranaceus root, Cordyceps sinensis, Curcuma longa, Dictamni dasy-carpi, Paeonia veitchii, Patrinia scabiosaefolia, Panax pseudo-ginseng, Poria cocos, Radix Panacis Quinquefolii, Rhizoma

Table 1. The preparation and composition of the herbal medicines of the included trials (Continued)

			atractylodis macrocephalae, Salviae miltiorrhizae, Scutellariae Baicalensis, Sophora tonkineensis root.
Han 1997	Bing Gan Capsule	capsule	Adenophora tetraphylla, Astragalus membranaceus root, Arnebiae seu lithospermi, Artemisia capillaris, Bupleuri chinensis, Coix lachryma jobi, Curcuma longa, Dryopteris crassirhizoma, Heydyotis diffusa, Paeonia veitchii, Polygonum cuspidatum, Poria cocos, Rhizoma atractylodis macrocephalae, Salviae miltiorrhizae, Sophorae flavescentis.
Jiang 1999	Yi Zhu decoction	decoction	Artemisia capillaris, Black ants, Bupleuri chinensis, Glycyrrhiza uralensis, Ligustrum lucidum, Paeonia lactiflora, Phyllanthus species, Polygonum cuspidatum, Salviae miltiorrhizae, Scutellariae Baicalensis.
Pei 1996	Bing Gan Tang	decoction	Artemisia capillaris, Astragalus membranaceus root, Bupleuri chinensis, Forsythia suspensa, Glycyrrhiza uralensis, Heydyotis diffusa, Ligustrum lucidum, Lonicera japonica, Lycium barbarum, Polygonum cuspidatum, Schisandra chinensis, Sophorae flavescentis.
Raymond 1998	Complete Thymic Formula	tablet	Various herbs plus vitamins, enzymes, minerals, and bovine glandular extracts of thymosin, thymopoietin, and thymichumoral factor.
van Rossum 1999	Glycyrrhizin (Stronger Neo-Minophagen C)	injection	Glycyrrhizin is a clear solution extracted from the roots of the plant Glycyrrhiza glabra (liquorice).
Xiao 1999	Gan Su capsule	capsule	Broussonetia papyrifera, Dioscorea hypoglauca, Glycyrrhiza uralensis, Heydyotis diffusa, Paeonia lactiflora, Phyllanthus species, Poria cocos, Pseudostellaria heterophylla, Rhizoma atractylodis macrocephalae, Salviae miltiorrhizae, plus other herbs.
Yu 1995	Yi Er Gan Tang	decoction	Artemisia capillaris, Bupleuri chinensis, Curcuma longa, Glycyrrhiza uralensis, Ligustrum lucidum, Patrinia scabiosaefolia, Polygonum cuspidatum, Poria cocos, Rhizoma atractylodis macrocephalae, Salviae miltiorrhizae.

FEEDBACK

Medicinal herbs for hepatitis C virus infection

Summary

What is the herbal compound 'yi zhu'?

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Anne Lee, herbal physician
October 3, 2002

Reply

The herbal decoction 'yi zhu' is a compound of ten herbs, namely: Artemisia capillaris, Black ants, Bupleuri chinensis, Glycyrrhiza uralensis, Ligustrum lucidum, Paeonia lactiflora, Phyllanthus species, Polygonum cuspidatum, Salviae miltiorrhizae, Scutellariae Baicalensis. This information was included in Additional Table 01, entitled 'The preparation and composition of the herbal medicine of the included trials'.

Contributors

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WHAT'S NEW

Date	Event	Description
13 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JP Liu conceived, designed, drafted, and revised the protocol and the review, developed search strategy, and performed literature searches and data extraction.

E Manheimer performed searches, data extraction, and revised the protocol and the review.

K Tsutani performed searches, data extraction, and revised the protocol and the review.

C Gluud supervised these processes and revised the protocol and the review.

DECLARATIONS OF INTEREST

None known. We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g., employment, consultancy, stock ownership, honoraria, or expert testimony).

SOURCES OF SUPPORT**Internal sources**

- The Copenhagen Trial Unit, Denmark.
- Beijing University of Chinese Medicine, China.
- NAFKAM, University of Tromsø, Norway.

External sources

- The 1991 Pharmacy Foundation, Denmark.
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MeSH check words

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