

# Hepatitis C: A Retrospective Study, Literature Review, and Naturopathic Protocol

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## Abstract

The authors performed a retrospective review of 41 consecutive hepatitis C patients. Of the 14 patients with baseline and follow-up data who had not undergone interferon therapy, seven had a greater than 25-percent reduction in serum alanine aminotransferase (ALT) levels after at least one month on the protocol. For all patients reviewed, the average reduction in ALT was 35 U/L ( $p=0.026$ ). These data appear to suggest that a conservative approach using diet and lifestyle modification, along with safe and indicated interventions, can be effective in the treatment of hepatitis C. Controlled trials with serial liver biopsy and viral load data are necessary to confirm these preliminary findings.

The standard medical treatment of hepatitis C infection is only associated with sustained efficacy in a minority of patients. Therefore, the search for other treatments is of utmost importance. Several natural products and their derivatives have demonstrated benefit in the treatment of hepatitis C and other chronic liver conditions. Other herbal and nutritional supplements have mechanisms of action that make them likely to be of benefit. This article presents comprehensive protocol, including diet, lifestyle, and therapeutic interventions.

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## Introduction

Hepatitis C virus currently infects an estimated 2-3 million people in the United States, and as many as 175 million worldwide.<sup>1</sup> Although recent evidence suggests hepatitis C virus (HCV) infection is associated with less risk of progressive liver disease than previously thought,<sup>2</sup> HCV is still estimated to cause 8-10 thousand deaths annually in the United States and is the leading cause of liver transplantation.<sup>1</sup>

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Standard HCV treatment includes interferon- $\alpha$  and ribavirin. This treatment is expensive, and is associated with significant adverse effects.<sup>3</sup> Combination treatment is associated with a sustained virologic response (defined as lack of detectable HCV RNA in the serum six months after stopping therapy) in only 30 percent of patients with HCV genotype 1b, the most common of the major genotypes in the United States.<sup>3</sup> Currently, no treatment is recommended for HCV-positive patients without elevated alanine aminotransferase (ALT),<sup>4</sup> although these people appear to have a low level of chronic hepatitis.<sup>5</sup> Clearly, there is a need for inexpensive, non-toxic treatments for early stages of HCV infection.

The retrospective data presented in this paper were compiled over a period of five years in the private practice of one of the authors (WBM). While the protocol instituted in 1995 does not include all of the agents included in the literature review section, it was decided to include these retrospective data to demonstrate that an intervention based on colchicine, ursodeoxycholic acid (UDCA), silymarin, and antioxidants can lead to significant improvement in HCV patients. The authors emphasize the fact that the protocol employed in the retrospective study has been revised and expanded since the data collection reported here, and that the slight lack of continuity between the old protocol and the present proposed protocol based on the literature review is representative of an evolving treatment plan.

### Retrospective Review of HCV Patients

The charts of 41 consecutive HCV patients (beginning in May 1995) from the private practice of one of the authors (WBM) were examined. Data were compiled only for those patients who had ALT data available from before treatment and at least one month

**Table 1: Breakfast Muesli**

Rolled oats .....	4 lbs.
Oat bran .....	2 lbs.
Fresh ground flax.....	1 lb.
Granulated lecithin .....	1 lb.
Fresh ground milk thistle seed ....	1 lb.
Whole raw almonds.....	1/2 lb.
Whole raw sunflower seeds .....	1/2 lb.
Wheat germ.....	1 lb.

Instructions: grind the flax and milk thistle seeds. Mix all ingredients together. Refrigerate the mixture until ready to use. Eat 4 oz. every morning served with dilute fruit juice and live yogurt as breakfast. Recipe makes 40 day supply.

after institution of the protocol (range 1-50 months). One patient was removed from the cohort due to a recent course of interferon therapy. No other patients reviewed were under treatment with interferon. When more than one ALT measurement was available in the year preceding treatment, the baseline ALT was calculated as the average of these values (n=5). Similarly, when multiple follow-up measurements were available, the average of the available values (n=5) was used for comparison.

The protocol used in the reviewed charts included: colchicine (1.2 mg daily, five days per week); UDCA (300 mg bid pc); silymarin (80% standardized extract, 150 mg twice daily); antioxidants containing 400 IU d-alpha tocopherol, 500 mg vitamin C, 15 mg beta carotene, and 50 mcg selenium amino acid chelate (1-2 times daily); N-acetyl-L-cysteine (1 gram twice daily ic); cod liver oil (1-2 tsp daily), containing 2000-2500 IU vitamin A per teaspoon; and a breakfast muesli designed to emulsify bile salts (Table 1). Treatments added for some (but not all) patients included an Ayurvedic herbal formula (Liv-52 — see the anti-tumor necrosis factor section for herbs in

the formula) 1 twice daily; another herbal mixture containing *Phyllanthus nigrum* or *amarus*, *Picrorrhiza kurroa*, *Zingiber officinale*, *Boerhaavia diffusa*, *Andrographis paniculata*, *Cichorium intybus*, *Emblica officinalis*, *Embelia ribes*, *Terminalia chebula*, *Terminalia arjuna*, *Piper longum*, and *Eclipta alba* (1 twice daily), and deglycyrrhized licorice (500 mg 2-4 times daily ic), as a digestive tonic, not as a substitute for the antiviral effects of the whole herb. It is reiterated this protocol has been updated since these patients were first treated.

Fourteen patients (age 26-77 years) met the criteria for inclusion in the data analysis. The average baseline ALT level for these patients was 127 U/L (range: 47-256). The average ALT values for patients on the protocol for a minimum of one month was 92 U/L (range: 25-235;  $p=0.026$ , paired t-test). Of the 14 patients reported, seven showed an ALT reduction of greater than 25 percent (range: 29-76 percent). The other seven patients had no change or a slight increase in ALT.

No patient reviewed retrospectively developed symptoms indicating advancing liver disease, including liver pain, enlarged liver, jaundice, ascites, generalized edema, or liver-related bowel dysfunction. Most patients reported an increased sense of well being on the treatment program. The patient excluded from analysis due to recent interferon treatment showed an ALT reduction from a pre-treatment level of 553 to a post-treatment value of 132. Although serial HCV-RNA analysis availability was too sparse to make a statistical analysis, one patient was noted to have achieved undetectable virus along with normalized liver enzymes on a single measurement. No serial biopsy data were available for report. The relative merits of the different outcome measures are discussed in the conclusion.

## A Review of the Current Literature on HCV

Many specific natural therapies appear to be useful in the treatment of HCV. Several have been subjected to clinical trial, and others have solid theoretical basis for their use. This review will summarize the most promising natural treatments available for HCV.

Although the discussion of these therapies is divided into categories, it should be pointed out there is significant overlap in the mechanism of action of many of these agents. Vitamin E, for example, is an antioxidant compound that has been shown to reduce hepatic fibrosis. Sho-saiko-to, discussed here as an anti-fibrotic herbal mixture, also is known to have significant antioxidant capacity.

## Diet and Lifestyle Factors in Treatment

There are a number of dietary and lifestyle factors to consider in the treatment for HCV (Table 2).

### *Macronutrient intake:*

A retrospective study showed that high intake of fats, coupled with reduced protein and carbohydrate intake, increases the risk of progression to cirrhosis associated with chronic HCV infection.<sup>6</sup> It is currently unknown whether the deleterious effects of fats are limited to specific fatty acids. Preliminary evidence from a small prospective trial showed phosphatidylcholine high in omega-3 fatty acid side chains to be beneficial in chronic liver disease, including hepatitis C.<sup>7</sup> Omega-3 fatty acids from vegetable or fish sources are known to reduce synthesis of tumor necrosis factor, the importance of which will be discussed below.<sup>8</sup> It is currently unknown whether specific amino acids are beneficial in HCV infection. It is possible that branched-chain amino acids may be beneficial in patients with more advanced liver disease, particularly in the prevention of hepatic encephalopathy.<sup>9</sup>

**Table 2:** Suggested Diet and Lifestyle Modifications for Patients with HCV

Dietary recommendations:

- A. Eat 4 oz of the breakfast muesli (see table 1) daily.
- B. Maintain an adequate protein intake: 45-75 grams/70 kg adult.
- C. Maintain an adequate intake of marine oils in the diet; eat fish regularly as a source of protein.
- D. Reduce intake of sweetened foods, not just refined sugars but fruit juices as well.
- E. Maintain an adequate intake of water: 2 L daily for an adult.
- F. Maintain an adequate intake of raw and steamed fruits and vegetables: eat at least one serving of raw ( or lightly steamed), unprocessed food at each meal.

Lifestyle recommendations:

- A. Eliminate alcohol entirely.
- B. Eliminate smoking entirely.
- C. Ensure daily restorative sleep.
- D. Prevent superinfection with HAV or HBV through vaccination of individuals without established immunity to these viruses.

Supplementation with branched-chain amino acids has been found to mildly increase natural killer cell activity in patients with viral-induced (mostly due to HCV) cirrhosis.<sup>10</sup>

*Iron:*

Pre-interferon treatment, iron depletion is associated with a reduction in ALT levels and possibly with an increased treatment response.<sup>11,12</sup> A trend toward greater amounts of hepatitis C viral RNA has also been noted with increasing levels of serum iron.<sup>13</sup> Epidemiological evidence suggests a vegetarian diet can reduce iron stores,<sup>14</sup> but short-term prospective trials have not confirmed this.<sup>15</sup> Regular tea drinking with meals can significantly reduce iron absorption over one year.<sup>16</sup> Use of supplemental iron in patients with HCV appears contraindicated, except in cases of demonstrated iron deficiency.

*Non-nutritive factors:*

Intake of alcohol in patients with HCV has been correlated with degree of liver fibrosis, increased risk of cirrhosis, decreased response to interferon, and higher rate of mortality.<sup>17</sup> One prospective study showed smoking was associated with increased risk of HCV-associated hepatocellular carcinoma (HCC).<sup>18</sup>

*Vaccination:*

Co-infection with hepatitis B (HBV) is common in HCV carriers. Immunity to HBV can be established by the presence of hepatitis B surface antibody in a hepatitis screening panel. Although the mechanism is not clear, the prognosis is reported to be worse in patients infected with both viruses.<sup>19</sup> To date, the efficacy of HBV vaccination in HBV-negative patients has not been evaluated. Regardless, HBV vaccination should be offered to all HBV

antibody-negative HCV patients with an explanation of the risk factors for HBco-infection.

HCV patients who become super-infected with hepatitis A (HAV) have a substantially greater risk of fulminant hepatitis and death compared to the general population.<sup>20</sup> Given a worldwide incidence of HAV infection, together with evidence that HAV vaccine is effectively immunogenic in HCV carriers,<sup>21</sup> HAV vaccination should be recommended for all HCV carriers.

#### *Obesity:*

Significant association between body mass index and fibrosis in HCV infection has been noted.<sup>22</sup> A recent editorial suggests tight glycemic control could be important in the management of patients with viral hepatitis and diabetes.<sup>23</sup>

#### **Anti-fibrotic Agents**

Irregular regeneration of hepatocytes appears to be the single greatest risk factor for development of HCC in HCV patients.<sup>24</sup> This irregular regeneration is thought to be secondary to ongoing necrosis of hepatocytes associated with lymphocytic infiltration.<sup>24</sup> Agents that can delay this necrosis would theoretically be useful in delaying the onset of cirrhosis or HCC.

#### *Colchicine:*

Colchicine is an alkaloid isolated from the autumn crocus (*Colchicum autumnale*). In animal models of liver damage, colchicine treatment was found to significantly reduce fibrosis during hepatocytic regeneration.<sup>25</sup> Several prospective trials have found a significant, although mild, improvement in liver function tests associated with colchicine treatment in cirrhotic patients.<sup>26-28</sup> One of these trials found survival was three times higher in colchicine-treated patients than in the placebo group over eleven years.<sup>26</sup> The only trial to examine liver

histology found neither significant improvement nor deterioration over the two-year treatment period.<sup>27</sup>

Nine patients with HBV and either contraindication or no response to interferon therapy underwent treatment with colchicine (1 mg qd, 5 days weekly for 6 months). All patients were HBV-DNA positive at the beginning of the trial, and each had histological and serologic evidence of liver damage. At the conclusion of the trial, six of the patients had cleared HBV-DNA and normalized transaminases. The three non-responding patients had no change in liver enzymes.<sup>29</sup> While the mechanism of action of colchicine makes it possible a favorable outcome would be seen in HCV patients, these results should not be interpreted as being directly applicable to HCV treatment.

Colchicine is often administered 1 mg daily in a five-day cycle, with two days off. This dosage schedule reduces the incidence of diarrhea.<sup>26</sup> The other major side-effects seen with colchicine treatment are leukopenia and thrombocytopenia.<sup>26</sup> Colchicine has not undergone clinical trial in HCV patients.

#### *Ursodeoxycholic acid (UDCA):*

UDCA is a hydrophilic bile acid found in low concentrations in human bile. It has been shown to be cytoprotective in multiple liver disorders due to its ability to displace toxic hydrophobic bile acids in the liver and intestines.<sup>30</sup> One long-term study of UDCA in HCV infection unresponsive to or unsuitable for interferon treatment found significant decreases in serum transaminases, lactate dehydrogenase (LDH), and gamma-glutamyl transpeptidase (GGT) compared to baseline in treated subjects. The improvement was similar among different HCV genotypes.<sup>31</sup> Liver histology was not measured in this trial. A controlled trial in 56 chronic hepatitis patients, 45 of whom were HCV-antibody positive, found 600 mg/day of UDCA for one year was associated with approximately a 25-percent

drop from baseline in transaminase levels. No improvement was noted in liver histology in treated subjects compared with baseline or placebo.<sup>32</sup> The authors concluded that UDCA has only an ancillary role in the treatment of HCV. UDCA has been found to cause reductions in anti-nuclear and anti-smooth muscle antibodies in patients with autoimmune-associated hepatitis C.<sup>33</sup>

Conjugation of UDCA with taurine makes the bile acid more hydrophilic. Treatment with tauroursodeoxycholic acid has been found to be associated with reduction in serum transaminase levels in HCV.<sup>34</sup> Tauroursodeoxycholic acid has not been compared to UDCA in clinical trial, however.

#### *Silybum marianum (milk thistle):*

The milk thistle plant, the source of a flavonoid extract known as silymarin, has been used in the treatment of hepatic conditions for 2000 years.<sup>35</sup> One study (n=21) showed administration of 420 mg/day oral silymarin for six months to be similar to 600 mg/day UDCA in ALT reduction in patients with chronic liver disease. Although the discussion indicates that some of these patients were HCV-positive, it is unclear whether the treatment effect was similar in those who were infected. Silymarin treatment was not associated with the reduction in GGT seen with UDCA, suggesting the mechanism of hepatoprotection by silymarin was not due to reversal of cholestasis.<sup>36</sup>

Another trial (n=8, 5 HCV positive) examined the hepatoprotective effect of a complex of silybin (a flavonoid component of the silymarin extract) and phosphatidylcholine. The phosphatidylcholine was added to improve the absorption of silybin. After two months of treatment, significant reductions in ALT and aspartate aminotransferase (AST) were noted.<sup>37</sup> The authors did not report whether the magnitude of the treatment effect was similar between those who were HCV positive and those who were not. These results were confirmed by a slightly larger double-

blind, randomized trial (n=20, 15 HCV positive). Patients were given either silybin/phosphatidylcholine complex (equivalent to 240 mg of silybin) or placebo for one week. Significant reductions in AST, ALT, and GGT were seen in treated subjects compared both to baseline and to the placebo group.<sup>38</sup>

The effect of 450 mg per day silymarin was tested in double-blind manner in 200 patients with alcoholic cirrhosis. No benefit on survival or clinical course was seen in the treatment group in the three-year trial. Of the known HCV-positive patients, however, none of 13 in the treatment group died compared with four of 16 in the control group (p=0.059, NS).<sup>39</sup> Another trial of silymarin in cirrhotic patients found the protective effect of treatment was greatest in early stage patients (Child stage 'A').<sup>40</sup>

Silymarin extracts are rarely associated with significant adverse effects. Milk thistle appears to have many different mechanisms of action, including protection against lipid peroxidation in membranes, chelation of metal ions, DNA protection, and changes in hepatocyte protein synthesis. For further discussion of pharmacology and mechanisms of action see the review by Flora et al.<sup>41</sup> While the evidence in favor of *Silybum marianum* is preliminary, there is reason to believe these extracts can reduce hepatocyte necrosis in a variety of liver conditions. Silymarin is a good candidate for further clinical trial in HCV.

#### *Sho-saiko-to:*

The Japanese herbal medicine Sho-saiko-to (TJ-9) is a commonly used treatment for chronic hepatitis in some parts of the world. TJ-9 has been shown in animal studies to inhibit the action of hepatic stellate cells, thus slowing the fibrosis process.<sup>42</sup>

Cirrhosis patients were randomized to receive either 7.5 grams per day TJ-9 or no additional treatment for five years. Of a 94-person subset of the larger study population

analyzed for anti-HCV, 76 were positive. After five years follow-up, non-significant increases in survival and decreases in mortality were seen in the treatment group. These changes became significant when analysis was limited to those patients who were HBV-surface antigen negative.<sup>43</sup> The authors speculated that TJ-9 is particularly effective in the treatment of HCV. A multi-center controlled trial of chronic hepatitis patients (both HBV and HCV) found that 5.4 grams of TJ-9 per day was associated with a significant reduction in both AST and ALT.<sup>44</sup> The medication was well-tolerated in both human trials. Interstitial pneumonia has been reported as a side-effect of this treatment in several case studies, however.<sup>45,46</sup>

### Antioxidant Agents

Oxidative damage appears to be an important factor in the progression of chronic HCV. Products of oxidative damage have been correlated with the grade of liver fibrosis<sup>47</sup> and hepatocellular DNA damage<sup>48</sup> in HCV patients. While only a few of the widely used antioxidants have been studied in the treatment of HCV, other antioxidants (e.g., vitamin C and carotenoids) may be of benefit as well.

#### *Vitamin E:*

Six HCV patients who had not responded to interferon therapy were supplemented with 1200 IU d-alpha-tocopherol for eight weeks. Post-treatment biopsy showed reduction in measures of inflammatory activity, including activation of hepatic stellate cells and collagen gene expression, compared to pre-treatment specimens. Average ALT levels were reduced from 135 to 101 U/mL by treatment, a change not statistically significant. Viral titers and histological degree of inflammation and fibrosis were unchanged by therapy.<sup>49</sup>

A randomized double-blind trial studied the effect of 800 IU d-alpha-tocopherol daily in 23 patients refractory to interferon

therapy. Significant reductions in ALT and AST were noted in 48 percent of treated subjects. Liver enzymes returned to near pre-treatment value after cessation of vitamin E, and responded to an open label trial of vitamin E treatment with similar reductions of ALT and AST. HCV RNA remained detectable in the serum of all patients at the conclusion of the trial.<sup>50</sup>

In a small pilot trial, patients undergoing initial interferon therapy (n=24) were randomized to receive one of three treatments: (1) interferon only; (2) interferon plus n-acetylcysteine (1,800 mg/day) and sodium selenite (400 mcg/day); or (3) interferon, n-acetylcysteine, sodium selenite, and vitamin E (544 IU/day). Liver enzyme levels, HCV RNA, and interferon response were similar in the first two groups. Patients receiving vitamin E had a greater response to treatment (OR=2.4, 95% CI:1.05-5.5) compared with the two groups without vitamin E. Viral loads were also reduced to a significantly greater degree in the vitamin E treated subjects (p=0.028).<sup>51</sup>

#### *Selenium:*

Supplementation with 200 mcg of selenium from a yeast source (mainly in the form of selenomethionine) was associated with a 50-percent reduction in all-site cancer mortality over a mean of 4.5 years. Incidence of hepatocellular carcinoma was not presented in this study.<sup>52</sup> A prospective trial found that the odds of HCC in chronic hepatitis patients (both B and C) were inversely related to plasma selenium levels.<sup>53</sup> Serum selenium deficiency has been associated with mutation of RNA viruses other than HCV to more virulent forms.<sup>54</sup> The role of genetic mutation in HCV infection is not presently clear, although it has been shown that a greater number of viral quasi-species is related to better outcomes after liver transplantation.<sup>55</sup>

### *N-acetyl-L-cysteine (NAC):*

Plasma reduced glutathione, a major extracellular antioxidant, has been shown to be extremely low in treated and untreated HCV patients compared with healthy controls.<sup>56</sup> Administration of 1800 mg NAC daily during the second course of interferon therapy to HCV patients who had failed to respond to the first course of interferon (n=14) led to a significant increase in plasma glutathione levels. These patients experienced a reduction in ALT from a pretreatment average of 124 to 37 after six months of treatment. NAC treatment without concurrent interferon had no significant effect on ALT levels.<sup>56</sup> In another study, a group of 36 interferon-naïve HCV patients had plasma glutathione concentrations similar to those of healthy controls. A double-blind, placebo-controlled trial of 1800 mg/day NAC during interferon treatment in this glutathione-replete population showed no benefit from the supplementation on ALT levels or response to therapy.<sup>57</sup> Any benefit from NAC supplementation in HCV patients appears to be confined to those who have low plasma concentrations of glutathione and are currently undergoing interferon treatment.

### *Lipoic acid:*

A series of three case studies in HCV patients reported that a combination antioxidant treatment containing 600 mg per day lipoic acid with 900 mg/day silymarin and 400 mcg/day selenium, was associated with an ALT reduction of at least 60 percent in each patient.<sup>58</sup> This finding has been confirmed by the clinical experience of one of the authors (DWL). The effectiveness of lipoic acid as an antioxidant in other hepatic conditions also supports its use in the treatment of HCV.<sup>59</sup>

## **Immunostimulatory/Antiviral Agents**

### *Thymic extracts:*

In an open trial in patients with non-A, non-B hepatitis, five of 15 patients treated with a bovine thymus extract experienced significant reduction in ALT levels.<sup>60</sup> A double-blind, placebo-controlled trial studied the effect of an oral bovine thymus glandular product also containing undisclosed herbs, vitamins, enzymes, and minerals in HCV patients previously unresponsive to interferon therapy.<sup>61</sup> Administration of six tablets twice daily of the formula (total concentration of thymic compounds undisclosed) was not associated with significant improvement in ALT or viral load after six months of treatment. The authors stated no conclusions could be made based on the results from the treatment of interferon-naïve patients with thymus compounds.

The synthetic thymus polypeptide thymosin alpha-1, which is thought to be similar to thymosin fraction 5, was studied in conjunction with interferon in treatment-naïve patients. Intramuscular administration of 1 mg thymosin alpha-1 twice weekly during interferon treatment was associated with significantly greater reductions in ALT and HCV RNA compared to interferon alone. No significant difference, however, was noted in patients with the HCV-1b genotype.<sup>62</sup> The only trial to date of thymosin alpha-1 as monotherapy was reported in abstract form only, and had disappointing results.<sup>63</sup> Currently, there are more questions than answers about thymic extract therapy. It is uncertain which of these extracts are orally available, and when parenteral administration is necessary. At least one thymus preparation, thymodulin, is orally active in humans.<sup>64</sup> Also, it is unclear whether, like interferon therapy, benefits vary in genotypic subsets. Thymic extracts have a long history of use in viral infection, however, and merit further evaluation.



*Glycyrrhiza glabra:*

Aqueous extract of *Glycyrrhiza glabra* (licorice root) is the major component of Stronger Neo-Minophagen C (SNMC), an intravenous preparation used in Japan in treatment of HCV. SNMC contains 0.2-percent glycyrrhizin (a component of *Glycyrrhiza*), 0.1-percent cysteine, and 2.0-percent glycine in physiologic solution. Retrospective analysis found administration of 100 ml SNMC 2-7 times a week for a median of 10 years led to a 50-percent reduction in HCC incidence over a 15-year period. ALT was less than 50 IU in 35 percent of treated patients compared with 6 percent of controls.<sup>65</sup> Other human trials have confirmed the benefit of SNMC in HCV patients.<sup>66,67</sup>

The mechanism of action of glycyrrhizin is not understood currently. Extracts of *Glycyrrhiza glabra* have been shown to have antiviral activity *in vitro* against a number of unrelated viruses.<sup>68</sup> No reduction in HCV RNA was noted in a double-blind trial of SNMC, however.<sup>67</sup>

Although the studies of the efficacy of glycyrrhiza in HCV were performed with IV administration, glycyrrhizin is orally absorbed.<sup>69</sup> Glycyrrhetic acid, the major metabolite of glycyrrhizin formed in the large intestine, is also well absorbed orally.<sup>70</sup> It is unclear at present what oral doses approximate the intravenous therapeutic dose and whether glycyrrhetic acid has similar activity to glycyrrhizin. Pseudoaldosteronism, with an associated increase in blood pressure, can be a side-effect of licorice root.<sup>71</sup> This side-effect was noted in one of 87 patients treated with SNMC in clinical trial.<sup>66,67</sup> Non-SNMC extracts may be more likely to cause blood pressure increase, as the glycine in SNMC is thought to prevent this effect.<sup>67</sup> Patients under long-term *Glycyrrhiza* therapy should have blood pressure and serum potassium monitored regularly.

*Phyllanthus species:*

This herb has been shown *in vitro* to down-regulate the transcription of HBV mRNA.<sup>72</sup> Preliminary human research in HBV has been conflicting.<sup>73,74</sup> There are no data regarding *Phyllanthus* species in the treatment of HCV.

**Anti-tumor Necrosis Factor Agents**

It has been hypothesized that tumor necrosis factor-alpha (TNF- $\alpha$ ) is the central mediator of the inflammatory process in HCV.<sup>75</sup> Serum levels of TNF- $\alpha$  have been correlated with elevated ALT<sup>76</sup> and increased severity of fibrosis in HCV patients.<sup>77</sup> Decreased TNF- $\alpha$  concentration has been noted in patients with sustained response to interferon therapy.<sup>78</sup>

*TNF-reducing herbs:*

Many herbs commonly used by practitioners of complementary and alternative medicine are potent reducers of TNF- $\alpha$ . Included among these are *Camellia sinensis* (tea),<sup>79</sup> *Zingiber officinale* (ginger),<sup>80</sup> *Tanacetum parthenium* (feverfew),<sup>81</sup> and *Ginkgo biloba*.<sup>82</sup> The flavonoid quercetin, found in many herbs, also has significant TNF- $\alpha$ -inhibitory activity.<sup>83</sup> It should be noted that none of these herbs are traditionally considered to be treatments for chronic liver conditions, and their use in HCV at this point is theoretical.

An Ayurvedic herbal combination, Liv-52, has been used in the treatment of various liver disorders. Although it has not been evaluated in the treatment of HCV, it did inhibit TNF- $\alpha$  in an animal study,<sup>84</sup> providing a possible mechanism for the hepatoprotective effect noted in its traditional use. Liv-52 contains *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Terminalia millefolium*, *Cassia occidentalis*, and *Tamarix gallica*.

**Table 3:** Suggested Diagnostic and Case Management Strategies for Patients with HCV

Initial visit

- A. Appropriate history and physical exam
- B. Laboratory testing
  - 1. CBC
  - 2. Liver function test (LFT)
  - 3. Serum chemistry profile, including electrolytes, lipids
  - 4. Ferritin and TIBC
  - 5. Thyroid panel
  - 6. Urinalysis
  - 7. Verification of HAV and HBV immune status
  - 8. Viral quantification by PCR
  - 9. Viral genotype
- C. Refer for liver biopsy

Visit schedule

- A. 1st office call
- B. Return in 1-3 weeks to review laboratory results, individualize treatment intensity to level of disease activity
- C. Follow-up office visits every 3 months

Follow-up case management strategy

- A. History and physical exam every 3 months
- B. Repeat CBC, LFT, and serum chemistry profile every 3 months
- C. Repeat viral load every 12-18 months
- D. Repeat liver biopsy every 12-18 months

*Endogenous TNF- $\alpha$  modifiers:*

Certain hormones are known to modulate TNF secretion, including corticosteroids,<sup>85</sup> DHEA,<sup>86</sup> and melatonin.<sup>87</sup> Corticosteroid treatment has demonstrated failure to induce viral remission in chronic hepatitis C, and is associated with adverse effects, including increase in risk of cirrhosis.<sup>88</sup> Supraphysiological doses of DHEA are associated with adverse effects as well, but physiologic replacement therapy appears well-tolerated.<sup>89</sup> Melatonin was shown to reduce TNF secretion in advanced cancer

patients.<sup>90-91</sup> Another study found melatonin administration was associated with an increase in TNF- $\alpha$  levels in advanced cancer patients after three months.<sup>87</sup> The latter study is likely flawed, however, as patients served as their own controls. As TNF secretion rises significantly in late stage cancer, a placebo group would have been necessary to distinguish between a treatment effect and natural disease progression. The use of DHEA or melatonin as TNF-reducing agents in HCV is presently of theoretical benefit.

**Table 4:** Potential Naturopathic Treatment Interventions for Patients with HCV

Primary intervention (supported by human research)

Intervention	Dosage	Instructions/notes
<b>Colchicine</b>	1.2 mg q AM, five days per week	Monitor CBC for possible thrombocytopenia or leukopenia
<b>UDCA (Actigal)</b>	300 mg bid pc	May cause loose stools
<b>Silymarin</b>	120 mg bid of 80% standardized extract	Generally well tolerated
<b>Vitamin E</b>	800 IU qd of d-alpha-tocopherol	Succinate form of vitamin E may have maximal absorption
<b>Glycyrrhiza glabra</b>	1/4-1/2 tsp 1:1 fluid extract, bid-qid	Monitor blood pressure and serum electrolytes regularly
Sho-saiko-to (TJ-9)	7.5 grams qd	Can be associated with interstitial pneumonitis

Secondary intervention (supported by animal and/or *in vitro* research or of limited benefit)

Intervention	Dosage	Instructions/notes
<b>N-acetyl-L-cysteine</b>	500-600 mg tid ic	Benefit only proven concurrently with interferon
<b>Selenium</b>	200 mcg qd	Selenomethionine likely to be of more benefit than selenite
<b>Cod liver oil</b>	2 tsp qd (containing 4000-5000 IU vitamin A and 400-500 IU vitamin D)	Vitamin A levels not likely to cause hepatotoxicity
Thymus extract	Doses vary widely with preparation	Benefit is as yet unclear
Liv-52	1 bid	Generally well tolerated
<b>Lipoic acid</b>	100-200 mg tid	Evidence of efficacy limited to three case studies

Tertiary interventions (benefit largely theoretical)

Intervention	Dosage	Instructions/notes
Folic acid	800-5000 mcg qd	Low folate status is associated with carcinogenesis
Vitamin B-12	1000 mcg qd po, or 100-1000 mcg qid I.M.	Low B-12 status is associated with carcinogenesis
<b>Vitamin C</b>	2000-8000 mg qd	May chelate iron as well as prevent oxidative damage
DHEA (if reduced)	Replacement of physiological levels (5-25 mg qd)	Start dosage low and increase over four weeks in females
Melatonin	3-20 mg hs	Start dosage low and increase 3 mg at a time over three weeks

Note: These categories refer to the research basis for use. Agents listed in bold face are currently in the initial protocol of the authors. Individual authors vary with respect to other agents.

## Miscellaneous Agents

Vitamin B12 has a lipotropic effect and is protective against carbon tetrachloride-induced liver damage in animals. Vitamin B12 (100 mcg IM four times daily) was reported to be of benefit in the treatment of acute hepatitis.<sup>92</sup> Vitamin B12 and folic acid are necessary for DNA replication. Deficiencies of these two vitamins have been implicated in carcinogenesis.<sup>93,94</sup>

## Conclusion

Given the poor prognosis and paucity of effective treatments for HCV, it appears important to examine complementary medicine treatment possibilities. Most of the treatments described here have the dual advantages of being inexpensive and having a favorable therapeutic index. It is the experience of the authors that a comprehensive program of diet and lifestyle modification, together with some of the interventions discussed here can often reduce or even normalize liver enzyme levels in HCV. Table 3 outlines a suggested diagnostic and case management protocol.

The authors wish to emphasize that the suggested protocol is not meant to be a cookbook approach. The interventions listed in Table 4 constitute a list of therapies, organized by the level of research support for each. The intensity of the treatment should be tailored to the clinical severity of the disease and the response of the patient. A patient with persistently normal liver enzymes and a low fibrosis score on biopsy requires less intervention than does a patient with a higher degree of fibrosis or cirrhosis.

No agent described in this paper is known to eradicate the virus. It is the conviction of the authors that until there is a safe and effective means of reliably eliminating viremia in HCV, this disease should be managed as a chronic condition similar to autoimmunity. In this model, the role of the physician is to help the patient with strategies that keep disease manifestations and liver damage at a

minimum, while using the least invasive therapeutic intervention.

The standard of care for chronic HCV infection is interferon monotherapy. This is followed by concurrent interferon and ribavirin therapy in those who do not achieve sustained responses to the interferon therapy.<sup>95</sup> Interferon treatment is not a suitable treatment for all patients, however. Serious and fatal side-effects have been noted in patients undergoing interferon treatment.<sup>95</sup> Many patients refuse interferon treatment due to financial, religious, and philosophical reasons. Most importantly, interferon therapy, even in combination with antiviral medication, has no sustained effect in more than 50 percent of patients.<sup>95</sup> The opinion of the authors is that the suggested protocol is the treatment of choice in the patient who cannot or will not undergo interferon therapy or who does not have sustained response to interferon treatment.

While the chart review data presented here are encouraging, it is noted there are several limitations to this type of analysis. The gold standard for monitoring disease progress in HCV is serial liver biopsy; ALT measurement was used as the least expensive and invasive means of assessing disease activity.<sup>95</sup> ALT is known to be a labile value in HCV infection, and correlates only weakly with degree of hepatic fibrosis.<sup>95</sup> ALT can also fall with the development of cirrhosis, although this is doubtful in most of these patients as signs and symptoms of cirrhosis were absent.

The necessity of limiting analysis to patients who returned for follow-up visits is a potential confounding variable. It is possible the data are skewed to reflect more positive responses as those who did not respond to treatment, or had difficulty following a complex protocol, did not return for further visits. This type of analysis also does not allow for compliance analysis, which leaves open the possibility that the treatment non-responders were not able to follow the protocol. Additionally, the lack of a control group makes

a placebo response difficult to assess. Prospective and controlled trials with measurement of serial liver biopsy are necessary to clarify these pilot findings.

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