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REVIEW

Complementary and alternative medications in hepatitis C infection

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Abstract

Chronic hepatitis C (CHC) infection affects almost 3% of the global population and can lead to cirrhosis, liver failure, and hepatocellular carcinoma in a significant number of those infected. Until recently, the only treatments available were pegylated interferon and ribavirin, which traditionally were not very effective and have considerable side effects. For this reason, interest in complementary and alternative medications (CAM) in the management of hepatitis C has been investigated. Some CAM has demonstrated therapeutic potential in chronic hepatitis C treatment. Unfortunately, some CAM has been shown to have the potential to cause drug-induced liver injury. This article will review and evaluate many of the natural molecules that interact with the hepatitis C virus (HCV) life cycle and discuss their potential use and safety in HCV therapy, as well as highlight some important interactions between medical and complementary treatments.

Key words: Hepatitis C infection; Natural molecules; Direct acting antivirals; Hepatotoxicity; Herbal treatments

Core tip: Over the last 10 years there has been a substantial increase in reports of natural compounds displaying anti-viral activity against hepatitis C. At this time, there is no firm evidence supporting complementary and alternative medications for hepatitis C virus infection. Due to a limited number of trials and small numbers of subjects included in them, it is not possible to fully evaluate the risk of adverse events connected with the use of these products.

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INTRODUCTION

Hepatitis C virus (HCV) infection affects an estimated 180 million people globally and is a leading cause of chronic hepatitis, cirrhosis, and liver cancer[1,2]. To prevent the complications of chronic hepatitis C (CHC), the goal of therapy is complete viral eradication. For the past decade, a combination of pegylated interferon-α (peg-IFN) and ribavirin was used to treat CHC with disappointing viral eradication rates. These rates were particularly suboptimal in patients with genotype 1 HCV, which is responsible for approximately 60% of worldwide infections[3]. Sustained virological response (SVR) rates for genotype 1 HCV are approximately 40% following 48 wk of peg-IFN/ribavirin and are even lower in patients with HIV co-infection, high baseline viral load, advanced fibrosis, or those of African descent[4-7].

The life cycle of HCV can be divided into three major steps: (1) entry of the virus into its target cells by receptor-mediated endocytosis; (2) cytoplasmic and mem-

brane-associated replication of the RNA genome; and (3) assembly and release of the progeny virions[8]. In recent years, there has been improvement in SVR rates with the development and approval of the first HCV-specific direct-acting antiviral agents (DAAs), namely boceprevir and telaprevir[9,10]. In contrast to the non-specific antiviral activity of peg-IFN and ribavirin, DAA are designed to inhibit viral proteins involved in the HCV life cycle. Still, the first DAAs require coadministration with peg-IFN and ribavirin, and many patients remain intolerant to treatment-associated side effects, including fevers, influenza-like symptoms, headache, cytopenias, fatigue, anorexia, rash, and depressive symptoms.

CAM is being used increasingly across the globe for many chronic diseases[11,12]. The Cochrane Library included nearly 50 systematic reviews of complementary medicine interventions as of 2003[13]. Many people turn to CAM when conventional medicine fails, or they believe strongly in its effectiveness. During the last few years, a substantial increase of reports on natural compounds displaying an anti-HCV activity has been published. There is data that some of these medicinal herbs might have therapeutic potential in CHC, or may alleviate side effects of conventional therapy[13]. CAM use is common among people with CHC. A survey of 1145 participants in the National Institutes of Health (NIH)-supported HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) trial found that 23% of the participants used herbal products[14]. Although sometimes thought by the public to be safer then conventional therapy, there are many reports about liver toxicity and other adverse events from some herbal products[11,15]. The aim of this review is to evaluate the efficacy and safety of treating HCV infection using complementary and alternative medicine.

MEDICINAL HERBAL AND DIETARY SUPPLEMENTS WITH ANTI-HCV ACTIVITY

Silymarin

An extract of the milk thistle plant, silymarin *(Silybum marianum*), has been used to treat chronic liver disease since the time of the ancient Greeks[16]. Owing to its purported hepatoprotective properties, it is the most commonly used herbal product by individuals with chronic liver disease in the United States[16,17]. A recent publication from the HALT-C study group indicated that 33% of patients with CHC and cirrhosis reported current or past use of silymarin[14]. A follow-up study found silymarin use among CHC patients was associated with reduced progression from fibrosis to cirrhosis, but had no impact on clinical outcomes[16].

The major active component of silymarin, silibinin (a mixture of the two diastereoisomers silybin A and silybin B), is thought to be responsible for silymarin's hepatoprotective properties[18]. Silymarin appears to inhibit HCV infection at two or more different levels: (1) it inhibits HCV replication in cell culture; and (2) it displays anti-inflammatory and immunomodulatory actions that may contribute to its hepatoprotective effect[19,20]. The inhibition of HCV replication has been attributed to inhibitory action on the NS5B RNA-dependent RNA polymerase.

Clinical studies that have evaluated milk thistle for a variety of liver diseases have yielded inconsistent results and low bioavailability of oral silymarin components[21]. Studies with Ⅳ silibinin have shown substantial antiviral effect against HCV in liver transplant recipients, and even in nonresponders with good safety outcomes[22-24]. Although oral administration of silymarin is not effective for the treatment of HCV, intravenous silibinin formulation may represent a future potential therapeutic option.

Green tea extract

Green tea, made from the unfermented leaves of *Camellia sinensis*, is comprised of several polyphenolic compounds called catechins, and can be concentrated into a green tea extract (GTE). Epigallocatechin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE, comprising typically approximately 40% of the total polyphenol content[25]. EGCG is a potent inhibitor of HCV entry in primary human hepatocytes independent of the genotype, by blocking virus attachment. This novel inhibitor may provide a new approach to prevent HCV infection, especially in the setting of liver transplantation of chronically infected HCV patients[26,27]. Beyond its antiviral effect on HCV, EGCG may have potential use as a chemopreventative agent for hepatocellular cancer as EGCG may inhibit cancer cell growth. This mechanism of action is thought to be due to tyrosine kinase inhibition and modulation of target gene expression associated with induction of apoptosis and cell cycle arrest in cancer cells[28-34].

GTE is a common ingredient in several dietary supplements, some of which have been withdrawn from the market due to safety concerns. An example of this is *Exolise* (Arkopharma, France), a weight loss supplement containing high EGCG levels that was withdrawn from the market in April 2003 due to 13 cases of attributable liver injury[35]. Between 1966 and 2008, 216 case reports of toxicity with green tea extracts were identified by the United States Pharmacopeia, of which 34 were concerning for liver toxicity[36]. Recent animal studies with high doses of GTE and EGCG have described dose-dependent hepatotoxicity resulting in severe morbidity and mortality[37]. However, chronic moderate to high dose daily GTE and EGCG use in healthy human volunteers, and selected patients with cirrhosis, was safe and did not impair liver function[38-40]. Although GTE may be very useful in further treatment of CHC and prevention of HCC, its hepatotoxic potential must be acknowledged and monitored carefully in future studies.

Naringenin

HCV associates with β-lipoproteins [very low density lipoprotein (vLDL) and low-density lipoprotein (LDL)]

circulating in blood[41]. In addition, HCV replication can be up-regulated by fatty acids and inhibited by statins; this suggests an interaction between HCV, cholesterol, and lipid metabolism[42]. Recent research has found that of HCV secretion is dependent on both apolipoprotein B (ApoB) expression and vLDL assembly in a chromosomally integrated complementary DNA (cDNA) model of HCV secretion[43].

Naringenin is the predominant flavanone present in the grapefruit and is responsible for its bitter taste. Naringenin has been shown to reduce cholesterol levels both *in vitro* and *in vivo*[44,45]. Furthermore, naringenin inhibits ApoB secretion by reducing the activity and the expression of the microsomal triglyceride transfer protein (MTP) and the acyl-coenzyme A cholesterol acyltransferase 2 (ACAT)[44,46]. Due to the close link between HCV assembly/secretion and lipoprotein metabolism, there has been extensive study on the impact of naringenin on the secretion of HCV particles[43]. A dose-dependent decrease of core protein, HCV-positive strand RNA, infectious particles, and ApoB has been observed in the supernatant of infected primary hepatocytes in culture after naringenin treatment[43]. Overall, naringenin blocked the assembly of intracellular infectious viral particles without affecting intracellular levels of the viral RNA or protein. Although still at the cell culture phase, naringenin may offer new insight into a promising and novel HCV therapeutic target.

Glycyrrhizin

Glycyrrhizin, a natural compound extracted from the roots of *Glycyrrhiza glabra*, has been used for more than 20 years as a treatment for chronic hepatitis[47]. It has been used for many centuries in traditional Chinese medicine as an anti-allergic agent. Because of its sweet taste it is also used as a food additive, for example in beverages and licorice[48]. In an attempt to use glycyrrhizin as a treatment for "allergic" hepatitis it was found to lower the transaminases. In a study by Suzuki *et al*[49] in 1977, plasma transaminases activity improved significantly with glycyrrhizin in patients with chronic liver disease compared to a placebo group.

The mechanism by which glycyrrhizin improves the biochemistry and histology in liver disease is unknown. It is thought to have anti-inflammatory, antioxidant and immunomodulatory activities. Due to this there has been much interest in use of glycyrrhizin in CHC. In the only randomized clinical trial of glycyrrhizin, ALT levels declined modestly during treatment, compared with placebo, but this was not sustained after cessation of treatment and there was no significant effect on HCV RNA levels[50]. In the another trial, statistically significant differences in liver enzyme levels, but not viral loads, between treatment groups were identified during treatment, however, again no sustained response occurred at follow-up[51]. Use of glycyrrhizin is not without side effects. It has been found to cause pseudo-aldosteronism, manifested by sodium retention, hypokalemia and hypertension[52]. Cardiac arrhythmia and acute rhabdomyolysis due to severe hypokalemia caused by excess licorice consumption have also been reported[52-54].

Oxymatrine

Oxymatrine is the major alkaloid extract from the root of *sophora flavescens*, a deciduous shrub native to China, Japan, South Korea and Russia. It is reported to have antiviral activity against HCV in cell cultures and in animal studies[55-57]. Clinical studies have shown that oxymatrine has some hepatoprotective activity in alcohol toxicity and hepatitis B infection, but not carbon tetrachloride, acetaminophen or cadmium chloride-induced acute hepatitis[58,59]. Oxymatrine is considered to be an antifibrotic, likely through inhibition of lipid peroxidation[60-62]. In a study of HCV-infected subjects randomized subjects to receive either an intramuscular injection of oxymatrine 600 mg/d or other support products such as oral vitamins 47% of the treated cases had complete HCV viral suppression after 3 mo, compared with only 5% in the control group[61]. No serious adverse events were reported. The treated group had significantly more ALT normalizations than the control group in the first 2 mo, but this improvement waned by the end of the third month of treatment. While treatment with oxymatrine holds promise, it is difficult to draw conclusions from the small studies currently available.

Traditional chinese herbal medications

The primary goal of Chinese traditional medicine is to create wholeness and harmony within a person, allowing the mind/body/spirit to heal itself. There have been several randomized clinical trials of traditional Chinese medicine in the treatment of hepatitis C, however, the methodological quality of these studies is generally considered poor[63-70]. In two trials of herbal formulations in combination with interferon-alfa, there was a trend toward greater clearance of HCV RNA and ALT normalization with the combination treatment compared with patients receiving monotherapy[63,64]. In the only placebo-controlled trial of solo therapy with traditional Chinese medicine, a significant reduction in ALT levels during treatment occurred, though no virologic effect was identified[69]. Detailed descriptions of adverse events were not provided for most of these trials. The safety of these medicines is unclear due to the individualized nature of many of the herbal compounds involved, the large number of different herbs in each formulation, and the relatively small number of subjects within each clinical trial.

Vitamin D

The traditional role of Vitamin D (Vit D) was thought to be based upon its interaction in calcium homeostasis, *via* regulation of intestinal calcium absorption and of bone health. However, over the last several years Vit D has been shown to have a much more complex role in many other host functions, including its interaction with

chronic hepatitis C. 25-OH Vit D is made in the liver *via* cytochrome P450 (CYP27A1) activated hydroxylation of Vit D, brought into the body either by intestinal absorption or endogenous synthesis through sun-exposed skin. It is then converted to 1.25 OH Vit D (calcitriol) in the kidneys, the most active form, where it becomes available to bind to Vit D receptors throughout the body[71,72].

A growing body of clinical evidence has demonstrated an increased prevalence of Vit D deficiency in patients with CHC. As such, Vit D supplementation has been proposed as an adjunct to current standard regimens for treatment of hepatitis C[72]. One study found that mean 25-OH Vit D serum levels were significantly lower in CHC (25 μg/L) than in the controls (43 μg/L)[73]. Importantly, low Vit D has been linked to increased fibrosis and impaired sustained virologic response (SVR) in IFN-based therapy[71]. One clinical trial demonstrated that the addition of Vit D to the standard IFN plus ribavirin treatment significantly increased SVR in patients with genotype 1 CHC[74]. Regarding the underlying molecular mechanisms, an *in vitro* study showed that Vit D remarkably inhibits HCV production in Huh7.5 hepatoma cells[75]. These cells express Vit D hydroxylases and can eventually generate calcitriol. Notably, treatment with calcitriol resulted in HCV inhibition through induction of IFN-beta. Overall, 25-OH Vit D levels appear to be an important prognostic marker in helping determine the likelihood of SVR. 25-OH Vit D levels should be checked routinely before HCV treatment and supplementation provided to deficient patients, in an effort to enhance treatment response.

Antioxidants

Antioxidants are one of the most common dietary supplements taken by patients with CHC[14]. The use of these supplements is based on the fact that oxidative stress has been attributed to both host inflammatory processes and induction by viral proteins. By increasing antioxidants, one may be able to decrease oxidative stress and therefore decrease liver injury[76]. Existence of oxidative stress in CHC is well documented, as oxidized protein and nucleic acid markers are increased and antioxidant levels are decreased[77-80]. Studies have shown levels of oxidative stress markers to correlate with disease severity, HCV RNA, iron overload, and insulin sensitivity[78,79]. Oxidative stress has also been shown to be an early event in carcinogenesis and is a risk factor for development of HCC in patients with chronic HCV[81].

Multiple trials have shown antioxidants, such as Vitamin E and N-acetyl cysteine, only lead to small reductions in ALT after chronic administration in some instances[82-93]. Further, the decrease in ALT levels in most studies is marginal and is not sustained after stopping the treatment, raising the question of their clinical significance. No study has shown an improvement in outcome. In addition, no study has shown clear benefit of antioxidants as adjuvant to interferon based therapy of HCV. 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 are commonly associated with nausea and vomiting and intravenous administration of *N*-acetyl cysteine can result in anaphylactoid reactions, which may be more common in patients with chronic liver disease[94]. Therefore, evidence supporting use of antioxidants as useful therapeutic agents in CHC is lacking.

HERBAL SUPPLEMENTS AND DRUG INDUCED LIVER INJURY IN CHRONIC HCV

Drug-related hepatotoxicity is a serious health problem, with broad implications for patients, healthcare providers, the pharmaceutical industry and governmental regulatory agencies. The Drug Induced Liver Injury Network (DILIN), a federally funded consortium of 12 centers in the United States, recently reported the preliminary results of its prospective study[94]. Dietary supplements were implicated in 9% of reported DILI cases. This may be potentially related to increasing use of herbal or dietary supplements in the US population. The importance of these supplements as a cause of DILI is further underscored by a retrospective Japanese study, in which 10% of 879 cases of single agent DILI from 1997 to 2006 were attributed to dietary supplements and 7% to Chinese herbal drugs[95].

In general, chronic liver diseases such as HCV infection are thought to be associated with an increased incidence of hepatotoxicity induced by several specific drugs. Furthermore, patients with underlying liver disease potentially have worse outcomes than healthy individuals if they do develop DILI[96]. For example, the presence of underlying CHC has been shown to increase the risk of DILI caused by the antituberculosis drugs isoniazid and rifampin, as well as ibuprofen and methimazole[15,97,98]. Due to this, patients with chronic hepatitis C should be counseled and screened by physicians on potential risks associated with herbal medications.

DRUG-CAM INTERACTIONS

Another major area of awareness when patients are considering using CAM is whether or not drug-CAM interactions may exist that could impact the medical therapy. This issue is becoming even more complicated with the addition of new medications for the treatment of CHC infection such as simeprevir and sofosbuvir approved for use in the U.S. in December 2013. St. John's wort (*Hypericum perforatum*), a common CAM used for the treatment of depression, is an inducer of cytochrome P450 3A4[99]. This cytochrome is also the primary metabolizer of many medications, including the HCV protease inhibitors: telaprevir, boceprevir, and simeprevir. Additionally, St. John's wort is a potent intestinal P-gp inducer and may lead to a reduced therapeutic effect of

Table 1 Herbal supplements to discontinue and/or avoid while taking hepatitis C virus treatment

Herbal Product	Effect
Milk thistle (*Silybum marianum*)	Concomitant use of milk thistle may result in increased plasma concentrations of simeprevir
St. John's wort (*Hypericum perforatum*)	Concomitant use of St. John's wort may result in decreased plasma concentrations of telaprevir, boceprevir, simeprevir and sofosbuvir

the HCV nucleotide polymerase inhibitor sofosbuvir[100]. Concomitant use of St. John's wort and these HCV treatments is contraindicated and can lead to treatment failure by reducing blood concentrations. Additionally, concomitant use of milk thistle use is contraindicated with simeprevir. This combination may increase levels of simeprevir by milk thistle CYP3A inhibition leading to possible toxicity[101] (Table 1). Garlic extracts, grapefruit juice, and germander also have cytochrome P450 3A4 interactions[102].

CONCLUSION

Many human studies have shown improvements in subjective symptoms and liver biochemistries in HCV patients with CAM, but there is no convincing data to suggest a definite histological and/or virologic improvement with any of the herbal agents currently available. Vit D seems to have the best available data as adjunctive therapy to antiviral medications in patients with Vit D deficiency. Poorly designed studies, heterogeneous patient populations, lack of standardized preparations, and poorly defined nonobjective end points may partly explain the conflicting reports in the literature.

The safety profiles of the interventions discussed within this review are 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. Physicians need to be cognizant of known or occult use of CAM by their patients because hepatotoxicity and drug interactions may occur with many herbal medications, and may occur more frequently in patients with chronic liver disease.

There is an undoubted need for further research into the treatment of hepatitis C, and this review has identified several promising compounds, including Vit D, silymarin, oxymatrine, naringenin, and GTE. Some or all of these may be integral components of future HCV management.

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