The Treatment of Liver Disease with Botanical Agents

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DOI 10.14200/jrm.2013.2.0108

ABSTRACT

Traditional herbal medicine has gained increasing attention as alternative therapy for the treatment of liver disease, which has become a global health problem associated with the increased prevalence of harmful chemicals in the environment and the use of pharmaceuticals known to have detrimental effects on liver function as well as alcohol abuse. Herbal derived medicines such as Turmeric *(Curcuma longa),* Guduchi (*Tinospora cordifolia*), Amla (*Emblica officinalis*), Milk Thistle (*Silybum marianum*), Madder (*Rubia tinctorum*), Andrographis (*Andrographis paniculata*), *Bupleurum* and *Azadirachta indica* have shown hepatoprotective and regenerative effects mainly associated with their antioxidant and anti-inflammatory properties, and they have been used as adjunctive or stand alone agents for the treatment of several conditions affecting liver function. *Curcuma longa*, a culinary spice known as Turmeric, and *Bupleurum* have been used in traditional medicine for the treatment of liver disease. The active component of *Curcuma* is the flavonoid curcumin, which has been researched extensively for its beneficial effects on several liver diseases. The active components of *Bupleurum* are the saikosaponins, which have hepatoprotective effects and have shown activity against the hepatitis B virus. The hepatoprotective effects of *Silybum* are thought to be mediated by its constituent flavonolignans, which are commercially available in a crude extract labeled silymarin and a semipurified flavonoid, *Silibinin*. The efficacy of these hepatoprotective herbs is determined by routine testing of liver enzymes including AST, ALT, ALP and bilirubin. Although some side effects have been reported, these have not been validated by clinical studies, and the safety of these supplements has been demonstrated when used at the appropriate doses.

Keywords: Hepatoprotective effect; Liver disease; AST; ALT; Herbal medicine

CLINICAL IMPLICATIONS

Liver disorders are a major global health problem, and factors negatively affecting liver function include pollution, exposure to environmental chemicals, drug use (prescription and non-prescription), and alcohol abuse, as well as hormones and additives tainting the food supply. *Curcuma* (Turmeric)*, Tinospora*, *Emblica, Silybum* (Milk Thistle)*, Rubia, Andrographis*, and other herbal therapeutic agents have been shown to protect the liver from various hepatotoxic substances.[1-6] Many of the hepatoprotective and regenerative benefits of these herbs appear to be due to antioxidant and anti-inflammatory effects.[7-8]

KEY HERBS DISCUSSED

Turmeric *(Curcuma longa),* Guduchi (*Tinospora cordifolia*), Amla (*Emblica officinalis*) Milk Thistle (*Silybum marianum*)*,* Madder (*Rubia tinctorum*), Andrographis (*Andrographis paniculata*), *Bupleurum* and *Azadirachta indica*

PRIMARY INDICATIONS

Elevated liver enzymes, chemical/toxic exposure and chemical sensitivities, conditions affecting liver function, detoxifcation, prevention of toxicity due to specific pharmaceuticals, Gilbert's syndrome, jaundice, and as adjunctive treatment for hepatitis or liver cancer

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CLINICAL IMPLICATIONS (CONTINUED)

ADJUNCTIVE OR STAND-ALONE TREATMENT
Adjunctive or Stand-Alone

DOSE OF BIOACTIVE CONSTITUENTS
Milk Thistle Whole Plant Extract 900 mg daily, containing a minimum of 520 mg of *silymarin daily,* Synergistic Herbal Formula: Milk Thistle (*Silybum)* extract, Guduchi (*Tinospora),* Amla (*Emblica),* Rubia (*Rubia*), Andrographis (*Andrographis*), Yellow Dock (*Rumex),* Oregon Grape Root (*Mahonia*), Burdock (*Arctium*), Schizandra (*Schisandra)*, Globe Artichoke (*Cynara).*

BIOACTIVE CONSTITUENTS
***Silybum*:** Silymarin, Flavonolignans
***Curcuma*:** Curcumin
***Bupleurum* species:** Saikosaponin
***Tinospora*:** Dioterpenes, Arabinogalactan polysaccharides
***Emblica (Phyllanthus)*:** Flavonoids
***Azadirachta indica*:** Flavonoids
***Rubia*:** Rubiadin, Anthocyanins, Anthroquinones
***Andrographis*:** Andrographolide, Bicyclic diterpenoid lactones

CAPSULE DOSE
***Silybum*:** 175-600 mg *per day* (110 mg silymarin)
***Curcuma*:** Up to 8 g *per day* in divided doses for 18 months[1]
***Bupleurum* species:** 400-500 mg *twice per day*
***Tinospora*:** 400-800 mg *twice per day*
***Emblica*:** 400-800 mg *three times per day*
***Azadirachta indica*:** 500-1000 mg *twice per day*
***Rubia*:** 400-500 mg *twice per day*
***Andrographis*:** 400-800 mg *twice per day*

SIDE EFFECTS AND CAUTIONS
To monitor efficacy of these supplements clinicians suggest the following tests to routinely monitor progress. These tests include AST, ALT, ALP, and bilirubin. In high doses, effects can be seen within a week except for *Rubia*. These herbs are safe when used appropriately. *Bupleurum*, Neem and *Andrographis* and standardized *Curcumin* in high doses can cause gastric irritation in people with sensitive stomachs. *Andrographis* in high very doses can cause gastrointestinal distress, and loss of appetite. *Andrographis* should not be taken in pregnancy.

THEORETICAL UNSUBSTANTIATED SIDE EFFECTS
Neem and *Tinospora cordifolia* theoretcially may increase the risk of hypoglycemia. *Bupleurum* theoretically interferes with interferon-alpha. *Silybum* theoretically should be used with caution in patients with gallstones or a bile duct obstruction or in those with stomach ulcers or excess stomach acid or with blood thinners. However, no clinical or scientific evidence has validated any of these concerns.

COMMENTS
Avoiding exposure to known hepatotoxins (*e.g.,* cleaners such as dry-cleaning fluid, alcohol-based cleaners, pesticides, synthetic chemicals and solvents) should be encouraged. Milk Thistle standardized to 80% is actually a misnomer. Milk Thistle extract marketed in the US as 80% *Silymarin* was based on an inaccurate UV test to artificially increase the lab value of *Silymarin*. The true *Silymarin* 80% content actually is reflected by HPLC testing as 53%.

DISCUSSION

Herbal medicine offers a safe and supportive therapeutic option to improve liver function. In this era where humans are environmentally bombarded by harmful chemicals (*e.g.,* in air and food), the use of liver-strengthening herbs may assist the body to process and detoxify the effects of some toxic environmental substances. In addition to environmental toxins, pharmaceuticals can induce liver toxicity; pharmaceutical drugs known to induce hepatotoxic effects include nitrosamine, acetominophen, adriamycin, carbon tetrachloride, hexane, benzene, and aflatoxin.

In vivo and human clinical placebo controlled studies conducted to demonstrate the effectiveness of detoxifying herbs have evaluated the effectiveness of the herbs on blood concentrations of the liver enzymes (*e.g*., AST, ALT, GGT) found at time of initiation of treatment to post-therapeutic intervention with herbal dosing to assess efficacy of the treatment regimen.

THE USE OF *SILYBUM MARIANUM* TO PROMOTE LIVER HEALTH

In the herbal tradition, *Silybum marianum* is probably the most well-known herb for promoting liver health, and it has been the subject of numerous investigations demonstrating its hepatoprotective effects.[9] *Silymarin*, a collection of at least seven known flavonolignans,[10] and *Silibinin* (one of the primary flavonoids) are both credited with the herb's hepatoprotective effects.[11,12] Other flavonolignans found within *Silymarin* include *Silybin* A and B, *Silychristin*, *Silydianin*, and *Isosilybin* A and B.[11,12]

Studies with animal models have shown *Silybum* and its individual flavonolignans to positively affect liver metabolism. The hepatoprotective effect of *Silybum* has been so well documented that some European and U.S. hospitals utilize it intravenously as an antidote for acute liver toxicity due to ingestion of poisonous mushrooms.[13] *Silymarin* displays immunomodulatory effects on virally-induced liver inflammation.[14] Certain *Silymarin* constituents are also reported to have anti-carcinogenic effects.[15]

Animal models of nonalcoholic-related steatohepatitis suggest *Silybum* therapy may be beneficial based on improvements of elevated liver enzymes, gene expression assays, and other biochemical and immunological markers.[16] Further, animal studies suggest that *Silybum* protects the liver from aflatoxins and carbon tetrachloride.[17, 18]

In a Phase I clinical trial, *Silybin* A and B were used on patients with noncirrhotic hepatitis C. *Silybum* therapy showed promise in treating hepatitis C, and was safe and well tolerated.[14] Another human clinical trial in hepatitis C patients found that *Silymarin* therapy inhibited the proliferation of pro-inflammatory cytokines from infected T cells.[19]

Silymarin also has iron-chelating effects. A randomized, double-blind, placebo-controlled clinical trial demonstrated the positive effects of *Silymarin* and desferoxamine in patients with beta-thalassemia major. After three months, *Silymarin* and desferoxamine were more effective than either desferoxamine alone or placebo in reducing serum ferritin, lowering the iron overload, and normalizing elevated liver enzymes.[20]

In a clinical trial of acute hepatitis patients, *Silybum* therapy eliminated the symptoms of elevated bilirubin (*i.e.,* jaundice, icterus, and dark urine) more quickly than in the placebo group.[21]

THE USE OF *CURCUMA LONGA* TO PROMOTE LIVER HEALTH

Curcuma longa (a member of the Zingiberaceae family), a culinary spice known as Turmeric, gives Indian curries their typical bright-yellow color. *Curcuma* is traditionally used in Chinese and Indian herbal medicine for treating liver disease. It has been extensively studied, not only for it beneficial effects on the liver, but for its systemic immune, anti-inflammatory, and antioxidant effects.[22] *Curcuma* has been studied as an alternative therapy for patients with both liver and digestive diseases;[23] Curcumin is a flavonoid that has been credited with powerful antioxidant and anti-carcinogenic effects.[24]

Animals pretreated with curcumin showed less damage to the liver when exposed to carbon tetrachloride, a powerful hepatotoxin.[25,26] Curcumin has

also been shown to protect the liver from benzene toxicity.[27] Additionally, the co-administration of curcumin and aflatoxin was shown to decrease LDH and ALT when elevated,[28,29] and Curcumin was shown to protect liver cells from ethanol and acetominophen toxicity.[30,31]

Other research investigations have shown that Curcumin can inhibit NF-κB which, in turn, upregulates pro-inflammatory and profibrotic cytokines. Curcumin reduces the ability of alcohol, iron overload, biliary stasis, carbon tetrachloride, and adriamycin (doxorubicin)[32] to damage the liver.[31] Further, studies have demonstrated the ability of curcumin to provide protection against decreased liver function due to viral hepatitis by enhancing both synthesis and protective levels of hepatocellular proteins.[33]

In a variety of inflammatory conditions, hepatic stellate cells are known to undergo transformation that ultimately leads to liver fibrosis. Curcuma and Curcumin have been shown to help a diseased liver recover normal hepatic stellate cells.[34] Curcumin also stimulates the gallbladder to excrete bile at a faster rate, and may be beneficial in the treatment of biliary colic and bile stones/sludge. While studies have shown that Curcumin has powerful systemic effects, it is also poorly absorbed. Curcumin—with the added black pepper alkaloid (Piperine), or Curcumin—with phosphatidylcholine (Lecithin) is much more bioavailable.[35, 36]

It has been shown to act as a chemosensitizer and radiosensitizer for tumor cells, while at the same time protecting healthy cells from harmful effects to the liver from chemotherapy and radiation.[37] Future clinical studies may further delineate a role for Curcumin as adjunctive therapy for the treatment of cancer.

Silybum marianum of the thistle tribe of the Aster family

BUPLEURUM AND THE TREATMENT OF LIVER DISEASE

In traditional Chinese medicine, Chai hu (*Bupleurum*) is an important herb in the treatment of liver disease. *Bupleurum* yields a number of pharmacologically active compounds, though the most relevant for the treatment of liver disease are the saikosaponins, a type of steroidal saponin glycoside.[38] Similar to the previously described herbs, the saikosaponins have been shown to be protective in animal models of hepatotoxicity. Pre-treatment of rats with saikosaponin-d was able to protect the liver from carbon tetrachloride-induced cellular damage.[39] In this study, the herbal extract appeared to inhibit lipid peroxidation. Other researchers have demonstrated saikosaponin-d to be a potent inhibitor of collagen deposition in carbon tetrachloride-induced liver fibrosis.[40] Moreover, the extract normalized markers of liver inflammation (*e.g.*, TGF-β-1).

Saikosaponin-c is active against the hepatitis B virus (HBV).[41] This is due in part to the ability of Saikosaponin-c to inhibit cells from releasing the hepatitis B antigen and to impair HBV DNA replication.[42] On the other hand, Saikosaponin-d exhibits a proapoptotic effect on cancer cell lines by affecting the cellular production of p53, nuclear factor kB, and the Fas/Fas ligand.[43] A possible adverse interaction between *Bupleurum* and interferon-alpha has been suggested; therefore, concurrent use with interferon-alpha is contraindicated.

THE USE OF *TINOSPORA* TO PROMOTE LIVER HEALTH

*Tinospora cordifolia (*a member of the *Menispermaceae* family) is an *Ayurvedic* herb known as Guduchi. *Tinospora cordifolia* and *Phyllanthus emblica* (also known as *Emblica officinalis*, and a member of the Phyllanthaceae family) are often used in combination in *Ayruvedic* medicine for the treatment of liver diseases.

Tinospora was shown to support normal metabolism and has been shown to inhibit carbon tetrachloride-induced liver toxicity.[44-46] In guinea pigs treated for tuberculosis with a regimen known to cause hepatotoxicity, *Tinospora* prevented elevation of the liver enzymes, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as alkaline phosphatase.[47] In another animal study, three medications commonly known to induce liver damage were given to rats for 90 days; *Tinospora* and *Phyllanthus* were simultaneously administered in the experimental rat group which showed fewer histological changes typically associated with hepatotoxicity.[48]

A human clinical trial examined the use of *Tinospora* in 30 patients with jaundice due to malignant obstruction and associated sepsis and immunosuppression.[49] Patients were randomized into two groups; both groups received vitamin K, antibiotics, and biliary drainage. One group received *Tinospora* and the other group received placebo for 3 weeks after institution of the biliary drainage. At the end of the 3 week period, biochemical and immunologic assessments were made. Hepatic function was similar in both groups, but the group receiving *Tinospora* displayed better immune function. While 50% of the placebo group experienced septicemia, none occurred in the treatment group. Only 40% of the patients not receiving *Tinospora* survived surgical biliary drainage, while over 92% of the patients receiving *Tinospora* survived the surgical drainage.[49]

THE USE OF *EMBLICA OFFICINALIS* TO PROMOTE LIVER HEALTH

*Emblica officinali*s (also known as Amla or Indian Gooseberry) produces bright-yellow fruits that are high in flavonoids and Vitamin C. Studies have shown *Emblica* upregulates mitochondrial activity which in turn affects potassium channels in the liver.[50] *Emblica* has been shown to protect the liver from various hepatotoxins including arsenic and Nitrosamine and inhibits systemic oxidative stress due to renal disease.[51-53]

In studies, protection against the hepatotoxic effects of Nitrosamine (a known hepatotoxin and mutagen) by *Emblica* has been demonstrated.[54]

Further, *Emblica* may be able to reverse histological changes and assist the liver in repairing and recovering from early pathological manifestations. Similar hepatoprotective effects have been demonstrated with *Emblica* following exposure to hexane compounds.[55] Hexane typically damages the liver, elevating peroxides and depleting the liver of glutathione and dehydrogenase-detoxifying enzymes. Research studies have shown *Emblica* to prevent cellular changes in the liver and promote antioxidant detoxification in the liver.[56, 57] *Emblica* improved lipid metabolism and protein expression, suggesting utility in prevention of oxidative stress from long-standing hyperlipidemia.[58]

AZADIRACHTA INDICA AND THE TREATMENT OF LIVER DISEASE

The leaves of *Azadirachta indica*, a traditional Indian plant from the *Meliaceae* (or mahogany) family, have been used in *Ayurvedic* medicine to treat liver ailments as well as parasitic, fungal, and microbial infections. Marketed as *Neem*, the plant is also a natural insecticide against aphids and common agricultural pests.[59–61]

Azadirachta enhances lipid and protein processing in the liver. Extracts have been shown to protect the liver from phenobarbitol[62] and nitrosamine toxicity.[63] *Azadirachta* appears to have a systemic chemoprotective effect by aiding the liver's metabolism of hormones.[64] Prophylactic treatment of Swiss albino mice with a *Neem* leaf preparation was shown to slow the growth of Ehrlich's carcinoma without causing any associated hepatotoxicity as evidenced by normal liver enzymes (AST and ALT) and hepatic histology.[65]

A wide array of active compounds have been identified in *Azadirachta* and at least 140 have been shown to have potential medicinal and therapeutic effects thus far.[66] The insecticidal and pesticidal compounds include compounds called

Azadirachtins.[67] Many studies and many commercial products mention Neem "oil" which is extracted from the seeds of *Azadirachta* and known to contain a complex mixture of compounds including high amounts of terpenoids, limonoids and volatile sulpher containing compounds.[68] One study reported Neem oil to affect aspartate transferase (AST), alanine transferase (ALT) and alkaline-phosphatase (ALPK) enzyme systems in insects.[69]

THE USE OF *RUBIA TINCTORUM* TO PROMOTE LIVER HEALTH

Rubia tinctorum or *Manjishta* is a member of the Rubiaceae family found in Southeast Asia. In the West, it is known as *Madder* (or *Red Madder*) due to its brilliant red color and use as a plant dye. Its high anthocyanin content (similar to the compounds in berries and red wine credited with antioxidant effects) provides the red dye's color.[70] One such anthocyanin, *Rubiadin*, may protect the liver from carbon tetrachloride toxicity as evidenced by the normalization of elevated liver enzymes and the recovery of depleted glutathione enzymes.[71] *Purpurin*, a pigmented anthraquinone, has been shown to inhibit mutagenic effects on the liver following exposure to several of the substances in the Ames mutagenicity panel.[72] Activity against the hepatitis B virus has been attributed to quinone compounds in *Rubia* roots.[73]

Toxicology studies have found that *Rubia* is hepatotoxic in rats following chronic daily exposure of ≥300 mg per kilogram of body weight (equivalent to a dose of 48.4 mg/kg in humans).[74] However, the traditional amount of *Madder* in herbal formulas is substantially less. While *Madder* dye may have human carcinogenic effects with long-term exposure,[75, 76] small doses appear to have hepatoprotective effects.[77, 78]

THE USE OF *ANDROGRAPHIS PANICULATA* TO LIVER HEALTH

Much of the hepatoprotective activity of *Andrographis* has been credited to andrographolide (a bicyclic diterpenoid lactone).[73] Like other hepatoprotective plants, *Andrographis* acts on hepatocyte organelles.[74] In animal models, *Andrographis* has been investigated as a therapeutic agent in treating liver cancer.[75] Studies have shown that *Andrographis* improves general glycogenolysis, glucose transport, and metabolism by liver enzymes. In turn, this suggests that *Andrographis* supports basic liver metabolism and may help the liver recover when these functions are impaired.[75]

Andrographis paniculata (a member of the Acanthaceae family) may reduce the tendency of liver cells to lyse in the presence of high cytokine levels.[76]

Liver-specific inflammatory conditions and indeed most general inflammatory conditions result from excessive cytokine release. While cytokines are an important component of a healthy immune response, in some allergic (and inflammatory and immunologic) conditions, the release of cytokines contributes to tissue destruction. Likewise, in some liver abnormalities, cytokines trigger apoptosis of healthy hepatocytes and contribute to the loss of liver function.

While *Andrographis* may aid in the prevention of inappropriate apoptosis of functional liver cells, it may also enhance the apoptotic effect of chemotherapeutic agents on cancerous cells in the liver. In one study, *Andrographis* enhanced the efficacy of 5-fluorouracil against hepatocarcinoma,[79] suggesting a role for its adjunctive use with chemotherapy. *Andrographis* also supports high levels of glutathione in the liver, one of the liver's mechanisms for self-protection.[80] For example, glutathione depletion is believed to be the main mechanism of acetominophen-induced hepatotoxicity.[81] Furthermore, *Andrographis* has been shown to aid in protection of the liver from the damaging and inflammatory effects of hexane,[82] cyclophosphamide[83] and carbon tetrachloride.[84]

SUMMARY

In conclusion, the herbs described in this review have been shown to offer hepatoprotective and detoxifying benefits via a variety of mechanisms and have been used in combination for their synergistic effect.

Symptomatic improvement has been observed in patients with allergies (*e.g.,* chemical sensitivities) on a treatment regimen of these herbs. This improvement may be due to improved clearance of the allergenic substances. Likewise, a reduction in

liver and digestive symptoms (as well as improvement in liver function test results) may occur as early as one week following initiation of herbal treatment.

Many of the hepatoprotective and regenerative benefits of these herbs appear to be due to antioxidant and anti-inflammatory effects.[85] A published case study suggested that use of the herbs described in this review reduced liver metastatic tumors in a patient diagnosed with melanoma.[86, 87] Only *Rubia* has been shown to have a dosage restriction and possible toxicity.

The studies cited in this review suggest that these herbs may particularly benefit individuals with liver function abnormalities due to such causes as chemical-induced hepatotoxicity, hepatitis, and cirrhotic degeneration.

DISCLOSURE OF INTERESTS

Dr. Saunders reports personal fees related to employment or seeing patients from CCNM, the Dundas Naturopathic Centre, and from Beaumont Health Systems, Troy Hospital, MI, outside the submitted work. Dr. Winston reports personal fees from Herbalist & Alchemist, Inc, outside the submitted work. Dr. Stansbury and Dr. Zampieron have nothing to disclose.

REVIEW ESSAY

Many nutrients and herbs that have not been the subject of randomized controlled studies are used regularly by clinicians. They have also been used traditionally for hundreds, sometimes thousands of years. Review Essays contain the opinions of professionals and experts in the fields of nutritional and botanical medicine on how to most effectively use herbs and nutrients in clinical practice. The dosages recommended are based on clinical experience. Side effects that are described in "Unsubstantiated Theoretical Concerns" have not been seen in clinical practice or clinical studies but are speculative based on, for example, possible mechanisms of action.

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