

MILK THISTLE

(*Silybum marianum*)

Hepatoprotection at its best



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Milk Thistle: Hepatoprotection at its Best

BACKGROUND AND USES

Milk thistle (*Silybum marianum*) has a long and important history in herbal medicine dating back over 2,000 years in European herbal traditions. Dioscorides, an early Greek physician in Rome used the herb to induce vomiting. Pliny the Elder described its use in “carrying off bile” and as this historical gastrointestinal and liver connection grew, 15th and 16th century physicians described it as a liver and blood cleansing herb. In the late 16th century, Culpepper used it as a remedy for obstructions of the liver and the spleen, and specifically the infusions from the fresh root and seed for jaundice and for dissolving and excreting gall stones.¹ The Eclectic Physicians in America at the turn of the century used a tincture of the milk thistle for liver and kidney disorders and for gallstones. In the 1970’s, the German Commission E approved standardized milk thistle extracts for chronic inflammatory liver disease and cirrhosis of the liver.² Its use in hepatic and biliary disorders has been its principle use over the last several generations, and certainly within modern herbal medicine. Other historical uses include coughs, hemorrhoids, lactation stimulation, malaria, menstrual disorders, bladder/breast/prostate/skin cancer, radiation sickness, psoriasis, peritonitis and more.

Silybum marianum is a member of the aster family which includes the daisies and thistles, such as common thistle and artichoke. The root, leaf and seed have medicinal uses, but the flavonolignans in the seed are its most widely used form today.

Silymarin, the active extract of milk thistle is a silymarin-flavonolignan complex consisting of flavonolignans, silydianin, silychristine and silybin (aka silybinin, silibin or silibinin). The silymarin complex consists primarily of 50-70% silybin, the most biologically active. Standardized extracts typically contain an enhanced silymarin, usually about 70%, and have been the main focus of most of the research and a common form used in clinical practice. Silymarin is usually extracted with 95% ethanol although at least one German product prepares it with ethyl acetate.

PHARMACOLOGY AND MECHANISM OF ACTION

The mechanisms of action of silymarin are broad and can be summarized as having antioxidant and hepatic effects, renal effects, lipid peroxidation, a reduction in cholesterol synthesis, anti-carcinogenic effects, inhibition of leukotriene production, and insulin inhibition.

Many of the hepatoprotective properties of milk thistle are attributed to its antioxidant properties.^{3,4, 5, 6, 7, 8,9, 10, 11} The flavonoids that are present in milk thistle, such as silymarin and silybin, have been shown to act as anti-oxidants and free radical scavengers.

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Other mechanisms of action for the hepatoprotective properties of milk thistle have been proposed. The silybin in particular, has been shown to be protective against hepatotoxins such as acetaminophen, alcohol, carbon tetrachloride, tetrachlormethane, thallium, toluene and xylene when studied in vitro and in animals.^{12, 13, 14, 15, 16, 17, 18, 19, 20}

Silybin can have some regenerative effects on the liver as well, increasing DNA polymerase and increasing liver cell regeneration.^{21, 22, 23}

HEPATITIS AND CIRRHOSIS: SUMMARIZING THE EVIDENCE

Cirrhosis-Overview

There have been multiple studies conducted to evaluate the effects of milk thistle on cirrhosis, both alcoholic and non-alcoholic. In general, milk thistle lowers serum transaminase levels and improves survival, although there have been weaknesses in study designs varying from lack of controls, continued alcohol consumption and poorly defined inclusion criteria. While effect sizes are small or not statistically significant in some, there does appear to be benefits, although higher quality and long term studies need to be done. A systematic review of studies on the effectiveness of milk thistle in liver disease identified 16 randomized, placebo-controlled trials and 17 non-placebo trials.²⁴ Most of the studies used “Legalon”, a proprietary silymarin product, and used doses between 240 mg and 800 mg daily. Most results showed benefit of milk thistle, although the effects were small.

Alcoholic Cirrhosis

In a controlled trial of 200 patients with alcoholic cirrhosis, over a two year period, patients were randomized to receive 150 mg three times daily of silymarin or placebo.²⁵ Unfortunately, there was no significant difference in clinical and laboratory tests and there was no mortality benefit of silymarin.

In another trial of 170 patients with various causes of their cirrhosis (alcoholic, non-alcoholic and class A,B and C severities), patients received either silymarin 420 mg daily or placebo for at least two years.²⁶ In this study, there was a significant survival benefit in the silymarin patients with a 4 year survival rate of 58% in the silymarin group and 39% in the placebo group. The survival benefits were especially significant in those with alcoholic liver disease or class A (mild) cirrhosis.

A randomized trial of 172 patients with alcoholic and non-alcoholic biopsy-proved cirrhosis was done over a period of 4years.²⁷ Silymarin was given at a dose of 140 mg three times daily or placebo. While there were better survival rates in the silymarin

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group, lack of clarity in baseline characteristics and statistical analysis diminish the clinical value of this study.

Patients with alcoholic cirrhosis were studied in a 1 month clinical trial in which 600 mg daily of silymarin was given or placebo for 1 month.²⁸ Serum transaminases improved significantly in the silymarin group and none was seen in the placebo group. It is difficult to draw strong conclusions from such a short study involving cirrhosis, but the results do again suggest benefit of silymarin for cirrhosis.

A six month randomized trial in patients with alcoholic cirrhosis was conducted in 60 patients in which a silymarin was given, 150 mg three times daily or a placebo.²⁹ There were small decreases in lipid peroxidation and small increases in glutathione with the silymarin, but no significant changes in transaminase levels.

Chronic Alcoholic Liver Disease

Several controlled trials and a few uncontrolled trials have been done in patients with chronic liver disease. In a randomized controlled trial in 72 patients with chronic alcohol related cirrhosis and hepatitis,³⁰ silymarin 280 mg daily or placebo was given for an average of 15 months. No differences were seen in mortality, transaminase and bilirubin levels or prothrombin time.

Another study in chronic alcohol related hepatitis and cirrhosis fared better. Patients received either 420 mg of silymarin daily or placebo over 6 months.³¹ Serum bilirubin, transaminases and gamma-glutamyl transferase levels significantly improved in the silymarin group compared to placebo.

Significant decreases in transaminases as well as histologic improvements were seen in another study of alcohol induced liver disease patients with elevated liver enzymes.³² Over a 4 week time period, patients received either 420 mg per day of silymarin or placebo.

In the midst of many positive studies, this 3 month trial in 116 patients with biopsy proven alcoholic hepatitis including half of them with cirrhosis showed no significant changes in blood markers or biopsies when given 420 mg per day of silymarin.³³ This study is one of those in which some patients continued to consume alcohol.

There are several other controlled trials in patients with cirrhosis but results lacked clarity due to either inadequate or unreported randomization and blinding or lack of comparisons between treatment group and placebo.^{34,35, 36,37, 38}

Chronic Viral Hepatitis

A few trials have evaluated milk thistle as a treatment for chronic viral hepatitis. Most of these have demonstrated positive results for milk thistle in improving liver function tests. The limited evidence does suggest benefits for milk thistle, despite small studies and study design issues.

A complex of silybin and phosphatidylcholine, known as silylipide was studied in a randomized clinical trial of 20 patients with chronic hepatitis C and/or hepatitis B.³⁹ Patients received either 240 mg of silybin twice daily or placebo for one week. Significant reductions were seen in the transaminase levels in the Silylipide group compared to placebo.

Two small controlled trials were done in 45 and 15 patients with chronic viral hepatitis, and were reported on in the same publication.⁴⁰ Patients received 420 mg daily of silymarin or placebo. Statistical significant improvements in biopsies were seen in the silymarin groups but no significant improvements in transaminase levels.

A series of case reports in patients with chronic hepatitis B and C has shown improvements in serum transaminase levels after 120 mg of silybin per day over two months.⁴¹ Another case series reported on three patients with cirrhosis of the liver due to hepatitis C.⁴² Large improvements were seen in transaminase levels and viral load with a regimen of silymarin, alpha lipoic acid and selenium.

Acute Viral Hepatitis

Studies in acute viral hepatitis are limited by their quality and methodology although beneficial effects of milk thistle on serum transaminase levels and/or bilirubin have been seen in some, but not others.

A placebo-controlled trial in 59 individuals with acute hepatitis A or B was conducted in which patients received either 140 mg of silymarin three times daily or placebo for 3-4 weeks.⁴³ After the fifth day of treatment, reduction in serum transaminase and bilirubin levels were seen in the silymarin group and after 3 weeks, reductions in aspartate aminotransferase and bilirubin levels but not alanine aminotransferase levels were also seen in the silymarin group, but not the placebo group.

Two negative study results were published. One was in 151 patients with acute viral hepatitis, but with poor randomization.⁴⁴ No differences were seen over a 5 week period in transaminase, bilirubin, alkaline phosphatase and prothrombin time. The other was a controlled study in 87 patients with acute viral hepatitis.⁴⁵ There was no placebo group and poor reporting methods. A milk thistle product with vitamins B and C or milk thistle plus cocarboxylase plus vitamins B and C were given for 3 weeks. No significant

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differences were seen in transaminase levels although patients in each group reported feeling better.

One other positive study of note compared 40 patients with acute hepatitis although the causes were not clear in all the cases.⁴⁶ Patients received either 420 mg of silymarin daily in three divided doses or a steroid plus multiple vitamins. Significant improvements were seen in transaminase and bilirubin levels as well as prothrombin time, but not considered statistically significant after 4 weeks.

Mushroom and Drug Induced Liver Disease

There have been several case reports of intravenous infusion and oral delivery of milk thistle in mushroom poisonings. Some reports show dramatic recovery with improved liver function tests. In one study, 252 patients had acute Amanita phalloides mushroom poisoning.⁴⁷ They were given oral silymarin and had a higher survival rate than expected. While these are not controlled studies, in cases of acute mushroom toxicity where life altering liver disease and even death is highly potential, it would seem prudent to give patients something that might possibly work, rather than just let the illness take its natural course.

Treatment or prophylaxis with milk thistle has been used in the realm of liver damage that has been caused by toxins and drugs. Faster improvements and normal blood levels of alanine aminotransferase were seen after an uncertain dose of milk thistle extract in patients with acute toxic liver damage.⁴⁸ After chronic exposure to organic solvent vapors, 30 of 49 workers were treated with 420 mg per day of silymarin for 1 month while 19 received no treatment.⁴⁹ Significant improvements were seen in liver functions tests and platelet counts in the silymarin patients. Workers exposed to other paint and solvents may also benefit. A 15-20 day treatment with 420 mg per day of silymarin resulted in significant improvements in transaminase levels in the silymarin group with none in the placebo group.⁵⁰

Silymarin maybe be helpful in preventing liver toxicity in patients taking hepatotoxic drugs. Adequate studies have yet to be done, but liver toxicity from antipsychotic medications may be the most promising area with silymarin showing some promise in reducing serum transaminase levels and/or improvements in biopsy results.^{51,52, 53}

DOSING

Milk thistle products are often standardized to contain 70% to 80% silymarin. If a milk thistle extract were given that was standardized to 70% silymarin, then a usual dose would be 200 mg three times daily which would be delivering 420 mg of silymarin. When treating chronic liver disease, duration of use may be as short as two months up

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to several years and conceivably throughout the patient's lifespan in cases of chronic hepatitis, cirrhosis, and or fibrosis. Oral dosing should be individualized to the patient, their condition, and the milk thistle product being utilized. Consider the following:

- Cirrhosis: Silymarin, 280 to 450 mg per day in two or three divided doses.
- Chronic hepatitis: Silipide or silipide equivalents, 160 to 480 mg per day or silymarin 420 mg per day, in three divided doses.
- Acute viral hepatitis: Silymarin, 420 mg daily in three divided doses.
- Drug/toxin-induced hepatotoxicity: Silymarin 280 to 420 mg daily in three divided doses; but up to 800 mg/day can be considered.

ADVERSE REACTIONS/CAUTIONS/CONTRAINDICATIONS

Patients with known allergies to plants in the aster family, or to daisies, artichokes, common thistle or kiwi should consider avoiding milk thistle. Case reports have been published on anaphylaxis reactions. If such a reaction has occurred with any of the above plants, then milk thistle should be avoided altogether. Milk thistle is generally well tolerated and is a medicinal plant with an excellent safety profile. Occasional pruritus, headache, arthralgia and mild gastrointestinal symptoms have been reported.

Milk thistle should be used with caution in patients taking medications metabolized by the cytochrome P450 system and in patients who are taking hypoglycemic agents. Milk thistle can lower fasting glucose and hemoglobin A1c. There is also some potential that milk thistle may increase the efficacy of platinum compounds and doxorubicin.

PREGNANCY AND LACTATION

Milk thistle has been used historically to support lactation and improve milk flow although published evidence is insufficient positive or negative. Milk thistle is listed in many herbalists textbooks as an emmenagogue and therefore should be avoided during pregnancy.

SUMMARY

Milk thistle should be seen as a medicinal plant with a strong safety profile. While ongoing research is warranted, scientific evidence that has been published supports the use of milk thistle extracts in many forms of liver disease.

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ABOUT THE AUTHOR

Dr. Tori Hudson, Naturopathic Physician, graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in several capacities, including: Medical Director, Associate Academic Dean, and Academic Dean. She is currently a clinical professor at The National College of Naturopathic Medicine (NCNM), Southwest College of Naturopathic Medicine and Bastyr University. Dr Hudson has been in practice for 28 years, is the medical director of her clinic, "A Woman's Time" in Portland, Oregon, and director of product research and education for VITANICA.

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