



Silybum marianum (Milk Thistle)

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Description

Silybum marianum (milk thistle) has been used for centuries as an herbal medicine for the treatment of liver disease. Its use for liver disorders dates back to Pliny the Elder, a Roman naturalist, who described milk thistle as being “excellent for carrying off bile.” Milk thistle is an annual or biennial plant indigenous to Europe and is also found in some parts of the United States. It grows in rocky soils to a height of three to ten feet with an erect stem that bears large, alternating, prickly-edged leaves. The common name, milk thistle, is derived from the “milky white” veins on the leaves, which, when broken open, yield a milky sap. Flowering season is from June to August,

and each stem bears a single, large, purple flower ending in sharp spines. The fruit portion of the plant is glossy brown or gray with spots.¹ Modern extracts of the plant are produced from the small hard fruits (often incorrectly referred to as seeds) that have the feathery tuft (known as the pappus) removed. These are referred to as achenes.

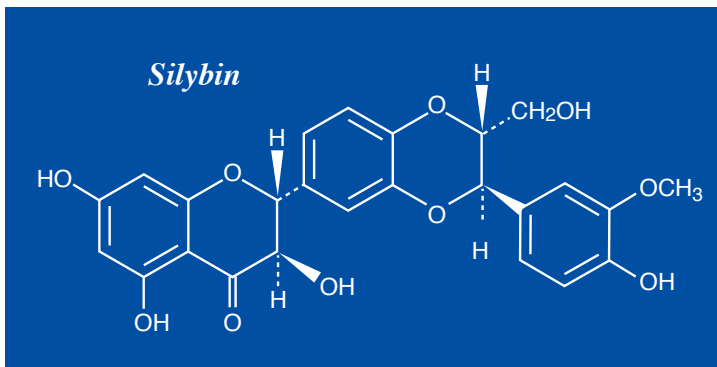
Active Constituents

In 1968, a flavonolignan complex in milk thistle fruit was identified and isolated. Named silymarin, this complex was found to be responsible for the medicinal benefits of the plant.² The silymarin complex is made up of three parts: silibinin (also called silybin), silydianin, and silychristin. Silibinin is the most active of the three, and is largely responsible for the hepatoprotective benefits attributed to silymarin.^{3,4} Milk thistle fruit contains 1.5-3.0 percent flavonolignans. Modern extracts are typically standardized to 70-80 percent silymarin.⁵

Pharmacokinetics

Silymarin is not water soluble, making tea preparations ineffective; therefore it is usually administered orally in encapsulated form. Because absorption of silymarin from the gastrointestinal tract is only moderate (23-47%), it is best administered as a standardized extract of 70-80 percent silymarin. In animals and humans, peak plasma levels are reached in four to six hours after

an oral dose. Silymarin is excreted primarily via the bile but some clearance is also achieved via the kidneys. The clearance half-life of silymarin is six to eight hours.⁶



Mechanisms of Action

Silymarin's hepatoprotective effects are accomplished both directly and indirectly. The primary actions are as follows:

Hepatocellular Protection

Silymarin, and more specifically silibinin, directly aids hepatocytes by binding to the outside of the cells and blocking the binding of potential hepatocellular toxins. This was first noted in experimental studies investigating toxins from *Amanita phalloides* (death cap mushroom).^{7,8} Ingesting this mushroom causes swift and severe damage to hepatocytes. Silymarin blocks the receptor sites by which the mushroom toxins enter the cells. In addition, toxins that have already penetrated hepatocytes are neutralized by silibinin. In animal studies, silymarin given within 10 minutes after *Amanita* toxin ingestion completely counteracted the toxic effects, and if given within 24 hours of toxin ingestion silymarin prevented death and greatly reduced liver damage.⁹ Similar hepatoprotective effects have been shown in *in vitro* and animal studies against ethanol and acetaminophen.^{10,11}

Antioxidant Activity

Silymarin is a potent free radical scavenger and has been noted to increase production of glutathione in hepatocytes.^{12,13} Silymarin has been shown in one animal study to raise intracellular glutathione level by as much as 50 percent.¹⁴ Silymarin also increases the activity of superoxide dismutase in erythrocytes.¹⁵

Regenerative Properties

Silymarin stimulates the regenerative ability of the liver to form new hepatocytes by stimulating the activity of DNA-dependent RNA-polymerase I.^{16,17} This results in an increase in rRNA synthesis and increased protein synthesis. *In vitro* studies suggest this action extends only to normal hepatocytes and not cancerous cells.¹⁸

Antifibrotic Activity

The ability of silymarin to block fibrosis in the liver was first shown in a study with rats subjected to complete bile duct occlusion.¹⁹ This action was later demonstrated in an open-label, uncontrolled study of 998 patients with liver disease due to a variety of factors, including alcohol abuse, chronic active hepatitis B or C, drugs, and chemical exposure.²⁰ Use of 140 mg of silymarin (equivalent to approximately 60 mg of silibinin) three times daily for three months led to a significant reduction in amino terminal procollagen III peptide (PIIINP), a marker of fibrosis. In 19 percent of the patients, this measure had dropped to the normal range expected for a healthy person.

Clinical Indications

Alcohol-Related Liver Disease and Cirrhosis

Standardized milk thistle extracts (containing 70–80% silymarin) are approved by the German Commission E for the treatment of “toxic liver damage and for supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis.”²¹ Clinical support to date has been most significant in the treatment of alcohol-related liver disease as well as cirrhosis (particularly due to alcohol abuse).

Several European randomized, placebo-controlled clinical trials have found that serum bilirubin, AST, and ALT levels were decreased in patients with alcohol-related liver disease who took a standardized milk thistle extract delivering 420 mg of silymarin per day.²²⁻²⁴ These clinical trials ranged from one to six months in length. In one trial, liver biopsy indicated positive changes in liver histology²³ while another noted a decrease in serum procollagen III peptide levels.²⁴

Three double-blind, placebo-controlled trials have examined the effect of milk thistle extract on patients with cirrhosis, with mixed results. One trial found four-year survival rates were improved (58% in silymarin group vs. 39% for placebo group) in cirrhosis patients taking 420 mg of silymarin per day for an average of 41 months.²⁵ Results were best in patients with alcohol-related cirrhosis and those designated Child A. Similar results were seen in a 12-month trial of adult diabetics with alcoholic cirrhosis.²⁶ However, a two-year clinical trial found no influence on hepatic health or survival rates in adults with liver cirrhosis.²⁷

A small pilot study on patients with primary biliary cirrhosis with a sub-optimal response to ursodeoxycholic acid also found no benefits from the use of milk thistle extract.²⁸

Hepatitis

Several small clinical trials in Europe have suggested that milk thistle extract may be beneficial in the management of chronic viral hepatitis. Studies using 420 mg of silymarin

per day for as long as nine months found a significant decrease in AST and ALT levels in patients with hepatitis B.^{29,30} Histological improvements were also noted in patients undergoing liver biopsy. Similar results have been noted with a product that combines silymarin and phosphatidylcholine.^{31,32} However, these results must be viewed as preliminary. Future clinical trials must focus on what role milk thistle extract may play in the treatment of viral hepatitis – particularly hepatitis C.

Hepatoprotection During Drug Therapy

Preliminary results suggest milk thistle extract may serve as a hepatoprotective agent for persons taking potentially hepatotoxic drugs such as psychotropics³³ and anthracycline during treatment for leukemia.³⁴ However, one clinical trial found no protective effects for milk thistle extract in patients taking tacrine.³⁵

Drug-Botanical Interactions

Although no drug interactions are listed for milk thistle, a new *in vitro* study suggests it may inhibit CYP3A4 activity.³⁶ The ramifications of these findings for humans are unknown.

Side Effects and Toxicity

Milk thistle extract is virtually devoid of any side effects and may be used by a wide range of people, including pregnant and lactating women. Since silymarin does have some choleric activity, it may have a mild, transient laxative effect in some individuals. This will usually cease within two or three days.

Dosage

The standard dosage of milk thistle extract, standardized to 70-80 percent silymarin, is 140 milligrams of silymarin three times daily. In persons with liver disease, it is recommended that this dose be used until clinical improvement is verified by laboratory tests. According to research and clinical experience, improvement should be noted in about eight weeks. However, in persons with chronic liver disease due to hepatitis or cirrhosis, ongoing use of silymarin may be necessary.

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