

# NATUROPATHIC MEDICINE

J. Lyn Patrick, ND

## Introduction

The philosophy of naturopathic medicine can best be described as the utilization of the healing power of nature. Several basic thoughts are at the core of this philosophy. Naturopathic healthcare providers approach health with prevention and education foremost in their minds. If disease enters the picture, the approach is to treat the whole person so that the natural healing powers of the body are able to resolve the root cause of the illness.

There are four accredited naturopathic medical colleges in the United States. If you choose to include naturopathic medicine in your *hepatitis C* treatment plan, it is important that you see a licensed naturopathic doctor. Naturopathic medicine is currently licensed in 14 states. Licensed or licensable naturopaths also practice in states where they may not hold licenses. The American Association of Naturopathic Physicians provides information on well-trained, naturopathic doctors in the United States (see the *Resource Directory*).

## The Principles of Naturopathic Treatment for Hepatitis C

Naturopathic healthcare providers use many different tools in the care and treatment of patients. These include botanical medicines (herbs), acupuncture, *nutritional supplements*, traditional Chinese medicine, homeopathic remedies, nutrition counseling and diet therapy, massage and/or spinal *manipulation*, exercise, and other forms of therapy.

The section discusses the naturopathic approach to hepatitis C management and the options a naturopathic provider might consider for someone with hepatitis C.

### The Liver as an Organ of Detoxification

The liver is a large organ. It weighs about 3½ pounds and filters almost two quarts of blood every minute. Filtering the blood is essential to survival because the liver receives blood directly from the intestines. The liver filters *proteins* and other nutrients and chemicals from the food we eat. The liver regulates blood sugar levels, stores fat-soluble *vitamins*, activates and breaks down *hormones* and drugs, and aids in the elimination of pollutants and *toxins*. The liver also manufactures nutrients, *enzymes*, and *hormones*.

For the liver to function well, it needs certain nutrients for the detoxification and *immune systems*. The liver requires B vitamins (B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, and folic acid), magnesium, zinc, copper, choline, betaine, and the *amino acids* methionine, taurine, and cysteine to break down medications, pollutants, and chemicals found in air, water, and food.<sup>1</sup>

### GLUTATHIONE

*Glutathione* is one of the most important chemicals needed for liver health. The body cannot function without glutathione. Loss of glutathione can cause kidney and *liver failure*. Low glutathione levels can be found in people with cataracts, *HIV* infection, *chronic hepatitis C*, and *cirrhosis*.<sup>2</sup> People with cirrhosis of the liver may have difficulty making glutathione. This may explain why glutathione levels 30% below normal have been found among people with cirrhosis of the liver.<sup>3</sup>

Glutathione is an *antioxidant*, a chemical that protects the liver from damage by other chemicals called *free radicals* and oxidants. Glutathione is produced in the liver and elsewhere in the body from some of the nutrients listed above. Glutathione is a sulfur-based substance that helps eliminate free radicals and *metabolize* (break down) medications and chemicals.

Glutathione is used by many types of cells as the main defense against *oxidative stress* (an overabundance of free radicals). *Iron* can cause oxidative stress, and damage from liver iron can be a contributing factor in the process of fibrosis. Because glutathione protects against damage from oxidants such as iron, it may slow the *fibrosis* process.

Glutathione is also a crucial activator of certain immune system cells called *cytotoxic T-cells*. Cytotoxic T-cells kill viruses and cancer cells.<sup>4</sup> Glutathione has been shown to have direct *antiviral* effects. Levels of reduced glutathione (the most important form of glutathione) can be significantly below normal in people who have alcoholic hepatitis or hepatitis C.<sup>5,6</sup>

Studies have shown that people with hepatitis C who had the lowest glutathione levels also had the highest *viral loads* and more evidence of liver damage.<sup>6</sup> Although no research has been done with the hepatitis C virus (*HCV*), glutathione has been shown to inhibit HIV in the test tube.<sup>7</sup> While this research does not prove that raising glutathione levels leads to lower viral loads, it does indicate that optimal levels of glutathione may be an important factor in controlling HCV infection.

## Limiting Exposure to Liver-Damaging Substances and Situations

People with HCV should avoid exposure to anything that may cause damage to the liver. Following are examples of substances that may place stress upon and possibly damage the liver.

### ALCOHOL

*Alcohol* consumption is a significant risk factor for liver cirrhosis. Chronic alcohol drinkers who do not have HCV are actually at a higher risk of developing cirrhosis than those who do have hepatitis C but do not drink.<sup>8</sup> Among people with HCV, the risk of developing cirrhosis is about 16 times higher in drinkers than in those who do not drink alcohol. It is important to remember that one study has shown, low levels of drinking (less than six ounces per week) are related to higher HCV viral loads and increased liver fibrosis.<sup>9</sup> National consensus conferences of doctors and scientists in France and the United States have recommended that people with hepatitis C refrain from drinking any alcohol.<sup>10</sup>

**Alcohol consumption is a significant risk factor for liver cirrhosis.**

The breakdown products of alcohol have direct *toxic* effects on liver cells and cause *inflammation*, which can also damage the liver. In addition, alcohol damages the liver by depleting it of glutathione. Even people who have HCV without *symptoms* and only mild elevations in *liver enzymes* can have liver damage that may be worsened by loss of glutathione from alcohol use. For more information on this topic see *Chapter 2, Alcohol and Hepatitis C*.

### ACETAMINOPHEN

The over-the-counter medicine *acetaminophen* (APAP, Tylenol®) can deplete the liver of glutathione.<sup>11</sup> Because glutathione levels may already be low in people with HCV, risking even lower levels with long-term acetaminophen use may be unwise. Use of acetaminophen for a headache every now and then will not affect liver glutathione levels. But frequent or daily use of this medicine may deplete glutathione stores.

Acetaminophen is the active ingredient in many over-the-counter pain relievers. It is also found in many cold remedies and prescription pain medications. If you need a pain reliever, ask your healthcare provider about alternatives to acetaminophen that provide similar pain relief. Naturopathic doctors prescribe botanical medicines for pain relief such as food extracts and herbs. Examples include Bromelain (an enzyme extracted from pineapples), *Picrorhiza kurroa* extract, *Boswellia serrata* extract, *Curcuma longa* (a turmeric root extract), and *Salix alba* (white willow bark).

### TOBACCO AND RECREATIONAL DRUGS

The liver breaks down all the toxic and *carcinogenic* compounds found in tobacco, marijuana, and other recreational drugs. Tobacco smoke contains more than 4,000 different chemicals, and marijuana contains many of the same carcinogenic compounds.

Research data clearly show that daily marijuana smoking significantly increases the risk of hepatitis C disease progression.<sup>12-14</sup> A recent study found that daily marijuana use was associated with a significantly higher rate of fat in the liver (*steatosis*),<sup>15</sup> which has been linked to more rapid disease progression in chronic hepatitis C. Similarly, higher levels of liver damage have been reported in association with cigarette smoking.<sup>16,17</sup> Both tobacco and marijuana use increase the risk of *liver cancer* for people infected with HCV.<sup>14,18-20</sup>

**Daily marijuana use is strongly associated with moderate to severe fibrosis.**

In general, recreational drugs and tobacco products should be avoided as they may damage your overall health and your liver health. If you are having difficulty with pain or loss of appetite, talk with your healthcare provider about alternatives to marijuana use to control these symptoms.

### OCCUPATIONAL EXPOSURES

Exposure to *pesticides*, *herbicides*, and other chemicals can cause liver damage and elevation of liver enzymes.<sup>21-23</sup> If your job exposes you to chemicals, solvents, fumes, pesticides, or herbicides, it is very important that you use *OSHA*-approved protective gear to prevent breathing the fumes or having physical contact with these chemicals. This includes exposure to paint and lacquer, solvents such as dry cleaning fluid, glues and epoxy, fabric coatings, and many others. If you have a history of chemical exposure and are concerned about the effects on your liver, there are proven ways to reduce the burden of these toxic compounds on your body. Elimination of these toxic compounds requires the supervision of a trained doctor. Naturopathic doctors and medical doctors trained in environmental medicine can supervise programs designed to eliminate these substances from the body. The [Encyclopedia of Natural Medicine](#) was written by licensed naturopathic doctors and is a good resource for information about naturopathic support for detoxification.<sup>24</sup>

## Diet and Hepatitis C

### SUGAR

One of the basic concepts of a naturopathic diet is the inclusion of only minimal amounts of processed foods and simple sugars (sucrose, glucose, corn syrup, etc.). This recommendation is based on research that examined the effect of large amounts of simple sugars on the immune system. In the study, eating 2.5 to 3.5 ounces of white sugar, honey, or fruit juice appeared to reduce the ability of specific *white blood cells* to attack foreign viruses and bacteria.<sup>26</sup> This immune suppressing effect started 30 minutes after eating and lasted for five hours afterward. Since the average American consumes over six ounces of sugar daily, the potential effect on the immune system is considerable.

The immune system is an important factor in hepatitis C. We know that those who clear HCV appear to have *lymphocytes* (white blood cells) that are better able to kill the virus than those who become chronically infected.<sup>27</sup>

### DIETARY FAT

A study that examined how dietary fat, *carbohydrate*, and protein levels affect liver disease progression found that a high fat diet coupled with low protein and carbohydrate intake increased the risk of progression to cirrhosis.<sup>28</sup> People who are overweight or obese tend to have more fat in their diet, which may lead to *steatosis* (fat in the liver cells). *Steatosis* can accelerate the progression of liver disease in people with chronic hepatitis C.<sup>29</sup> For more information on *steatosis* see [Chapter 4.1, Understanding Hepatitis C Disease – Liver Disease Progression](#).

As explained in [Chapter 15, Nutrition and Hepatitis C](#), not all fats are bad. Some types of fat actually appear to be beneficial for people with hepatitis C.

- Omega-3 fatty acids actually have helpful immune regulating effects and should always be included in a nutritional plan for optimizing the immune system.

- Studies of *phosphatidylcholine*, a type of fat found in fish and soybeans, showed it has a beneficial effect in reducing liver enzymes and increasing the response rate to *interferon*.<sup>30</sup> People who were given polyunsaturated phosphatidylcholine (1.8 grams/day) during treatment with interferon and for six months following treatment had significantly fewer *relapses* than those who did not take the fat supplement. Forty-one percent of the patients in the phosphatidylcholine group had a *sustained response* compared to 15% who received only interferon. Different forms of phosphatidylcholine have been used in hepatitis resulting from alcoholism, and have been effective in decreasing fibrosis.<sup>31</sup>

For a thorough discussion of the fundamentals of a naturopathic approach to eating a healthy diet, see *Chapter 15, Nutrition and Hepatitis C*.

## COFFEE

Studies on the consumption of coffee and its effects on liver disease have arrived at mixed conclusions over the years. However, recent studies have reported beneficial effects of filtered coffee on abnormal liver biochemistry, cirrhosis, and *hepatocellular carcinoma*.<sup>32-35</sup> The reason for this effect remains unclear, as does the amount of coffee consumed daily to achieve these benefits.

Research indicates that the effects of unfiltered coffee may be different from filtered coffee.<sup>32</sup> This difference may be due to the fact that there are other substances in unfiltered coffee that have been shown to increase liver enzyme levels in healthy people. Research has been conducted on two compounds found in coffee beans: cafestol and kahweol (called diterpenes). One study found these compounds increased ALT levels by 80% in 46 healthy subjects who were drinking 5 to 6 cups of strong, French press (unfiltered) coffee daily.<sup>36</sup> ALT levels dropped to 45% above normal 24 weeks after the study participants stopped drinking unfiltered coffee. Other studies have shown that cafestol and kahweol raise blood *cholesterol*, *triglyceride*, and low-density *lipoprotein* (a harmful fat) levels, and increase other risk factors for heart disease.<sup>37</sup> However, separate laboratory research indicates these same two compounds (cafestol and kahweol) may have protective effects with regard to the development of liver cancer.<sup>38, 39</sup>

In summary, the effects of coffee and its many components on the human body remain the focus of much clinical and laboratory research. The fact that coffee contains many different chemicals and that what may be present changes depending on how the coffee is prepared surely complicates this research. In addition, health considerations must always take into account the effects on all the body's organ systems, not just a single effect on a single organ system. Overall, people living with hepatitis C are best advised to err on the side of caution. So with respect to coffee, especially because the sum total of its effects remain unclear at this time, it may be safest to avoid coffee if possible. If you are a coffee drinker, filtered coffee is a better option than unfiltered. Filtering coffee eliminates both cafestol and kahweol. Water-processed, decaffeinated, filtered coffee decreases the potentially harmful effects coffee may have.<sup>40</sup>

## Nutritional Supplementation

A nutritious diet, nutritional supplementation, and botanical medicines are the foundations of the naturopathic approach to managing chronic hepatitis C. The nutritional supplements listed in *Chapter 16, Nutritional Supplementation* are mostly antioxidants. They work to decrease liver inflammation and raise glutathione levels. Glutathione is an important antioxidant and immune system regulator. The supplements listed in *Chapter 16, Nutritional Supplementation* are meant to be taken together as a total *protocol*, not as substitutes for each other or as choices that can be taken individually. As stated in *Chapter 15, Nutrition and Hepatitis C*, neither diet alone nor supplements alone are enough to help the body effectively manage chronic hepatitis C.

## Drug-Herb Interactions

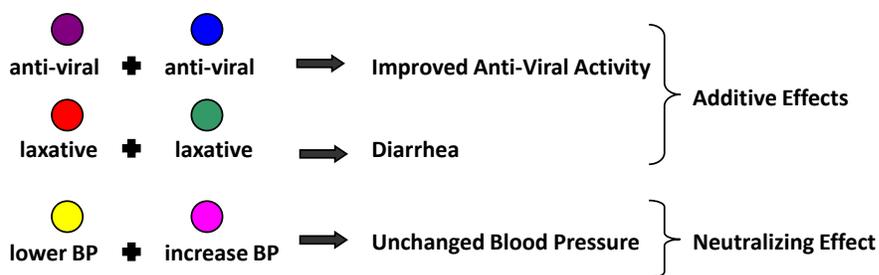
Most active substances in medicines and botanicals are processed (metabolized) by either the liver or the kidneys. It is important to realize that whenever you are taking more than one medication or botanical, there is a potential for interaction between the active ingredients. The potential for interactions applies to all medications (prescription drugs and over-the-counter formulations) and all botanicals (supplied by a healthcare practitioner or purchased over-the-counter).

For the purposes of this discussion, all prescription medications, over-the-counter remedies, individual herbs, and botanical preparations are considered and will be referred to as “drugs.”

Drug-herb interactions fall into four categories:

- altered absorption  
Drugs taken by mouth must be absorbed into the blood through the stomach and intestines. Two or more substances taken together can affect absorption in several different ways. Drugs taken together may bind to one another and decrease the overall absorption of both substances. Substances that affect the acidity in the stomach can also alter the absorption of other drugs. Any drug that has a laxative effect may decrease the absorption of other drugs taken by mouth. The important concept to understand is that two or more substances taken together may alter the amounts of active ingredients absorbed by the body.
- altered *renal* (kidney) elimination  
Some drugs are eliminated from the body primarily by the kidneys. They are excreted in the urine. When two or more medicinal substances that are eliminated by the kidneys are taken at the same time, the kidneys may be overwhelmed. Toxic amounts of one or more substances may build up in the bloodstream, especially if there is underlying kidney damage or if one of the drugs decreases normal kidney function.
- additive effects or toxicities  
Medicinal substances often have similar effects on the body. Some of these effects are beneficial, but others are toxic. Two medicinal substances that interact with one another in a similar way are said to have pharmacodynamic interactions. These interactions can be additive or neutralizing (see Figure 1). For example, *ribavirin* and certain anti-HIV medicines can cause *anemia*. When ribavirin is given along with one of these anti-HIV medications, anemia is more likely to occur than when either drug is given alone. Herbs and drugs can also have pharmacodynamic interactions. Even when two medicinal substances have the same beneficial action individually, combining the two may be detrimental. For example, a mild laxative may be helpful if you are having trouble moving your bowels. But combining a mild laxative with an herb that also has a laxative effect may cause diarrhea. Two medicinal substances with opposite actions may cancel out the effectiveness of one another. Many drug-herb interactions fall in this category.

Figure 1. Pharmacodynamic Interactions



- altered *hepatic* (liver) *metabolism*  
Some of the most complicated drug interactions and potentially serious drug-herb interactions for people with chronic hepatitis C are those involving altered liver metabolism. Much of the processing of medicinal substances in the liver is done by a group of enzymes called the cytochrome P-450 system. The activity of these liver enzymes that break down medicinal ingredients can be increased or decreased by drugs and herbs. When the activity of cytochrome P-450 enzymes is increased, drugs are broken down more quickly than expected. Circulating blood levels may be too low to bring about the desired effects. Conversely, when cytochrome P-450 activity is decreased, drugs may not be eliminated from the body as quickly as expected. Toxic levels of drugs may build up.

The effects of medicinal substances on liver metabolism are further complicated by the fact that a substance may increase the activity of some P-450 enzymes while decreasing the activity of others. The reactions of people with underlying liver disease such as chronic hepatitis C to substances metabolized by the liver are also somewhat unpredictable. A drug that is well tolerated by one person may cause serious problems in another person despite the fact that they appear to have similar *stages* of disease.

In summary, the potential for drug-herb interactions in people with liver disease is complex and often unpredictable. Substances with very different uses may well be processed by the same liver enzymes and interact in potentially serious, undesired ways. For example, you may not think there is any potential for interaction between an herb used to improve mood and a blood thinner since they have such different actions in the body. However, substances with these actions have been known to interact and cause very serious problems. (See the section on St. John's wort later in this chapter for additional information).

**Keep all of your healthcare providers informed about all medicines, herbs, and supplements you are taking!**

The potential for undesired and serious interactions is the reason you must keep all of your healthcare providers informed about all medicines, botanicals, and supplements you are taking. People with chronic hepatitis C should always be cautious about taking any medicinal substances. Always check with a healthcare provider before taking anything new. Also keep in mind that many over-the-counter formulas marketed to people with hepatitis C contain several different herbs. Keeping your providers informed about all of the prescription and over-the-counter substances you are taking is one of the most important responsibilities you have in your healthcare.

**Never take any medicinal product if you are uncertain about what it contains.**

Now that you have been cautioned about taking and combining medicinal substances (including herbs), we can discuss some of the potential benefits of botanicals for people with chronic hepatitis C.

## Botanicals Used to Treat Hepatitis C Liver Problems

### SILYBUM MARIANUM (MILK THISTLE)

*Silybum marianum* (milk thistle) has been used medicinally in Europe since the 13th century to treat liver-related diseases. It is available in Germany in both injectable and oral forms.<sup>41</sup>

Milk thistle is commonly used by people with liver disease. A 1999 survey evaluating the use of *complementary and alternative medicine* (CAM) among hepatitis C patients in liver clinics found that 42-73% of all patients who used other alternative therapies were also taking milk thistle. All participants who used only herbs to treat their liver disease (63%) identified milk thistle as one of the herbs taken.<sup>42</sup>

The active ingredients in milk thistle are contained in the extract silymarin. Silymarin is a mixture of active plant materials that includes silybinin, a plant compound known as a *flavonoid*. Although silybinin has not been shown to have any antiviral activity against HCV, some flavonoids do have antiviral properties.

Silymarin has specific effects on liver cells that have been seen in laboratory animal studies. Silymarin appears to stabilize or strengthen liver cells' ability to withstand the effects of substances that are toxic to the liver including recreational drugs, some medications, poisonous mushrooms, and chemicals. It prevents the damage that occurs when free radicals attack the fatty layer of liver cell membranes.<sup>43</sup> Silymarin also appears to inhibit the process of inflammation of liver cells that eventually leads to cirrhosis.<sup>44</sup> Silymarin increases glutathione levels in the liver. Some studies of hepatitis C patients have found abnormally low levels of glutathione.<sup>45,46</sup>

A 2005 review of the published research on the effects of milk thistle for alcoholic and/or hepatitis B or C liver diseases concluded that:

Milk thistle does not seem to significantly influence the course of patients with alcoholic and/or hepatitis B or C liver diseases. Milk thistle could potentially affect liver injury. Adequately conducted randomized clinical trials on milk thistle versus *placebo* may be needed.<sup>47</sup>

While there are no published studies on the effects of silymarin among large populations of hepatitis C patients, there have been several studies on the effects of silymarin among people with liver disease. In people with *acute hepatitis* (both A and B), silymarin was found to decrease the number of complications, speed recovery time, and improve *liver function test* scores.<sup>48</sup> In chronic liver disease (both alcoholic and chronic hepatitis), silymarin has been shown to decrease symptoms of *fatigue* and abdominal pain, and to significantly decrease liver enzyme levels.<sup>49</sup> Silymarin has also been shown to improve the survival rates of people with cirrhosis. Those with histories of alcohol-related liver damage fared better than those who had cirrhosis from drug use.<sup>50</sup> These studies were done prior to widespread testing for hepatitis C, so it is not known how many of the people in these studies were actually infected with HCV.

Not all studies with silymarin have shown a clear benefit in liver disease. A study of 125 patients with alcoholic cirrhosis who took 450 mg of silymarin per day for two years did not find any improvement associated with silymarin use.<sup>51</sup> Whether these results were influenced by the effects of alcohol abuse is not known.

A study on the effects of silymarin and liver damage in baboons found silymarin was effective in preventing fibrosis in alcohol-related liver damage.<sup>52</sup> The animals were given both alcohol and silymarin along with a nutritionally adequate diet for 3 years. The average dose of silymarin given to the baboons was the equivalent of 2,800 mg per day for a 150-pound person. This is significantly higher than the doses of silymarin used in previous human studies. The study found silymarin prevented fat accumulation in the liver and significantly decreased free-radical related damage to the liver, both of which can occur in people with chronic hepatitis C. This study does not mean taking silymarin will protect you from the damaging effects of alcohol. Only 2 of the 6 baboons getting alcohol and silymarin escaped liver damage. The point of this study is that the positive effects from silymarin were achieved at a dosage much higher than what has been used in human studies with silymarin to date. This dosage level does not appear to be harmful in animals or humans, although, diarrhea may result from increased bile secretion.

Researchers have also looked at using silymarin instead of standard treatment with interferon/ribavirin in hepatitis C. At doses of 420 to 1,260 mg per day, those on silymarin had no improvements in their liver enzymes or viral load.<sup>53</sup> Although higher doses of silymarin were used (1,260 mg) in seven patients, it is not clear how long each patient was actually taking the silymarin; the total time patients were on any dose of silymarin was somewhere between 7 to 29 weeks. Whether this is enough time for an effect to be seen is not clear.

Silymarin therapy has also been compared to a combination of ribavirin and two other drugs: ursodeoxycholic acid and amantidine, in order to see which therapy would be more effective in normalizing liver enzymes.<sup>54</sup> The group that received the drugs had a much higher chance of normalizing their liver enzymes: 58% of them had normal liver enzymes by the end of 24 weeks while only 15% those in the silymarin group had normal liver enzymes.

Another form of silymarin called silipide or silybin-phosphatidylcholine has also been studied. This form is more easily absorbed than other forms of silymarin. In a small study with eight patients (five had hepatitis C), liver function tests and markers that reflect cell damage in the liver were significantly improved in patients who had been taking the equivalent of 120 mg of silybin twice daily between meals for two months.<sup>55</sup>

Milk thistle is available over-the-counter in standardized extracts that contain 70% silymarin. The active ingredients of milk thistle are not water-soluble. Therefore, a tea made from milk thistle seeds is not useful. If the label for milk thistle does not list the silymarin content, there is no guarantee there is any silymarin in it. Standard dosages used in studies range from 400-1,140 mg per day of the standardized extract. The common dosage for active liver disease is 200 mg of standardized extract (containing 70% silymarin) taken three times daily. Silipide (the phosphatidylcholine form) is commonly dosed at 100 mg taken three times daily.

Silymarin is safe and has no known *toxicity*, though doses over 1,500 mg per day may cause diarrhea because of increased *bile* secretion. Silymarin is safe to use in pregnancy and while breast feeding.<sup>56</sup> Silymarin has been shown to alter the activity of some P-450 enzymes. Although there have been no studies to determine if taking silymarin along with ribavirin and interferon alters the levels of these drugs in the body, that possibility does exist.

### **GLYCYRRHIZA GLABRA (LICORICE ROOT)**

*Glycyrrhiza glabra* (licorice root) preparations have been used for over 20 years in Japan to treat both hepatitis B and C.<sup>57</sup> Glycyrrhizin, an extract made from the *Glycyrrhiza glabra* plant, is used as an intravenous injection on a daily basis for eight weeks. The preparation can be given at that frequency or reduced to several times a week, and can be continued for as long as 16 years.

A study of 193 hepatitis C patients being treated with intravenous glycyrrhizin for 2 to 16 years showed decreased risk of developing cirrhosis. Those on treatment were about half as likely to develop cirrhosis (21% compared with 37%).<sup>57</sup> The rate of liver cancer was also less than half in those who were treated compared to those who were untreated. Twelve percent of the treated patients and 25% of the untreated patients developed liver cancer. German studies with intravenous glycyrrhizin showed that, when given daily, glycyrrhizin was as effective an antiviral agent as interferon alone without ribavirin.<sup>58</sup>

The intravenous form of glycyrrhizin is not readily available in the United States, but the oral form is easily available over-the-counter. The effectiveness of the oral formulation of glycyrrhizin against hepatitis B was studied in China. Significant numbers of patients who had taken 7.5 grams of licorice root (concentrated to 750 mg licorice root extract) twice daily for 30 days experienced a normalization of liver enzyme levels. Twenty-five percent of the patients fully recovered from hepatitis B, while no one in the control group recovered.<sup>59</sup> Again, it is important to remember that hepatitis B and hepatitis C are caused by two different classes of viruses, so it is difficult to say whether licorice root has any effect on the hepatitis C virus.

Licorice root does have a potentially problematic side effect. A breakdown product of glycyrrhizin alters the production of the hormone aldosterone. This can cause increased blood pressure, water retention, and a reduction in blood *potassium*. The injectable form of glycyrrhizin has two amino acids (glycine and cysteine) added to prevent this side effect, but pure licorice root does not. If you are taking doses higher than 400 mg of glycyrrhizin daily, have your blood pressure monitored regularly. If you have a history of high blood pressure and/or have kidney failure, you should avoid taking licorice root.

### **OTHER BOTANICAL MEDICINES**

Catechin is an extract of the *Unicaria* (cat's claw) plant that has been researched extensively in England for its ability to improve liver function in people with hepatitis B.<sup>60</sup> Although study results were positive, the research on catechin was discontinued in the late 1980's because the use of the synthetic form of catechin resulted in a serious form of anemia in six patients.<sup>61</sup>

Recently, research in Africa has identified similar plant compounds in the *Garcinia* species that have antiviral activity and are used by native people to treat hepatitis.<sup>62</sup> The active compound is a flavinoid (a vitamin-like compound in many plants, fruits, and vegetables) and will continue to be the subject of research in treating both hepatitis B and C.<sup>63</sup> Other plant medicines used by native people in areas where hepatitis is common, such as those from the *Phyllanthus amarus* plant, have been shown to have direct antiviral effects on the hepatitis B virus.<sup>64</sup> *Picrorhiza kurroa* also has activity against hepatitis B, though neither of these plants have been tested specifically with hepatitis C.<sup>65</sup>

## **Botanicals Used to Treat Extrahepatic Hepatitis C Problems**

The serious effects of HCV on the liver are well known. HCV also has serious effects on other parts of the body. The fatigue, *depression*, and lack of energy reported by hepatitis C patients may be related to an effect of HCV on the central nervous system.<sup>66</sup> In one study, researchers found problems with memory and concentration were not necessarily due to a history of intravenous drug use, depression, or fatigue, but were more closely related to HCV infection and some

changes in brain function that were measured by a brain scan. A recent study found similar problems with higher brain function in 32 people with chronic hepatitis C.<sup>67</sup> These studies bring to light a possible cause of what hepatitis C patients have long described as “brain fog.” The changes seen in the brain scans were similar to changes seen in the brains of people with HIV infection. Although the way that HIV can damage the brain is still being studied, one of the mechanisms seems to involve the immune system found in the brain. When immune cells in the brain are stimulated by HIV infection, they produce free radicals that damage brain cells.<sup>68</sup> Treating the HIV-infected brain cells with *vitamin E* stopped damage and death in the affected brain cells.

Symptoms of forgetfulness and brain fog are common complaints of people with hepatitis C. Research data showing that changes can be seen in the brain tissue of people with hepatitis C is evidence that HCV infection has an effect on brain tissue. Although we do not know if these changes occur in the same way as HIV-induced brain cell damage, we do know that free radical damage is a factor in many brain diseases such as Parkinson’s disease,<sup>69</sup> Alzheimer’s dementia,<sup>70</sup> and many others. While it is reasonable for a person with HCV to take antioxidants for liver health, there are antioxidants that have been tested specifically for treating damage to brain cells and the symptoms of memory loss and lack of attention that result.

### GINGKO BILOBA

*Ginkgo biloba* extract has been shown to protect brain cells from damage due to aging and oxidative stress. Over 250 research studies have been published on ginkgo and brain function. *Ginkgo biloba* extract has been shown to be effective at improving blood supply to the brain. It also has a beneficial effect on attention span and brain function in elderly patients, resulting in significant improvements in memory, alertness, and mood.<sup>71</sup> Studies in those with Alzheimer’s dementia have shown beneficial effects on alertness, concentration, and memory.<sup>72</sup> When *Ginkgo biloba* extract was compared to four medications called cholinesterase-inhibitors that are used to treat mild to moderate dementia from Alzheimer’s disease, ginkgo was as effective as all four drugs with very few side effects.<sup>73</sup>

Depression is another common symptom of hepatitis C, even among people who are not being treated with western drug therapy (see *Chapter 5, Signs and Symptoms That May be Associated with Hepatitis C*). In one study, 28% of people being seen in a clinic for hepatitis C were diagnosed with depression.<sup>74</sup> *Ginkgo biloba* has been studied by one research group among older adults who had not responded to standard antidepressants.<sup>75</sup> The group that stayed on antidepressant medication without ginkgo experienced little improvement in their depression. However the group that took antidepressant medication plus ginkgo experienced significant improvement.

Ginkgo is an approved prescription drug in Europe, and has been proven safe and *nontoxic*.<sup>76</sup> All the published studies with ginkgo used an extract that contains 24% ginkgo heterosides. The extract was given in doses of 40-80 mg three times daily. A few case reports have been published in the medical literature of people who were diagnosed with bleeding in the brain who were also using high amounts (up to 1,200 mg per day) of ginkgo. It is not clear if the ginkgo was related to the bleeding. There are no *contraindications* (situations in which it should not be used) to ginkgo use stated by the German Commission E (a group that studies the uses and safety of herbs and nutritional supplements) if it is taken in prescribed doses of 120-240 mg per day.

### HYPERICUM PERFOATUM (ST. JOHN’S WORT)

St. John’s wort (*Hypericum perfoatum*) is a plant product that has been studied for its antidepressant action. A 2007 review published research studies on the use of herbal medicines to treat psychiatric disorders concluded that there is high-quality data to support the use of St. John’s wort for depression.<sup>77</sup> An earlier review of 27 human studies also indicated St. John’s wort is effective for mild to moderate depression. The St. John’s wort in these studies was given as a 0.2% hypericin-based preparation (one of the active ingredients).<sup>78</sup> The studies examined St. John’s wort alone and in comparison to the popular antidepressants fluoxetine (Prozac®) and imipramine (Tofranil®). The authors concluded that the studies clearly demonstrated St. John’s wort was equally effective with significantly fewer side effects than the standard antidepressants. However, it was also clear that St. John’s wort is not effective for severe depression. Prescription drugs work better for severe depression.

Harmful side effects have been reported from use of St. John's wort, although they appear to be uncommon. Over eight million people were given prescriptions for St. John's wort in Germany from 1990 to 2000. In this time period, 70 people complained of negative side effects including allergic reactions, stomach complaints, rashes after sunlight exposure, breakthrough bleeding on birth control pills, prolonged *prothrombin* (clotting) *time*, and interactions with the drug cyclosporin (given to organ transplant recipients).<sup>79</sup>

St. John's wort has been shown to affect the speed at which the liver breaks down certain drugs. This may lower levels of certain drugs in the bloodstream. Following is a list of drugs that are known to interact with St. John's wort. If you are taking any of these drugs, it is very important to talk with your healthcare provider before taking St. John's wort.

<p><b>Drugs That Interact with St. John's wort</b> prescription antidepressants oral contraceptives anticoagulants (Coumadin) theophylline indinavir digoxin cyclosporin</p>
--

## Reasons for Using Naturopathic Medicine and Who May Benefit

Naturopathic treatment options may benefit those who are motivated to adopt the following healthy lifestyle practices including:

- a nutritious diet low in sugar, red meat, and processed foods
- avoidance of smoking, alcohol, and recreational drugs
- regular exercise
- stress management

While these practices are helpful with any therapeutic approach, they are vital to the success of naturopathic treatment. If you choose a naturopathic approach, you need to be willing to take nutritional supplements and botanicals such as those mentioned in this chapter and in the chapter on nutritional supplementation (*Chapter 16, Nutritional Supplementation*), or those prescribed by your naturopathic doctor. You must also be willing to eat a healthy diet (see *Chapter 15, Nutrition and Hepatitis C*).

If cost is a concern, you need to be aware that most health insurance policies do not cover nutritional supplements and botanicals.

### **Helen: A Person for Whom the Naturopathic Approach was Appropriate**

Helen had been diagnosed with hepatitis C six years prior to coming to our office. She had no idea how she had been infected, and had not experienced any symptoms that she knew were related to hepatitis C. Although her viral load was low and her *liver biopsy* showed only mild inflammation, her gastroenterologist encouraged her to start *interferon-based treatment*.

Helen was resistant to interferon-based treatment because she was a single mother of three children, had a demanding job, and was supporting an ailing mother. She was afraid the potential side effects of treatment could make it hard for her to keep up with her responsibilities. She worried about being able to care for her children and provide financial support for her mother. Helen did not have a strong support system of friends and family who could step in and take care of her children if treatment made her tired or depressed.

Helen was willing to change her diet and she had given up alcohol when she was first diagnosed. She was also willing to find time to exercise with her children. She committed to taking the antioxidant protocol and botanicals. Her gastroenterologist agreed to follow her liver enzymes and repeat the liver biopsy to see if any improvement had occurred. Helen was relieved that she could do something other than watch and wait, and that the treatment approach she was taking fit into her belief system.

Her liver enzymes normalized and Helen had a repeat liver biopsy three years later. The biopsy showed that the level of inflammation had normalized to that of someone without hepatitis. Her *hepatologist* agreed that standard interferon-based treatment was not necessary for Helen as long as her laboratory tests remained normal and she continued to get liver biopsies every five years.

## Reasons For Not Using Naturopathic Medicine

The appropriate treatment for people with end-stage liver failure is western medical care including possible liver transplantation. Alternative medicine, including naturopathic medicine, cannot effectively treat end-stage liver failure. Without a firm commitment to the necessary lifestyle changes, you probably will not benefit from a naturopathic approach. From the naturopathic perspective, it is difficult for the liver to heal when it is under siege from tobacco smoke, alcohol, recreational drugs, and/or the chemicals found in processed foods. For naturopathic treatment to work, you need to be willing to “clear the way” before you can expect any changes from of a naturopathic treatment protocol.

### **Robert: A Person for Whom the Naturopathic Approach Alone Was Not Appropriate**

Robert is a 43-year-old lawyer who contracted hepatitis C during a brief period of intravenous drug use when he was in his twenties. He was diagnosed when a yearly physical showed his liver enzymes were elevated 10-15 times above the normal level. His viral load was high and his liver biopsy revealed cirrhosis.

Robert had not experienced symptoms other than some intestinal bloating and a little fatigue after work. He blamed these symptoms on his heavy work schedule, eating on the run, and the stress of his demanding job. Robert was interested in treating his hepatitis C, but wanted to use an alternative approach. He wanted to take an herbal pill that would “get rid of the virus once and for all without the side effects that the drugs have.” He wanted to continue working full time. He also drank alcohol often and smoked a pack of cigarettes per day.

Robert was quite willing to take supplements and antioxidants, but when it came to lifestyle changes, he was not so sure. He did not want to make any drastic changes, though he was willing to cut down on his alcohol and nicotine use and “maybe start eating a little better.” However, he was not willing to give up anything altogether. He was aware that he was not dealing with stress very well. He had high blood pressure and daily tension headaches. He did not have time to exercise or do anything that would take him away from his work. Robert was also seeing a gastroenterologist who had warned him that his condition was serious and he needed treatment, but Robert wanted an “easier” route to recovery.

It was suggested to Robert that he pursue western antiviral therapy in addition to a naturopathic approach for several reasons. It was crucial that Robert quit drinking and his naturopathic doctor knew that. She also knew that Robert would not be able to get western treatment if he continued to drink. She hoped that with the support of Robert’s gastroenterologist, they could convince Robert to stop using alcohol and begin treatment.

Robert’s situation was dangerous. He had significantly elevated liver enzymes and cirrhosis. He was at risk for advanced hepatitis C including the possibilities of liver transplant and/or liver cancer. Robert did not have a lot of time to waste, so a combined approach was probably the best approach for him. This would have allowed him to use supplements and some botanicals to help his liver while undergoing western treatment for the hepatitis C. With a combined treatment approach, he could have a positive response to treatment.

After a serious talk with his gastroenterologist and his naturopathic provider, who both urged him to consider interferon-based treatment to stop the progression of his cirrhosis and possibly save his life, Robert agreed that he needed to do something more serious than take a botanical. He started going to AA meetings with a friend who had stopped drinking and was able to stay sober for 6 months. Robert then started interferon and ribavirin along with antioxidants and botanical medicines that would not interfere with the effects of interferon. He was also able to quit smoking with the aid of an acupuncturist and changed his diet, cutting out red meat and fast food.

Robert continued to receive acupuncture for the duration of his treatment. He was encouraged when his doctor told him his viral load was undetectable just 12 weeks after starting treatment. Although Robert was not able to work full-time during treatment, he was able to work part-time for the duration of treatment.

Six months after treatment was completed, Robert was still virus negative and decided that his 60-hour work schedule was a thing of the past, and that he would continue to stay sober one day at a time.

## Summary

Naturopathic medicine offers people with HCV another tool in their efforts to manage their disease. Many people infected with HCV who include naturopathic medicine in their treatment protocol use it primarily as a way to enhance the body's ability to heal itself. Many feel that by doing this, they can keep the virus under control until more is known about it and better treatment options are available. Other people infected with HCV use naturopathic medicine as their primary care option. If and how naturopathic care fits into your treatment protocol is up to you

If naturopathic care is something you are interested in, it is important that you find out as much as you can about it. Many books and Internet sites are available that can help you better understand what naturopathic medicine has to offer. Some of these are listed in the *Resource Directory*.

## References

1. Pizzorno J. *Total Wellness*. Rocklin, California: Prima Communications; 1996.
2. Droge W, Pottmeyer-Gerber C, et al. Glutathione augments the activation of cytotoxic T lymphocytes *in vivo*. *Immunobiology*. 1986;172(2):151-156.
3. White AC, et al. Glutathione deficiency in human disease. *J Nutr Biochem*. 1994;5:218-226.
4. Burgunder JM, Lauterburg BH. Decreased production of glutathione in patients with cirrhosis. *Eur J Clin Invest*. 1987;17:408-414.
5. Loguercio C, Blanco FD, De Girolamo V. Ethanol consumption, amino acid and glutathione blood levels in patients with and without chronic liver disease. *Alcohol Clin Exp Res*. 1999;23(11):1780-1784.
6. Barbaro G, Di Lorenzo G, Soldini M. Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. *Am J Gastroenterol*. 1996;91(12):2569-2573.
7. Staal FJ, Roederer M, Anderson MT, et al. Glutathione deficiency and human immunodeficiency virus infection. *Lancet*. 1992;339:909-912.
8. Alter H, Seef L. Recovery, persistence and sequelae in hepatitis C infection: a perspective on long-term outcome. *Sem Liver Disease*. 2000;20(1):17-35.
9. Pessione F, Degos F, Marcellin P. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology*. 1998;27(6):1717-1722.
10. Dienstag JL. Management of hepatitis C: a consensus. *Gastroenterology*. 1997;113(2):375.
11. McClain CJ, Price S, et al. Acetaminophen hepatotoxicity: an update. *Curr Gastroenterol Rep*. 1999;1(1):42-49.
12. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis. *Hepatology*. 2005;42(4):975-976.
13. Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, Terrault NA. Influence of cannabis use on severity of hepatitis C disease. *Clin Gastroenterol Hepatol*. 2008;6(1):69-75.
14. Mallat A, Hézode C, Lotersztajn S. Environmental factors as disease accelerators during chronic hepatitis C. *J Hepatol*. 2008;48(4):657-665.
15. Hézode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*. 2008;134(2):432-439.
16. Pessione F, Ramond MJ, Njapoum C, et al. Cigarette smoking and hepatic lesions in patients with chronic hepatitis C. *Hepatology*. 2001;34(1):121-125.
17. Hézode C, Lonjon I, Roudot-Thoraval F, et al. Impact of smoking on histological liver lesions in chronic hepatitis C. *Gut*. 2003;52(1):126-129.
18. Mori M, Hara M, Wada I. Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors

- associated with hepatocellular carcinoma risk in Japan. *Am J Epidemiol.* 2000;151(2):131-139.
19. Hara M, Tanaka K, Sakamoto T, et al. Case-control study on cigarette smoking and the risk of hepatocellular carcinoma among Japanese. *Cancer Sci.* 2008;99(1):93-97.
  20. Zhu K, Moriarty C, Caplan LS, Levine RS. Cigarette smoking and primary liver cancer: a population-based case-control study in US men. *Cancer Causes Control.* 2007;18(3):315-321.
  21. Michalek JE, Ketchum NS, Alchatar FZ. Postservice mortality of US Air Force veterans occupationally exposed to herbicides in Vietnam: 15-year follow-up. *Am J Epidemiol.* 1998;148(8):786-792.
  22. Longnecker MP, Rogan WJ, Lucier G. The human health effect of DDT and PCBs and an overview of organochlorines in public health. *Annu Rev Public Health.* 1997;18:211-244.
  23. Redlich CA, Beckett WS, Sparer J, et al. Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Int Med.* 1988;108(5):680-686.
  24. Pizzorno J, Murray M. *Encyclopedia of Natural Medicine.* Rocklin, California: Prima Communications; 1998.
  25. Sanchez A, Reeser J, Lau HS, et al. Role of sugars in human neutrophilic phagocytosis. *Am J Clin Nutr.* 1973;26(11):1180-1184.
  26. Ringsdorf W, Cheraskin E, et al. Sucrose, neutrophil phagocytosis and resistance to disease. *Dent Surv.* 1976;52(12):46-48.
  27. Lirussi F, Sanchez B, et al. Natural killer cells in patients with chronic hepatitis C (CHC). *Gut.* 1998;42 (Supp 1):A32.
  28. Corrao G, Ferrari PA, Galatola G. Exploring the role of diet in modifying the effect of known disease determinants: application to risk factors of liver cirrhosis. *Am J Epidemiol.* 1995;142(11):1136-1146.
  29. Hu KQ, Kyulo NL, Esrailian E, et al. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol.* 2004 Jan;40(1):147-54.
  30. Niederau C, Strohmeyer G, Heintges T, et al. Polyunsaturated phosphatidylcholine and interferon alfa for treatment of chronic hepatitis B and C: a multi-center, randomized, double-blind, placebo-controlled trial. Leich Study Group. *Hepatogastroenterology.* 1998;45(21):797-804.
  31. Lieber CS. Alcoholic liver disease: new insights in pathogenesis lead to new treatments. *J Hepatol.* 2000;32(1 Suppl):113-128.
  32. Cadden IS, Partovi N, Yoshida EM. Review article: possible beneficial effects of coffee on liver disease and function. *Aliment Pharmacol Ther.* 2007;26(1):1-8.
  33. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology.* 2007;132(5):1740-1745.
  34. Bravi F, Bosetti C, Tavani A, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology.* 2007;46(2):430-435.
  35. Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, and transaminase enzymes. *J Hepatol.* 2007;46(5):980-982.
  36. Urgert R, Meyboom S, Kuilman M, et al. Comparison of the effect of cafetiere and filtered coffee on serum concentrations of liver aminotransferases and lipids: six-month randomized controlled trial. *BMJ.* 1996;313(7069):1362-1366.
  37. Urgert R, Schultz AGM, Katan et al. Effects of cafestol and kahweol from coffee grounds on serum lipids and serum liver enzymes in humans. *Am J Clin Nutr.* 1995;61(1):149-154.
  38. Huber WW, Teitel CH, Coles BF, et al. Potential chemoprotective effects of the coffee components kahweol and cafestol palmitates via modification of hepatic N-acetyltransferase and glutathione S-transferase activities. *Environ Mol Mutagen.* 2004;44(4):265-276.
  39. Higgins LG, Cavin C, Itoh K, Yamamoto M, Hayes JD. Induction of cancer chemopreventive enzymes by coffee is mediated by transcription factor Nrf2. Evidence that the coffee-specific diterpenes cafestol and kahweol confer protection against acrolein. *Toxicol Appl Pharmacol.* 2008;226(3):328-337.
  40. Etherton GM, Kochar MS. Coffee. Facts and Controversies. *Arch Fam Med.* 1993;2(3):317-322.
  41. Flora K, Hahn M, Rosen H, et al. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol.* 1998;93(2):139-143.
  42. Strader D, Bacon B, Hoofnagle J, et al. Use of CAM by patients in liver disease clinics. NIH Conference on Complementary and Alternative Medicine in Chronic Liver Disease. Bethesda, Maryland. 1999.
  43. Bosisio E, Benelli C, Pirolo O. Effect of the flavanolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. *Pharmacol Res.* 1992;25:147-154.
  44. Boigk G, Stroeder L, Herbst H, et al. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. *Hepatology.* 1997;26:643-649.
  45. Campos R, Garrido A, Guerra A, et al. Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver. *Planta Med.* 1989;55:417-419.
  46. Bernhard MC, Junker E, Hettlinger A, et al. Time course of total cysteine, glutathione, and homocysteine in plasma of patients with chronic hepatitis C treated with interferon-alfa with and without supplementation with N-acetylcysteine. *J Hepatol.* 1998;28(5):751-755.
  47. Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases--a systematic cochrane hepatobiliary group review with meta-analyses of randomized clinical trials. *Am J Gastroenterol.* 2005 Nov;100(11):2583-91.
  48. Magliulo E, Gagliardi B, Fiori GP. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centres. *Med Klin.* 1978;73(28-29):1060-1065.
  49. Feher J, Deak G, Muzes G, et al. Hepatoprotective activity of silymarin (Legalon) therapy in patients with chronic liver disease. *Orv Hetil.* 1989;130(51):2723-2727.
  50. Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol (Netherlands).* 1989;9(1):105-113.
  51. Pares A, Planas R, Torres M, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blinded, randomized and multi-center trial. *J Hepatol.* 1998;28:615-621.
  52. Lieber CS, Leo MA, Qi C, et al. Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. *J Clin Gastroenterol.* 2003;37:336-339.
  53. Huber R, Futter I, Ludtke R. Oral silymarin for chronic hepatitis C- a retrospective analysis comparing three dose regimens. *Eur J Med Res.* 2005;10:68-70.
  54. El-Zayadi AR, et al. Non-interferon-based therapy: an option for amelioration of necro-inflammation in hepatitis C patients who cannot afford interferon therapy. *Liver Int.* 2005;25:746-751.

55. Moscarella S, Giusti A, Marra F. Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: preliminary results. *Curr Ther Res.* 1993;53:98-102.
56. Alschuler L. Milk thistle: goals and objectives. *Int J Integrative Med.* 1999;1:29-34.
57. Arase Y, Ikeda K, Murashima N, et al. The long-term efficacy of glycyrrhizin in chronic hepatitis C patients. *Cancer.* 1997;79(8):1494-1500.
58. Wildhirt E. Experience in Germany with glycyrrhizic acid for the treatment of chronic viral hepatitis. In: Nishioka K, Suzuki H, Mishiro S. (Eds.). *Viral Hepatitis and Liver Disease.* Springer-Verlag. Tokyo, Japan. 1994:658-661.
59. Xianshi S, Huiming C, et al. Clinical and laboratory observation on the effect of glycyrrhiza in acute and chronic viral hepatitis. *J Tradit Chin Med.* 1984;4:127-132.
60. Susuki H, Yamamoto S, Hirayama C. Cianidanol therapy for HBe-antigen-positive chronic hepatitis :a multicentre, double-blind study. *Liver.* 1986(1);6:35-44.
61. Salama A, Mueller-Eckhardt C. Cianidanol and its metabolites bind tightly to red cells and are responsible for the production of auto- and / or drug-dependant antibodies against these cells. *Br J Haematol.* 1987;66(2):263-266.
62. Iwu M. Dietary botanical supplements with antiviral and anti-inflammatory properties used in the treatment of liver disorders in traditional African medicine. Complementary and Alternative Medicine in Chronic Liver Disease Conference. National Institutes of Health. Bethesda, Maryland. 1999.
63. Ferrea G. In vitro activity of a combretum micranthim extract against herpes simplex virus types 1 and 2. *Antiviral Res.* 1993;21:317-25.
64. Ott M, Thygarajan SP, Gupta S. Phyllanthus amarus suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. *Eur J Clin Invest.* 1997;27(11):908-915.
65. Mehrotra R, Rawat S, Kulshreshta DK, et al. In vitro studies on the effect of certain natural products against hepatitis B virus. *Indian J Med Res.* 1990;92:133-138.
66. Forton, DM, Thomas HC, Murphy CA, Allsop, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology.* 2002;35:433-439.
67. [Neuropsychological function in Greek patients with chronic hepatitis C. Karaivazoglou K, Assimakopoulos K, Thomopoulos K, Theocharis G, et al. *Liver Int.* 2007 Aug;27(6):798-805.]
68. Viviani B, Corsini E, Binaglia M, et al. Reactive oxygen species generated by glia are responsible for neuron death induced by human immunodeficiency virus-glycoprotein 120 in vitro. *Neuroscience.* 2001;107(1):51-58.
69. Fahn S. The endogenous toxin theory of the etiology of Parkinson's disease and a pilot trial of high-dose antioxidants in an attempt to slow the progression of illness. *Ann NY Acad Sci.* 1989;570:186-196.
70. Floyd RA, et al. Neuroinflammatory diseases: an hypothesis to explain the increased formation of reactive oxygen and nitrogen species as major factors involved in neurodegenerative disease development. *Free Rad Biol Med.* 1999;26(9/10):1346-1355.
71. Curtis-Prior P, Vere D, Fray P. Therapeutic value of *Ginkgo biloba* in reducing symptoms of decline in mental function. *J Pharm Pharmacol.* 1999; 51(5):535-41.
72. Ramassamy C, Clostre F, Christen Y, Costentin J. In vivo *Ginkgo biloba* extract (EGb 761) protects against neurotoxic effects induced by MPTP: investigations into its mechanisms of action. In: Christen Y, Costentin J, Lacour M (Eds.). *Effects of Ginkgo biloba extract (EGb 761) on the central nervous system.* Elsevier. Paris, France. 1992:27-36.
73. Wettstein A. Cholinesterase inhibitors and ginkgo extracts: are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months duration. *Phytotherapy.* 2000;6(6):393-401.
74. Dwight MM, Kowdley KV, Russo JE, et al. Depression, fatigue, and functional disability in patients with chronic hepatitis C. *J Psychosom Res.* 2000;49(5):311-317.
75. Schubert H, Halama P. Depressive episode primarily unresponsive to therapy in elderly patients: efficacy of *Ginkgo biloba* extract (EGb 761) in combination with antidepressants. *Geriatr Forsch.* 1993;3:45-53.
76. Gaby A. *Ginkgo biloba* extract: a review. *Altern Med Rev.* 1996;1(4):236-242.
77. Linde K, Ramirez G, Mulrow C, et al. St. John's wort for depression. An overview and meta-analysis of randomized clinical trials. *BMJ.* 1996; 313(7052):253-258.
78. Sarris J. Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother Res.* 2007 Aug;21(8):703-16.
79. Schulz V, Hansel R, Tyler VE. *Rational Phytotherapy: A Physician's Guide to Herbal Medicine.* 4<sup>th</sup> Ed. New York, NY: Springer; 2000.