The Longwood Herbal Task Force

(http://www.mcp.edu/herbal/default.htm) and

The Center for Holistic Pediatric Education and Research

(http://www.childrenshospital.org/holistic/)

Milk Thistle (*Silybum marianum*)

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Principal Proposed Uses: Hepatoprotectant, enhancement of biliary function

Other Proposed Uses: Renal protectant, anti-inflammatory

Overview

Milk thistle is widely used in Europe for hepatic and biliary disorders, and is beginning to be used to protect against nephrotoxicity as well. It protects the liver from several hepatotoxins, including *Amanita* mushrooms, acetaminophen and alcohol. Its primary active ingredient is silymarin, which is a potent antioxidant composed of several flavonoid compounds. Further studies are needed to evaluate milk thistle's renal protectant effects, such as prevention of cisplatin toxicity, its use in treating alcoholic liver disease, and its use to prevent cancer or as a complementary treatment for cancer. There are no known long-term risks to adults associated with milk thistle use. Its safety in pediatrics, pregnancy, and during lactation are unknown.

Historical and Popular Uses

Milk thistle has been used medicinally in Europe since the first century. Pliny the Elder claimed that it was helpful in improving bile flow. It was also mentioned in the writings of Dioscorides, Jacobus Theodorus and Culpepper[1]. Its leaves, flowers and roots have historically been considered a vegetable in European diets, and its fruits (achenes), which resemble seeds, have been roasted for use as a coffee substitute. The leaves of the plant are eaten in fresh salads and as a spinach substitute, the stalks eaten like asparagus, and the flower heads served as one would an artichoke.

In Traditional Chinese Medicine, milk thistle seeds are known as *Shui Fei Ji*; in China milk thistle is used to protect the liver, increase bile secretion and protect against oxidative injuries such as radiation.

Ripe milk thistle seeds are used in Europe in the treatment of various hepatobiliary problems, such as hepatitis, cirrhosis, gallstones, and jaundice, as well as for kidney ailments[2]. Milk thistle is used as an antidote for *Amanita* mushroom poisoning and to protect the liver and kidneys from toxic medications[3]. It is used to treat hepatitis and biliary disease, lower cholesterol, and even improve psoriasis. Some herbalists also recommend it to treat insufficient lactation. The German Commission E recommends it for the treatment of dyspeptic complaints, toxin-induced liver damage, and hepatic cirrhosis and as a supportive therapy for chronic inflammatory liver conditions[4]; sales there exceeded $180 million in 1997[5].

Botany

Medicinal species: Silybum marianum L. Gaertn., *Cardus marianus* L.

Common names: Holy thistle, marian thistle, Mary thistle, milk thistle, Our Lady's thistle, St. Mary thistle, wild artichoke, Mariendistel (Ger), Chardon-Marie (Fr)[6,7]. Milk thistle should not be confused with blessed thistle, *Cnicus benedictus*. Milk thistle is sold as Legalon® in Germany.

Botanical family: Compositae/Asteraceae

Plant description: Milk thistle is a tall, biennial herb, five to ten feet high, with hard, green, shiny leaves that have spiny edges and are streaked with white along the veins. The solitary flower heads are reddish-purple with bracts ending in sharp spines. The small hard fruits in the flowers, known technically as achenes, resemble seeds and are the part of the plant used medicinally.

Where it's grown: Southern and western Europe, South America and North America in the eastern United States and California.

Biochemistry

Milk Thistle: Potentially Active Chemical Constituents

- Flavonoids/flavonolignans: silymarin (which includes silybin [silibinin], silidianin, silychristin [silichristin] and isosylibin), apigenin, dehydrosilybin, deoxysilycristin, deoxysildianin, siliandrin, silybinome, silyhermin, neosilyhermin Other: silybonol; myristic, oleic, palmitic and stearic acids; betaine hydrochloride

The dried seeds contain 1-4% silymarin flavonoids[8]. Silymarin is a mixture of at least three flavonolignans, including silybin (silibinin), silidianin, and silychristin. It is the primary active ingredient in milk thistle, and is also found in related species such as artichokes.

The bioavailability of enterally administered silymarin is limited; the compound is poorly soluble in water, and only 20-50% is absorbed from the gastrointestinal tract after ingestion. Absorption is significantly enhanced if silybin is administered in a complex with phosphatidlycholine[9, 10]. There is rapid absorption after an oral dose with the peak plasma concentration reached after two to four hours and an elimination half-life of six hours[5]; it undergoes extensive enterohepatic circulation. Three to eight percent is excreted in the urine, and 80% is excreted in the bile as glucuronide and sulfate conjugates[11]. Bioavailability can vary up to three-fold depending on the formulation; the brand used in most European studies, Legalon®, contains approximately twice as much available silybin as other preparations[12, 13]

Silybin is the most biologically active component with regard to antioxidant and hepatoprotective properties; it is concentrated in the bile, achieving concentrations 60 times higher than that found in the serum[14, 15].

Other flavonolignans identified in *S. marianum* include dehydrosilybin, deoxysilycistin, deoxysilydianin, silandrin, silybinome, silyhermin and neosilyhermin. In addition, milk thistle contains apigenin; silybonol; myristic, oliec, palmitic and stearic acids; and betaine hydrochloride, which may have a hepatoprotective effect[16].

Experimental Studies

Potential Clinical Benefits of Milk Thistle

1. Cardiovascular: none
2. Pulmonary: none
3. Renal and electrolyte balance: Renal protectant
4. Gastrointestinal/hepatic: Hepatoprotectant; treatment of hepatitis, antilipidemic
5. Neuro-psychiatric: none
6. Endocrine: Antidiabetic and pancreatic protectant
7. Hematologic: none
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: Anti-inflammatory
11. Antimicrobial: none
12. Antineoplastic: Chemoprevention
13. Antioxidant: Antioxidant
14. Skin and mucus membranes: Psoriasis: Traditional use, no data.
15. Other/miscellaneous: none

1. **Cardiovascular:** none
2. **Pulmonary:** none
3. **Renal and electrolyte imbalance:** Renal protectant
   i. *In vitro data:* In human mesangial cell cultures that had been incubated with glucose, silybin inhibited the formation of malondialdehyde, a product of lipid peroxidation[17].
   ii. *Animal data:* In rats, silybin prevented cisplatin-induced glomerular and tubular nephrotoxicity as measured by BUN, creatinine and fibronectin and histological changes in renal tubules[18, 19].

   In rats, two weeks of treatment with silybin did not prevent cyclosporine-induced decreases in glomerular filtration rate or increases in serum creatinine, but it did prevent cyclosporin-induced lipid peroxidation[20].

iii. Human data: none

4. **Gastrointestinal/hepatic:** Hepatoprotectant, treatment of hepatitis, antilipidemic

   a. Hepatoprotective: *In vitro*, in animal studies and in human trials, silymarin, particularly silybin, is protective against hepatotoxins as diverse as acetaminophen, alcohol, carbon tetrachloride, tetrachloromethane, toluene, and xylene[21-26].

      i. *In vitro data:* Milk thistle is hepatoprotective in many experimental models of liver damage. It protects in three ways: by enhancing DNA polymerase, stabilizing cell membranes and scavenging free radicals[27]. Silybin stimulated DNA polymerase, increasing the synthesis of ribosomal RNA and stimulating liver cell regeneration; it also stabilized cellular membranes and increased the glutathione content of the liver[28-32]. Silybin acted as a free radical scavenger, increasing the activity of both superoxide dismutase and glutathione peroxidase in human cell lines[33, 34]. It also inhibited the 5-lipoxygenase pathway in Kupffer cells, minimizing inflammation in the liver[35].

      Silymarin protected hepatocytes from acetaminophen-induced toxicity *in vitro*[36-38]. Silybin almost completely inhibited the uptake of amatoxin by perfused rat liver[39].

      In rat Kupffer cells, silybin inhibited leukotriene and free radical formation, and blocked the lipoxygenase pathway[33, 35]. In rat hepatocytes, silybin inhibited lipid peroxidation and cell damage[40].

      ii. *Animal data:* Milk thistle extracts protect animals against the damaging effects of a variety of hepatotoxins including viruses, chemicals and naturally-occurring toxins such as *Amanita* mushrooms and alcohol.

      Pretreating rats with silymarin protected them from the lethal effect of Frog Virus 3[41].

      Pretreatment of rats, mice, rabbits and dogs with silymarin provided substantial and significant protection from the lethal effects of *Amanita* mushroom poisoning[42-45]. In dogs, silybin (50 mg/kg) was completely protective against death from *Amanita* mushroom poisoning even when given as late as 40 hours after exposure to the toxin[46].

Pretreating rats and mice with silymarin before exposure to chemical hepatotoxins, such as carbon tetrachloride, thallium, acetaminophen and halothane, significantly reduced lipid peroxidation and hepatotoxicity[21, 47-51].

Similarly, in rats, silymarin and silybin counteracted alcohol toxicity to the liver, as measured by serum gamma glutamyl transpeptidase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST) activity[52-54].

In rats with bile duct obstruction, silymarin significantly inhibited hepatic fibrosis[55].

iii. *Human data:* Europeans use silymarin to treat liver damaged by a variety of different toxins[3].

In an open label study of 2,637 patients with a variety of chronic hepatic disorders, treatment with a milk thistle extract (Legalon®) for eight weeks resulted in substantial and significant decreases in elevated liver enzyme levels and physician satisfaction with treatment in 88% of cases; side effects were reported by fewer than 1% of patients[56].

Milk thistle extracts (such as silybin) are widely used in Europe to treat *Amanita* mushroom poisoning, and have reduced mortality rates by 60-80%[57-59]. Giving silybin intravenously (20-50 mg/kg/day for three to four days) up to 48 hours after mushroom ingestion appears to be an effective measure to prevent severe liver damage. In a retrospective analysis of 205 patients with *Amanita* mushroom poisoning, there were 46 fatalities among the 189 patients treated without silybin and no fatalities among the 16 patients who received silybin[60]. In another series of 18 patients with *Amanita* poisoning treated with silybin, 17 patients survived; the only fatality was a suicidal patient who had taken a large amount of mushroom and did not receive treatment until 60 hours after the ingestion[61]. In a four-person family that ate *Amanita phalloides* mushrooms, the patients' condition worsened during the first three days of standard therapy; silybin was then administered for seven days, and all family members survived with normal hepatic enzyme and morphologic characteristics two months later[62].

Milk thistle extracts have also been used to treat adults with alcoholic liver damage, but randomized trials have reported mixed results. In several randomized, controlled, double-blind clinical trials involving more than 300 patients with alcohol-induced liver disease, those treated with silymarin (Legalon® 420 mg daily) had a statistically significant improvement in liver enzymes and hepatic histology within four weeks[63-66]. In another double-blind study among patients with histologically proven chronic alcoholic liver disease, those treated with silymarin for six months had significant improvement in certain immune functions[67]. In a double-blind prospective randomized trial among 170 patients diagnosed with alcoholic cirrhosis, those treated with silymarin had significantly reduced mortality over the next four years compared with those receiving placebo (42% vs. 62%, $P<0.05$)[68]; these results were replicated in another study[69].

However, in two placebo-controlled, randomized double-blind studies among alcoholics with severe cirrhosis of the liver, those treated with silymarin (from 280 mg daily to 150 mg three times daily) did not have any significant improvements in survival rate[70, 71]. And in a randomized double-blind trial of 116 patients with alcoholic hepatitis, those who received silymarin (420 mg daily for three months) did not improve significantly more than the placebo group[72]; however, differences in this study might have been obscured because 46% of the participants were able to stop drinking.

In a randomized, placebo-controlled double-blind trial of 60 women receiving chronic psychotropic therapy (butyrophenones or phenothiazines) who had increased AST and ALT, those who received silymarin (800 mg daily in two divided doses) for 90 days had reduced lipoperoxidative hepatic damage compared to those who received placebo; this protective effect was greater when treatment with psychotropic drugs was also suspended[73].

Silymarin has also been used in Europe to treat adults with occupational exposures to hepatotoxic chemicals such as solvents[74, 75].

b. Treatment of hepatitis: Some herbalists use milk thistle extracts to treat patients with hepatitis C[76].

i. *In vitro data:* See above for hepatoprotective effects

ii. *Animal data:* See above for hepatoprotective effects

iii. *Human data:* In a series of eight patients with chronic active hepatitis treated with oral silipide (a silybin-phosphatidylcholine complex) equivalent to 120 mg of silybin twice daily for two months, there were statistically significant reductions in AST and ALT[77]. In a double-blind, randomized controlled trial of 20 patients with chronic active hepatitis, therapy with 240 mg silybin complex (silipide) twice daily for seven days resulted in statistically significant reductions in AST, ALT, and gamma-glutamyltranspeptidase (GGT) compared to the placebo group ($P<0.01$)[78]. These results were replicated in another small study[79].

In a double-blind study of 57 patients with acute viral hepatitis, the 29 who received silymarin (140 mg three times daily for three weeks) had significantly lower bilirubin, AST and ALT levels within three to four weeks than the 28 treated with placebo[80]. However, another trial in 151 patients with acute viral hepatitis was unable to demonstrate any significant benefit from silymarin[81].

c. Antilipemic

i. *In vitro data:* In rat liver homogenates, silybin decreased cholesterol synthesis[82]. In perfused livers from rats fed a high cholesterol diet, silymarin normalized the clearance of low density lipoproteins[83].

ii. *Animal data:* In rats, silymarin provided significant protection against dietary-induced hypercholesterolemia[84]. Rats who were fed a high cholesterol diet then given silymarin had improved hepatic LDL clearance[85]. In rats, silybin reduced biliary excretion of cholesterol salts by 60-70%, while leaving biliary flow rates unchanged[86]. In rabbits fed high cholesterol diets, silymarin exerted anti-atherosclerotic effects[87].

iii. *Human data:* Because silymarin may inhibit hepatic synthesis of cholesterol, it has been suggested that milk thistle products be investigated as a treatment for patients with hypercholesterolemia[88]. Among 15 cholecystectomy patients, those who received silymarin (420 mg daily for one month) had a significant decrease in biliary cholesterol

concentration vs. those treated with placebo, suggesting decreased hepatic cholesterol synthesis[89]. In a seven-month open clinical study in 14 type-II hyperlipidemic outpatients, treatment with silymarin (420 mg daily) was associated with a decrease in total cholesterol and an increase in HDL-cholesterol levels[90].

5. **Neuro-psychiatric:** none
6. **Endocrine function:** Antidiabetic and pancreatic protectant
   i. *In vitro data:* none
   ii. *Animal data:* In rats, silymarin protected the pancreas from damage in experimentally-induced diabetes mellitus[91]. In rats pretreated with cyclosporin, silybin did not affect glucose levels; silybin and cyclosporin had an additive inhibitory effect on insulin secretion[92].
   iii. *Human data:* In a placebo-controlled trial in 60 alcoholics with hepatic cirrhosis and insulin resistant/dependent diabetes, those treated with silymarin (Legalon® 200 mg three times daily) had significant decreases in fasting glycemia, mean daily blood glucose, glycosuria, and insulin needs over six months[93,94].
7. **Hematologic:** none
8. **Rheumatologic:** none
9. **Reproductive:** none
10. **Immune modulation:** Anti-inflammatory
    i. *In vitro data:* Silymarin exerted no significant effects on unstimulated polymorphonuclear (PMN) cell motility, phagocytic or chemotactic activities; however, when the PMNs were stimulated, silymarin inhibited myeloperoxidase release. Incubation of PMNs with silybin prevented the action of the leukocyte motility inhibitor, fMLP[95, 96]. Silymarin inhibited leukotriene production and had an antifibrotic effect[97].
    ii. *Animal data:* none
    iii. *Human data:* In healthy volunteers, silybin enhanced leukocyte motility[95]. In a double-blind, placebo-controlled trial of 40 patients with alcoholic cirrhosis, treatment with silymarin increased lectin-induced lymphoblast transformation, decreased the percentage of

OKT8+ cells and suppressed lymphocytotoxicity significantly more than in the placebo treated group[98].

11. **Antimicrobial:** none
12. **Antineoplastic:** Chemoprevention
    i. *In vitro data:* Silymarin and silybin had chemopreventive effects in human and mouse epidermal, prostrate and breast and cancer cell lines[99-106]. Silymarin had cytoprotective effects on mouse liver cells, rat tracheal tissues and human testicular cancer cell lines exposed to carcinogens[107, 108]. Preincubating cells with silybin prior to Adriamycin (doxorubicin) exposure prevented Adriamycin-induced inhibition of cell growth[109].

    Because of its potent antioxidant effects, there is concern that milk thistle might interfere with established chemotherapeutic agents that exert cytotoxicity via peroxidative pathways. However, in human ovarian and breast cancer cell lines, silybin had synergistic cytotoxic effects with cisplatin and doxorubicin; there was no evidence of interference with cytotoxicity[110].

    iii. *Animal data:* Silymarin exerts protective effects against carcinogenesis in different mouse models of epithelial tumors; for example, mice pretreated with silymarin were protected from the effects of chemical and UVB induced tumors[100, 103, 111, 112].

    Silymarin's stimulatory effects on hepatic DNA appear to be selective for healthy cells. In a study in rats with hepatomas, silymarin did not lead to tumor growth[113].

    iii. *Humans data:* There is a case report of a 52-year-old man with biopsy-proven hepatocellular carcinoma which was unresectable and which resolved "spontaneously" following self medication with 450 mg silymarin daily[114].
13. **Antioxidant:** Antioxidant: Flavonoids, such as silymarin (and particularly silybin), are known to be potent antioxidants and free radical scavengers[115-121].
    i. *In vitro data:* In rats, two weeks of treatment with silybin prevented cyclosporin-induced lipid peroxidation[20]. Silybin inhibited peroxidation of low density lipoprotein (LDL) *in vitro*[122].

    In human mesangial cell cultures that had been incubated with glucose, silybin worked as an antioxidant, inhibiting the formation of malondialdehyde, a product of lipid

peroxidation[17]. In human leukocytes, silymarin protected against hydrogen peroxide-induced induced DNA damage[123]. In human and rat pulmonary and hepatic microsomes, silybin provided antioxidant and free radical scavenging protection against chemical-induced lipid peroxidation[124, 125]. Silymarin also had antioxidant effects in human platelets[126].

ii. *Animal data:* In rats stressed with chronic iron overload, silybin provided significant antioxidant protection against hepatic toxicity[127].

In rats, pretreatment with silymarin provided protection against ischemia-induced gastric ulcers[128].

iii. *Human data:* In patients with alcoholic cirrhosis, silymarin enhanced erythrocyte and lymphocyte levels of superoxide dismutase, thereby enhancing antioxidant effects[129].

14. **Skin and mucus membranes:** Psoriasis: Traditional use, no data
15. **Other/miscellaneous:** none

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals, and pharmaceuticals. This is particularly concerning with imports from developing countries.

Furthermore, allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions to milk thistle have been reported. There is one case report of a British woman who apparently had a severe allergic reaction to a milk thistle capsule; it was unclear whether the reaction was to milk thistle or some other ingredient in the capsules[130]. There is another report of anaphylaxis in a patient who had a known allergy to kiwi fruit[131].

Potentially toxic compounds in milk thistle: None identified

Acute toxicity: Because of milk thistle's stimulating effect on the liver and gallbladder, some herbalists caution that a mild laxative effect may be experienced for the first few days of use. However, in numerous randomized controlled trials, side effects from milk thistle have not been any greater than with placebo. In animals, silymarin has not had significant adverse effects even when given in very high dosages. In a series of several thousand patients, the incidence of side effects was very low and limited primarily to mild gastrointestinal upset[56].

Chronic toxicity: There are no known long-term risks associated with milk thistle.

Limitations during other illnesses or in patients with specific organ dysfunction: None reported

Interactions with other herbs or pharmaceuticals: Milk thistle could decrease the insulin requirements of diabetic patients with alcoholic liver cirrhosis, but there are no studies suggesting altered glucose metabolism in patients without liver disease.

Safety during pregnancy and/or childhood: The safety of long-term use of milk thistle during pregnancy, lactation and childhood has not been established, but it is presumed safe based on its long historical use as a food[132].

Typical Dosages

Provision of dosage information does NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.

Doses are given for single herb use and must be adjusted when using herbs in combinations. Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Adult dosages: Reputable herbalists recommend a range of doses. Amounts used in studies range from 280 mg to 800 mg of silymarin daily. Most studies have used a concentrated, standardized product containing 70-80% silymarin. Studies using a silybin-phosphatidylcholine complex have used dosages of 100 mg three times daily because absorption is enhanced with this preparation[5]. In Europe, silybin is given parenterally (20-50 mg/kg/day for three or four days) to treat acute hepatotoxicity including *Amanita* mushroom poisoning.

Standardized milk thistle extract: 100-200 mg p.o. three times daily, taken with meals[133, 134]

Tea is not the preferred route of administration since silymarin is poorly soluble in water, but if the milk thistle seeds are roasted and broken open they can be used as tea. The usual dose is 12-15 grams of roasted, cracked seeds divided into three doses daily, taken with meals[4].

Tincture: 3-6 ml (about 1/2-1 tsp.) three times daily with meals.

Pediatric dosages: Unknown

Availability of standardized preparations: Extracts should be standardized to at least 70% silymarin. The German product Legalon® has been used in most studies.

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