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Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review

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***Background/Aims*: Hepatitis C is an escalating global health problem. The recommended treatment regimen is associated with considerable expense, adverse effects and poor efficacy in some patients. Complementary therapies are widely promoted for and used by patients with hepatitis C. The aim is to systematically assess the efficacy of complementary therapies in treating chronic hepatitis C.**

***Methods*: Systematic searches were conducted in six databases, reference lists of all papers were checked for further relevant publications and information was requested from experts. No language restrictions were imposed.**

***Results*: Twenty-seven eligible randomised clinical trials were located involving herbal products and supplements. No randomised clinical trials were identified for any other complementary therapy. In 14 of the trials, patients received interferon-α in combination with the complementary therapy. Less than half the trials (11/27) were of good methodological quality. Compared with the control group, significant improvements in virological and/or biochemical response were seen in trials of vitamin E, thymic extract, zinc, traditional Chinese medicine, *Glycyrrhiza glabra* and oxymatrine.**

***Conclusions*: We identified several promising complementary therapies, although extrapolation of the results is difficult due to methodological limitations. More research is warranted to establish the role of these and other therapies in the treatment of hepatitis C.**

***Keywords*: Hepatitis C; Complementary medicine; Herbal medicine; Systematic review**

1. Introduction

Hepatitis C is a global health problem; the World Health Organization has estimated that approximately 3% of the world population (170 million people) have been infected with the virus [1]. In England approximately 27 000 individuals have been diagnosed with hepatitis C. However, many people do not develop symptoms of clinically evident acute viral hepatitis at the time of infection and prevalence studies suggest that 0.4% of the population (200 000 individuals) may be chronically infected with the hepatitis C virus [2]. The long-term effects of persistent hepatitis C infection include chronic hepatitis, cirrhosis and hepatocellular carcinoma [1]; consequently hepatitis C is amongst the leading causes of liver transplantation. It has been suggested that without effective treatment strategies the morbidity and mortality associated with hepatitis C may increase three-fold by the year 2015 [3].

Currently recommended treatment for previously untreated and relapsed patients is a combination of pegylated interferon and ribavirin, resulting in a sustained virological response in approximately 50–60% of patients [4]. However, this regimen is expensive, adverse effects are frequent [5] and large numbers of patients are not suitable candidates for treatment for a variety of reasons [6]. Complementary and alternative medicine (CAM) is therefore popular amongst patients with hepatitis C; a recent survey conducted in liver disease outpatient clinics in the US found that 41% had used some form of CAM at least once during the preceding 4 weeks [7].

The aim of this review is to systematically assess the evidence from randomised clinical trials for the efficacy of

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complementary therapies in the treatment of chronic hepatitis C. Whilst such treatment may have a number of major goals, such as decreasing the incidence of hepatocarcinoma or cirrhosis, amelioration of symptoms and treatment of extra-hepatic complications, this review will focus on the effects of treatment on viral replication and eradication of the hepatitis C virus.

2. Methods

2.1. Identification of clinical trials

In order to identify clinical trials involving complementary and alternative therapies in the treatment of hepatitis C, systematic literature searches were conducted in the following electronic databases: Medline (via Pubmed), Embase, CINAHL, Amed (Alternative and Allied Medicine Database, British Library Medical Information Centre), The Cochrane Library and the British Library Index of Conference Proceedings (all from their inception to October 2002).

The search terms used were: hepatitis; hepatitis, chronic; hepatitis, viral, human; hepatitis C; complementary therapies; acupuncture; acupressure; phytotherapy; phytomedicine; medicine, Chinese traditional; medicinal plant; herb; leaf; seed; extract; medicine, kampo; hozai; ayurvedic medicine; homeopathy; essential oil; dietary supplement; vitamin; mineral; manipulative therapy; manipulation; chiropractic; osteopathy; biofeedback; Alexander technique; craniosacral therapy; shiatsu; massage; Qi Gong; reiki; spiritual healing; aromatherapy; reflexology; hydrotherapy; music therapy; meditation; yoga; autogenic training; guided imagery; hypnotherapy; hypnosis; tai chi; milk thistle; *Silybum marianum*; silymarin; silybinin; licorice; glycyrrhizin; glycyrrhiza; glycyrrhizic acid; stronger neominophagen C; *Panax ginseng*; ginseng; *Plantago asiatica*; aucubin; *Curcuma longa*; turmeric; *Camellia sinensis*; green tea; *Phyllanthus amarus*; *Picrorhiza kurroa*; kutaki; picroside; catechin; green tea; catergen; cyanidanol-3; vitamin E; tocopherol; NAC; *N*-acetyl cysteine; antioxidant; selenium; thiamine; vitamin B; phosphatidylcholine; IdB1016; thymic extract; thymosin; thymostimulin; complete thymic formula; thymic protein A; SAMe; *S*-adenosyl methionine; TJ9; TJ108; sho-saiko-to; bin gang ling; bin gan; gansu; yi er gan; ting gan; qing gan; Qi Zhi; Yizhou; kalamalhar; mistletoe; *Viscum album*; Iscador Qu; hypericin; schizandra; *Sophora japonica*; matrine; vitamin C; ascorbic acid; bursal virus vaccine; MTH-68/B; oral enzyme therapy; phlogenzym; rutosid; *Panax pseudoginseng*; magnesium; alpha lipoic acid; amino acids; probiotics; spirulina; chlorella; lecithin; dandelion; slippery elm; St John's wort; *Hypericum perforatum*; echinacea; olive leaf; goldenseal; *Hydrastis canadensis*; garlic; *Allium sativum*; astragalus; psyllium; fenugreek; *Trigonella foenum graecum*; evening primrose; aloe vera; ginger and *Zingiber officinale*.

Further relevant papers were located by hand searching the reference lists of all papers. In addition experts in the field were contacted to provide published and unpublished material. Finally our own extensive files were hand searched for further relevant publications.

2.2. Inclusion/exclusion criteria

Only randomised clinical trials of complementary therapies administered to patients with a diagnosis of hepatitis C or non-A, non-B chronic hepatitis were included. Trials in which several subgroups of patients with different hepatitis aetiologies were studied and those in which the hepatitis virus was not specified were excluded. Both placebo controlled and comparative trials were considered. All retrieved data including uncontrolled trials, case reports, pre-clinical and observational studies were reviewed for safety information. No language restrictions were imposed.

2.3. Data extraction and quality assessment

All articles were read in full. Data relating to sample size, diagnosis, genotype and gender of patients, previous interferon exposure, intervention and control, treatment duration, primary outcome measures and results were extracted by the first author and validated by the second. The methodological quality of each clinical trial was assessed using the Jadad scoring system [8]. This scale ranges from 0 (poorest) to 5 (highest) and assesses methods of randomisation and blinding and descriptions of withdrawals and dropouts.

3. Results

The search strategy generated a total of 3085 references, of which 142 were considered to be potentially relevant. We did not locate any unpublished trials. A total of 67 clinical trials were retrieved for further evaluation of which 27, involving 1709 patients, were eligible for inclusion (Table 1). Reasons for exclusion included no specific hepatitis diagnosis, trials in which patients with both hepatitis B and C were included, trials in which only interim results have been published, or which did not measure clinical endpoints and trials which were not randomised.

3.1. Supplements

3.1.1. Antioxidants

Seven randomised clinical trials of antioxidants were located including a total of 463 patients [9–15]. In six trials, antioxidants were administered in combination with interferon-α No significant differences in virological response were seen between treatment regimens in any of the trials. Details of biochemical parameters were not provided in all reports but appear to correlate with virological responses. One trial compared vitamin E treatment with placebo; statistically significant reductions in alanine aminotransferase (ALT) were seen during treatment but reductions did not occur in all patients nor did complete normalisation of ALT levels occur. No virological effects were seen.

3.1.1.1. Safety. At the doses studied, these antioxidants appear to be well tolerated, with no specific adverse events reported in any of the trials. However, very large oral doses of *N*-acetyl cysteine used to treat paracetamol overdose are commonly associated with nausea and vomiting [16] and intravenous administration of *N*-acetyl cysteine can result in anaphylactoid reactions, which may be more common in patients with chronic liver disease [17]. Over a prolonged period, selenium at doses as low as 900 mg/day can produce signs of toxicity, such as depression, nervousness, emotional instability, nausea and vomiting, in some people [18]. In extreme cases excess levels of selenium have been associated with pathologic nail bed changes and the loss of finger nails, temporary hair loss and fatigue [19]. No further information regarding adverse events associated with vitamin E was identified.

3.1.2. Thymic extracts

A total of five trials ($n = 256$) of thymic extracts were identified [20–24]; four involved the synthetic polypeptide

thymosin alpha 1 (Tα1) and in one, patients received Complete Thymic Formula which contains bovine glandular extracts of thymosin, thymopoeitin and thymic humoral factors with various herbs, vitamins, enzymes and minerals.

Of the three trials in which patients received Tα1 in combination with interferon, the number of patients experiencing a complete virological or biochemical response at the end of treatment was significantly higher during treatment with the combination than with either interferon alone or placebo. There were also significant differences in the number of patients with a sustained response at 6 or 12 months after cessation of treatment. However, there were no significant differences in biochemical or virological response between treatment and placebo groups in the two trials in which patients received Tα1 or Complete Thymic Formula alone.

3.1.2.1. Safety. Treatment with thymic extracts appears to be well tolerated. It is possible that administering two drugs with potential immunostimulatory properties might increase the incidence of immune-associated adverse events, but there does not appear to be any evidence of this from the literature. Adverse events were reported in detail in one trial; whilst the frequency of adverse events was high, only nausea and vomiting were more common with combination treatment than with interferon-α. In another study, Tα1 was associated with local discomfort at the injection site in two patients [23], and complete thymic extract was associated with severe thrombocytopenia in one patient who was also receiving naproxen [24].

3.1.3. Zinc

One clinical trial of zinc supplementation in combination with interferon-α was identified [25]. Overall significantly more patients in the combination group were complete or incomplete responders (18/32 vs 8/36; $P < 0.006$) with the effect being most evident in those patients with less than 5×10^5 copies of HCV RNA/ml, although there were far more patients with a higher viral load in the interferon-only group (23 vs 8).

3.1.3.1. Safety. In this trial, a total of seven patients withdrew because of side effects; four from the interferon-α-alone group (erythema multiforme, severe fatigue with headache and an attack of loss of consciousness) and three from the combination group (loss of sleep, serious headache and interstitial pneumonia). The side-effect profile was similar in both groups and included flu-like symptoms and a mild reduction in platelet and white blood cell counts. Toxic effects of zinc supplementation tend to occur following prolonged intake at levels greater than 150 mg/day; effects can include copper deficiency anemia, reduced HDL cholesterol levels and depressed immune function [26].

3.2. Other supplements

One randomised clinical trial was identified involving Adelavin (an injectable hepatoprotective mixture containing liver extract and flavin adenin dinucleotide) [27]. The trial was of poor methodological quality and whilst the results appear promising, no statistical analyses were performed.

One randomised clinical trial of oral enzyme therapy was identified, again this trial was of poor methodological quality [28]. The lack of methodological, analytical and statistical details provided makes interpretation of the results very difficult.

No data relating to the safety profile of these supplements was located.

3.3. Herbal medicinal products

3.3.1. Traditional Chinese medicine

We located a total of seven randomised clinical trials of traditional Chinese medicine in the treatment of hepatitis C [29–35]. The methodological quality of six of the trials was considered poor, scoring only one out of a maximum of five on the Jadad scale.

In two trials of herbal formulations in combination with interferon-α, there was some suggestion of greater clearance of HCV RNA and ALT normalisation with the combination treatment compared with patients receiving monotherapy. In the only placebo-controlled trial of sole therapy with traditional Chinese medicine, there was a significant reduction in ALT levels during treatment in those receiving the herbal compound. No virological effects were seen. Two studies compared a traditional Chinese medicine with interferon-α; there were no significant differences between groups in either study. The remaining studies used less common treatment regimens in the control group. Although these results are promising, interpretation is difficult due to the unknown effects of the control treatment regimens.

3.3.1.1. Safety. Detailed descriptions of adverse events were not provided. In the only placebo-controlled trial [31], four patients experienced adverse events: palpitations [36], diarrhoea [37], abdominal discomfort [36]; all of them were taking the herbal formulation. Further assessment of the safety of these medicines is complicated, due to the individualised nature of many of the herbal compounds involved, the large number of different herbs in each formulation and the relatively small number of patients within each clinical trial.

3.3.2. Glycyrrhiza glabra (licorice)

Four randomised clinical trials of glycyrrhizin (all administered as Stronger Neo Minophagen C (SNMC) comprising of 0.2% glycyrrhizin, 0.1% cysteine and 2.0% glycine in physiological saline solution) were located. In two trials, patients received SNMC in combination with interferon-α [38,39]; there were no significant differences

Table 1
Randomised clinical trials of complementary therapies in the treatment of chronic hepatitis C

Reference	*n*	HCV 1 (%)	Male (%)	IFN-naïve (%)	Study design	Treatment	Treatment duration (weeks)	Main results	Jadad score
Antioxidants									
In combination with interferon									
Look [9]	24	79	58	100	O, C, PG	A, IFN-α 2a (4.5 MU *t.i.w.* s.c.); B, IFN-α plus NAC (1800 mg/day) and sodium selenite (400 μg/day); C, IFN-α plus NAC, sodium selenite and vitamin E (544 IE/day)	24	A, 3/8 normal serum ALT values and negative HCV RNA; B, 2/8 normal serum ALT values and negative HCV RNA; C, 6/8 normal serum ALT values and negative HCV RNA ($P < 0.11$)	3
Grant [12]	147	66	71	100	DB, PC, PG	A, IFN-α (3 MU *t.i.w.* s.c.) plus placebo; B, IFN-α plus NAC (1800 mg/day)	24 and 24 weeks follow-up	A, 3/74 sustained virological response at follow-up; B, 4/73 sustained virological response at follow-up, biochemical responses were concordant with virological responses in 97% of patients. No significant differences between groups	3
Bernhard [13]	36	–	81	–	DB, PC, PG	A, IFN-α (3 MU *t.i.w.*) plus placebo; B, IFN-α plus NAC (1800 mg/day)	24 and 24 weeks follow-up	A, 8/17 at 24 weeks and 3/17 at 48 weeks had no detectable HCV RNA in serum; B, 7/19 at 24 weeks and 2/19 at 48 weeks had no detectable HCV RNA in serum. No statistical details provided	3
Ideo [14]	120	67	71	0	O, C, PG	A, IFN-α N3 (6 or 9 MU *t.i.w.* s.c.); B, IFN-α N3 plus NAC (1200 mg/day p.o.) and vitamin E (600 mg/day p.o.)	24 and 24 weeks follow-up	No significant differences in biochemical or virological response at 24 or 48 weeks	3
Andreana [11]	36	67	–	0	O, C, PG	A, IFN-α 2b (5 MU *t.i.w.*) plus NAC (1200 mg/day); B, IFN-α 2b plus ofloxacin (600 mg/day)	8	A, 2/18 normal ALT values; 1/18 undetectable HCV RNA; B, 0/18 normal ALT values; 2/18 undetectable HCV RNA. No statistical details are provided	2
Neri [10]	77	100	57	–	O, C, PG	A, IFN-α (6 MU *t.i.w.* i.m.); B, IFN-α plus NAC (2400 mg/day p.o.)	24 and 40 weeks follow-up	No significant differences in viremia values at end of treatment ($P > 0.05$)	1
As sole therapy									
Von Herbay [15]	23	–	52	22	DB, PC, CO	A, vitamin E (800 IU/day p.o.); B, placebo	12	A, vitamin E—ALT ↓ 24% ($P < 0.01$); B, placebo—ALT ↑ 1% (NS)	3

Thymic extract								
In combination with interferon								
Sherman [20]	109	69	78	96	DB, PC, PG	A, IFN-α 2b (3 MU *t.i.w.* s.c.) plus TA1 (1.6 mg *biw* s.c.); B, IFN-α 2b plus placebo; C, placebo plus placebo	26 and 26 weeks follow-up	A, 13/35 ALT levels and 13/35 HCV RNA normalised at end of study; B, 6/37 ALT levels and 7/37 HCV RNA normalised at end of study; C, 1/37 ALT levels and 1/37 HCV RNA normalised at end of study ($P = 0.04$ and $P < 0.05$)	5
Moscarella [21]	34	56	71	100	O, C, PG	A, IFN-α 2b (3 MU *t.i.w.*) plus TA1 (1 mg *biw* s.c.); B, IFN-α 2b	24 and 52 weeks follow-up	A, 12/17 ALT levels normalised and 11/17 undetectable HCV RNA at end of study; B, 6/17 ALT levels normalised and 5/17 undetectable HCV RNA at end of study ($P < 0.05$)	2
Sherman [22]	56	–	–	–	DB, PC, PG	A, IFN-α (3 MU *t.i.w.*) plus TA1 (1.6 mg *biw* s.c.); B, IFN-α plus placebo; C, placebo plus placebo	26	A, statistically significant lower HCV RNA titres than C at all time-points ($P < 0.05$).	1
As sole therapy								
Andreone [23]	19	–	58	100	DB, PC, PG	A, TA1 900 μg/m^2 body surface area; B, placebo	24 and 24 weeks follow-up	A, 1/9 ALT levels normalised at end of study; B, 0/10 ALT levels normalised at end of study	4
Raymond [24]	38	82	79	5	DB, PC, PG	A, Complete Thymic Formula (12 tablets/day); B, placebo	12–24	HCV RNA was not eliminated in any patient. No significant differences in mean HCV RNA levels between groups	4
Oral enzyme therapy								
As sole therapy								
Stauder [28]	80	–	–	–	O, PG, C	A, oral enzyme preparation (Phlogenzym); B, IFN-α; C, Ribavirin; D, liver support therapy	12	In terms of liver enzyme levels, A was equivalent to B and superior to C and D (no further details provided)	2
Zinc								
In combination with interferon								
Takagi [25]	79	100	64	–	O, C, PG	A, IFN-α (10 MU/day) for 4 weeks then 10 MU *t.i.w.* for 20 weeks; B, IFN-α plus polaprezinc (150 mg/day p.o.) for 24 weeks	24	A, complete virological response 6 months after treatment in 4/36 patients; B, complete virological response 6 months after treatment in 12/32 patients	2
Liver extract								
In combination with interferon								
Sato [53]	15	100	60	–	O, C, PG	A, IFN-α (6 MU/day for 4 weeks then *t.i.w.* for 20 weeks); B, IFN-α plus Adelavin (2 ml/day i.m. for 24 weeks)	24 and 24 weeks follow-up	A, 2/7 normalisation of HCV RNA at end of treatment; B, 6/8 normalisation of HCV RNA at end of treatment No statistical details provided	1

Table 1 (*continued*)

Reference	*n*	HCV 1 (%)	Male (%)	IFN-naïve (%)	Study design	Treatment	Treatment duration (weeks)	Main results	Jadad score
Traditional Chinese medicine									
In combination with interferon									
Han [29]	56	–	75	–	O, PG, C	A, Bing Gan capsule (9 g/day p.o.) plus IFN (3 MU *t.i.w.* i.m.); B, IFN (3 MU *t.i.w.* i.m.)	24	A, trend towards better clearance of HCV RNA, anti-HCV antibody positivity and ALT normalisation	1
Pei [30]	76	–	67	–	O, PG, C	A, Bing Gan decoction (1 dose/day p.o.) plus IFN-a (400 IU/day p.o.); B, IFN-α (400 IU/day p.o.)	24 and 52 weeks follow-up	A, greater clearance of HCV RNA ($P = 0.001$), serum anti-HCV antibody and normalisation of ALT ($P = 0.001$)	1
As sole therapy									
Batey [31]	40	–	60	65	DB, PG, PC	A, CH-100 (5 tablets/day); B, placebo (5 tablets/day)	24	A, mean change in ALT levels from baseline 32%; B, mean change in ALT levels from baseline 0% ($P < 0.03$)	4
Chen [32]	56	–	–	–	O, PG, C	A, Bin Gan Ling decoction (300 ml/day p.o.) for 3 months then Bin Gan Ling capsule (6 g/day p.o.) for 2 months plus hypoxanthosine and vitamin C; B, IFN-α (3 MU/day i.m.) for 2 weeks then *t.i.w.* for 3 months plus hypoxanthosine and vitamin C	12 or 20 and 1 year follow-up	A, 13/31 normalised HCV RNA at end of treatment; B, 8/25 normalised HCV RNA at end of treatment ($P = 0.5$). No significant difference in normalisation of ALT levels	1
Jiang [33]	40	–	58	–	O, PG, C	A, Yi Zhu decoction; B, glycyrrhizin (50 ml in 250 ml 10% glucose/day i.v.) plus Ribavirin (0.7 g in 250 ml 10% glucose/day i.v.)	12	A, greater clearance of HCV RNA ($P = 0.02$) and normalisation of ALT levels ($P = 0.02$) at end of treatment	1
Xiao [34]	59	–	32	–	O, PG, C	A, Gan Su (18 capsules/day p.o.) plus IFN-α (3 MU/day i.m.) for 1 month then *t.i.w.* for 3 months; B, IFN-α (3 MU/day i.m.) for 1 month then *t.i.w.* for 3 months; C, Gan Su (18 capsules/day)	16 and 24 weeks follow-up	No significant differences between groups	1
Yu [35]	78	–	65	–	O, PG, C	A, Yi Er Gan Tang decoction p.o.; B, Glucurolactone plus Yiganling p.o. plus potassium, magnesium and aspartate i.v.	2 and 24–52 weeks follow-up	A, greater effects on ALT normalisation and time to serum ALT normalisation ($P < 0.0001$)	1

***Glycyrrhiza glabra* (licorice)**									
In combination with interferon-alpha									
Fujiyama [38]	101	66	80	–	O, C, PG	A, IFN-α 2b (10 MU/day s.c. for 2 weeks then *t.i.w.* for 22 weeks); B, IFN-α 2b plus SNMC (at least 40 ml i.v. at same dosing frequency for 24 weeks) then SNMC alone for 24 weeks; C, IFN-α 2b (10 MU/day for 4 weeks then *t.i.w.* for 20 weeks)	24 and 26–52 weeks follow-up	In terms of biochemical response C was significantly ($P < 0.05$) more effective than A at follow-up; no other significant differences between treatments at any time-point. In terms of virological response C was significantly ($P < 0.05$) more effective than B at follow-up; no other significant differences between treatments at any time-point	2
Suzuki [39]	40	74	59	–	O, C, PG	A, IFN-α (6 MU/day for 8 weeks); B, IFN-α plus SNMC (100 ml/day i.v. for 8 weeks)	8 and 52 weeks follow-up	A, normalisation of ALT 9/20 at end of treatment; sustained virological response at 6 months follow-up 5/20; B, normalisation ALT 13/20 at end of treatment; sustained virological response at 6 months follow-up 5/19 (NS)	2
As sole therapy									
van Rossum [40]	57	47	79	18	DB, PC, PG	SNMC (80, 160, 240 or 0 mg [placebo] i.v. *t.i.w.*)	4 and 4 weeks follow-up	% decrease in ALT from baseline 6, 23, 26 and 29 for placebo, 80, 160 and 240 mg, respectively, ($P < 0.03$). No effect at follow-up or on HCV levels	5
Tsubota [41]	170	82	62	100	O, C, PG	A, SNMC (200 ml i.v. *t.i.w.*); B, SNMC plus UDCA (600 mg/day p.o.)	24 and 8 weeks follow-up	A, % decrease in AST and ALT from baseline 8.8 + 28.1 and 10.2 + 39.7; B, % decrease in AST and ALT from baseline 23.4 + 35.5 and 32.8 + 39.5 ($P < 0.03$). No effect at follow-up or on HCV RNA levels	3
Oxymatrine (derived from *Sophora japonica*)									
As sole therapy									
Li [43]	43	-	46	-	O, C, PG	A, oxymatrine (600 mg/day i.m.); B, general liver protective agents e.g. vitamins	12	A, 8/17 normalised HCV RNA; B, 1/18 normalised HCV RNA ($P <$ 0.05). No effect on ALT levels	2

O, open; PG, parallel group; C, comparative; DB, double blind; PC, placebo controlled; NAC, *N*-acetyl cysteine; SNMC, stronger neominophagen C.

between treatments in the number of patients achieving biochemical or virological response in either study. In the only European randomised clinical trial of glycyrrhizin, there were some reductions in ALT levels during treatment, compared with placebo but this was not sustained after cessation of treatment and there were no significant effects on HCV RNA levels [40]. In the final trial, there were statistically significant differences in liver enzyme levels between treatment groups during treatment, however, these were not sustained at follow-up and there were no virological effects [41]. There was no placebo group in this trial; the comparison treatment was a combination of SNMC and ursodeoxycholic acid, the effects of which are unknown. These results are therefore difficult to interpret.

3.3.2.1. Safety. Hypokalemia, sodium retention, increase in body weight, elevated blood pressure and retention of sodium are all expected adverse effects of glycyrrhizin treatment [42]. However, there is no evidence for an increased occurrence of these during SNMC treatment in these studies. Two publications provide a thorough analysis of the adverse events experienced during the trial [40, p. 1165]; there were no significant differences between groups in the number of patients reporting an adverse event, although in the study by van Rossum et al. significantly more patients reported cold/flu symptoms in the 160 mg group compared with placebo. Suzuki et al. reported one adverse event (bleeding in the fundus) which occurred during combination treatment with glycyrrhizin and interferon-α [39]. In the final study, no patients complained of drug related symptoms or developed signs of an adverse reaction during the treatment period [41].

3.3.3. Oxymatrine (derived from Sophora japonica)

One open, randomised, parallel group clinical trial of mediocre methodological quality in which patients were treated with oxymatrine or with general liver protective agents was identified [43]. At the end of treatment there were statistically significant differences in the number of patients with normalised HCV RNA levels between groups. No further information regarding the safety of oxymatrine was located.

4. Discussion

Several herbal medicinal products and supplements have been identified with potential virological and/or biochemical effects in the treatment of chronic hepatitis C infection. Studies of thymic extract, zinc and Bing Gan decoction in combination with interferon-α and oxymatrine alone have demonstrated greater clearance of the hepatitis C virus than control treatment. Normalisation of liver enzymes has been greater during treatment with vitamin E, *Glycyrrhiza glabra*, CH100, Yi Zhu decoction and Yi Er Gan Tang decoction than with the control treatment.

However, interpretation and extrapolation of the results is difficult for several reasons.

First, few of the studies measured the sustained virological response at 6 months after cessation of treatment. This has become the optimum outcome measure in trials of conventional therapy since studies of interferon-α treatment indicate that 92% of patients with a sustained virological response at 6 months will remain seronegative for up to 6 years [44]. There is also evidence that a sustained virological response may be associated with regression of fibrosis [45]. Of the studies that did include this endpoint, only one trial, of the combination of interferon-α and zinc, reported a significant effect above interferon-α alone [25]. Secondly, the current recommended duration of interferon-α treatment is 48 weeks in patients with hepatitis virus genotype 1 [46], none of the trials included a treatment period of longer than 26 weeks and some were as short as 4 weeks. The control group did not receive currently accepted optimum interferon-α treatment in many of the comparative studies; therefore results from these trials cannot be extrapolated to standard treatment comparisons. Thirdly, it is recognised that an individual's response to interferon-α treatment will be affected by several factors e.g. hepatitis C virus genotype, gender, baseline viral level and previous exposure to interferon-α therapy [47]. Whether these are also important for predicting treatment response to complementary interventions is unclear, but they may have influenced the selection of patients for inclusion into trials with included patients already having failed to respond to a course of interferon-α, for example. And finally, there were methodological limitations with over half the trials, the most common being lack of blinding and incomplete reporting of randomisation methods and withdrawals.

Attempts were made to obtain data from unpublished trials and we are aware of several studies which have not been published in full, however, we were not able to obtain the unpublished results. There is evidence to suggest that studies with significant positive results are more likely to be published [48] and this may be more pronounced with unfamiliar complementary therapies [49]. It is possible that we did not locate all the trials on traditional Chinese medicine, as we did not search any Chinese language databases. A recent systematic review of herbal medicinal products for the treatment of hepatitis B located an additional 18 trials from Chinese language sources [50]. We decided not to perform searches in Chinese language databases as previous experience suggests that the resulting references do not provide sufficient detail to reliably assess methodological quality and consequently do not add significantly to the evidence base [51].

Disappointingly, we found no evidence for the use of complementary therapies in clinically important subgroups of patients who have often been denied access to therapy with interferon-alpha in the past (e.g. patients with HIV co-infection or psychiatric problems). Nor were we able to locate any randomised clinical trials of any other

complementary therapies, including several herbal medicinal products such as *Silybum marianum* which are very popular with patients. A survey of patients with hepatitis C attending an out-patient clinic found that 36% (42/117) were taking herbs, of which 14 (33%) were taking *Silybum marianum*; 67% of responders attributed benefit to their herbal therapy [52].

The safety profiles of the interventions discussed within this systematic review look encouraging at the doses studied. However, the long-term safety for use in the treatment of hepatitis C, either alone or in combination with conventional medicines, has not been established. Comparative and placebo-controlled trials suggest that patients experience no more adverse events with these interventions than with placebo or comparative medications, although short-term clinical trials are not designed to detect rare or delayed adverse events.

There is an undoubted need for further research into the treatment of hepatitis C, and this review has identified several promising interventions. A more detailed understanding both of the pharmacology of herbal medicinal products and supplements in relation to the hepatitis C virus and of the patient characteristics which might be important in predicting a favourable response to treatment would facilitate the design of future clinical trials. Anecdotal evidence suggests that many more complementary therapies are currently available to and popular with patients and further research into these interventions is warranted to establish their role in the treatment of chronic hepatitis C infection.

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