

Silybum marianum: Milk Thistle

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Distribution: South America and North America in the eastern United States and California; Southern and Western Europe.

Common names: Holy thistle, Marian Thistle, Our Lady's thistle, Mary thistle, St. Mary's thistle, Wild Artichoke, Mariendistel (Germany), Chardon-Marie (French). Former botanical name was *Carduus marianus*. Legalon® (Germany) and Thisilyn (U.S.) are the two most researched products. In Chinese, Milk thistle is known as Shui Fei Ji.



Similar plants: Milk thistle should not be confused with blessed thistle, *Cnicus benedictus*.

Family: Asteraceae (Compositae)

Parts Used: Seed. (In Europe, the leaves were historically used like spinach, once the spines had been removed, and the fruit was eaten like an artichoke).

Collection: collect seeds (carefully!) in late summer

Selected Constituents:

Plant: 2,3-dehydrosilychristin, 2,3-dehydrosilymarin, aluminum, arachidic acid, behenic acid, beta-carotene, calcium, chromium, cobalt, dihydrosilybin, fumaric acid, iron, isosilybin, linoleic acid, magnesium, manganese, neosilyhermin, palmitic acid, phosphorus, potassium, protein, selenium, silandrin, silicon, silybin, silydianin, silyhermin, silymonin, sodium, stearic acid, tin, zinc.

Fruit: 3-deoxysilychristin, apigenin, chrysoeriol, eriodictyol, naringenin.

Seed: dehydroconiferyl-alcohol, essential oil, histamine, kaempferol, protein, quercetin, silychristin, silymarin, taxifolin, tyramine.

Energetics: the energetic actions of milk thistle have been described as sweet and cooling, but also as pungent, warm and dry! As a liver tonic, the most appropriate description is probably the former.

Actions, clinical:

Liver: Controlled clinical trials in various hepatic disorders including toxin and drug-induced hepatitis, alcoholic liver disease, viral hepatitis and cirrhosis suggest that milk thistle decreases aminotransferase activity and improves various clinical parameters on a less consistent basis. In an evidence report/technology assessment paper by the U.S Department of Health and Human Services, a literature review revealed the following:

Of 16 prospective placebo-controlled trials, study design was found to be of variable quality, and interpretation overall was difficult. However, results showed that 4 of 6 studies on alcoholic liver disease showed significant improvement in at least one measure of liver function. Three of 3 studies on viral hepatitis showed improvement in clinical pathology, and 2 of the 3 showed improvement in histology. In 2 of 2 studies on cirrhosis (alcoholic and nonalcoholic), administration of milk thistle was associated with improvements. Of 3 trials evaluating milk thistle in the treatment or prevention of damage due to hepatotoxic drugs, results were mixed.

In 2 trials of dogs given hepatotoxic chemicals, silymarin or silibinin improved biochemical and histologic measures of hepatotoxicity, and survival was improved.

In one trial of post parturient cattle given milk thistle seeds, milk production was increased and ketonuria reduced, as compared to controls.

Kidney: silybin reduces oxidative damage to kidney cells in vitro. In rats, silybin prevented cisplatin induced nephrotoxicity, but did not prevent cyclosporine-induced glomerular damage except for lipid peroxidation.

Blood lipids: silymarin may inhibit hepatic synthesis of cholesterol and reduce blood lipids, as shown in vitro, animal studies, and human trials.

Pancreas: As an antioxidant, silymarin can protect the pancreas against certain forms of damage. In a controlled trial of human diabetics, patients experienced decreases in blood glucose and insulin requirements.

Actions, biochemical: Silymarin is a bioflavonoid complex made up of three parts: silibinin, silidianin, and silicristin. Silibinin is thought most active and probably responsible for the benefits attributed to silymarin. Silymarin is thought to:

- Act as an antioxidant
- Inhibit lipid peroxidation in hepatocyte plasma membranes, thereby protecting against many toxins
- Protect against genomic injury by suppression of lipoxygenase, hydrogen peroxide and superoxide.
- Increase hepatocyte protein synthesis
- Suppress nuclear factor (NF)-kappaB
- Chelate iron and decrease glutathione destruction in iron overload conditions
- Stabilize mast cells
- Slow calcium metabolism
Decrease activity of tumor promoters

20-40% of an oral dose is found in bile, and 3-8% is excreted in the urine. Silybin levels peak in bile between 2-9 hours post ingestion and excretion in the bile continues for 24 hours. Extensive enterohepatic circulation is suspected. Absorption is said to be enhanced if silymarin is administered with phosphatidylcholine.

Actions, energetic: probable Liver Yin tonic.

Indications:

Traditional and energetic: nourishes liver, stomach, intestines, kidneys. Used by the Eclectics for liver disease, splenic or hepatic congestion, varicose veins, uterine hemorrhage and menstrual problems. It is used by some herbalists to increase lactation.

Evidence based: liver disease due to toxic insult; inflammatory liver disorders; cirrhosis. Based on one trial in cattle, milk thistle may be appropriate in the treatment of ketosis, increasing milk yield and decreasing ketonuria

Notes of interest: The characteristic spiked leaves display white veins which were said to carry the breast milk of the Virgin Mary. Dioscorides is said to have used milk thistle and Gerard (1596) had this to say of it: "My opinion is that this is the best remedy that grows against all melancholy (bile-liver) diseases". Culpeper and the Eclectics also made use of milk thistle.

Contraindications: No known contraindications have been reported. Milk thistle has been recommended problems associated with the gallbladder during pregnancy, and so is likely to be safe even for pregnant and lactating animals.

Drug Interactions: Milk thistle reduces activity of CYP3A4 and UGT1A6/9 liver enzymes, and decreases mitochondrial respiration in human hepatocytes. It may impair metabolism and clearance of other drugs which are substrates of these enzymes. Milk thistle may decrease insulin requirements in some diabetics.

Toxicology and Adverse effects: Milk thistle is relatively nontoxic, and in one study, mice tolerated a dose of 20g/kg. The European Agency for Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products has determined that milk thistle is safe in food-producing animals when used as the homeopathic mother tincture (a weak alcohol tincture of 1 part dried seed and 2 parts alcohol) and all homeopathic dilutions. Allergic reactions have been reported.

Preparation notes: Flavonolignans are not very water soluble, so liquid extracts must be alcohol based.

Dosage: Milk thistle is usually supplied as a solid extract, standardized to 70-80% silymarin. Milk thistle should be used for at least 8 weeks before expecting results such as improvement in biochemistries.

- Dried herb: 15-20mg/lb SID
- Concentrated extract: 2-5 mg/lb BID-TID
- Alcohol extract: 2 -5 mg/lb BID-TID

Combinations: Most often used alone, but combines well with turmeric and artichoke.

Selected Websites

The European Agency for Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products:

<http://www.emea.eu.int/pdfs/vet/mrls/066599en.pdf>

King's American Dispensatory:

<http://www.ibiblio.org/herbmed/eclectic/kings/silybum.html>

U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality Evidence Report/Technology Assessment #21:

<http://hstat.nlm.nih.gov/hq/Hquest/db/3146/screen/DocTitle/odas/1/s/45486>

(summary available at: <http://www.ahcpr.gov/clinic/epcsums/milksum.htm>)

Longwood Herbal Task Force on Milk Thistle:

<http://www.mcp.edu/herbal/milkthistle/milkthistle.htm>

Selected Abstracts:

Search terms - silymarin, silybin, silybinin, silybum, silybum marianum

Reviews

Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs 2001;61(14):2035-63 . The high prevalence of liver diseases such as chronic hepatitis and cirrhosis underscores the need for efficient and cost-effective treatments. The potential benefit of silymarin (extracted from the seeds of *Silybum marianum* or milk thistle) in the treatment of liver diseases remains a controversial issue. Therefore, the objective of this review is to assess the clinical efficacy and safety of silymarin by application of systematic approach. 525 references were found in the databases, of which 84 papers were retained for closer examination and 36 were deemed suitable for detailed analysis. Silymarin has metabolic and cell-regulating effects at concentrations found in clinical conditions, namely carrier-mediated regulation of cell membrane permeability, inhibition of the 5-lipoxygenase pathway, scavenging of reactive oxygen species (ROS) of the R-OH type and action on DNA-expression, for example, via suppression of nuclear factor (NF)-kappaB. Pooled data from case record studies involving 452 patients with *Amanita phalloides* poisoning show a highly significant difference in mortality in favour of silybinin [the main isomer contained in silymarin] (mortality 9.8% vs 18.3% with standard treatment; $p < 0.01$). The available trials in patients with toxic (e.g. solvents) or iatrogenic (e.g. antipsychotic or tacrine) liver diseases, which are mostly outdated and underpowered, do not enable any valid conclusions to be drawn on the value of silymarin. The exception is an improved clinical tolerance of tacrine. In spite of some positive results in patients with acute viral hepatitis, no formally valid conclusion can be drawn regarding the value of silymarin in the treatment of these infections. Although there were no clinical end-points in the four trials considered in patients with alcoholic liver disease, histological findings were reported as improved in two out of two trials, improvement of prothrombin time was significant (two trials pooled) and liver transaminase levels were consistently lower in the silymarin-treated groups. Therefore, silymarin may be of use as an adjuvant in the therapy of alcoholic liver disease. Analysis was performed on five trials with a total of 602 patients with liver cirrhosis. The evidence shows that, compared with placebo, silymarin produces a nonsignificant reduction of total mortality by -4.2% [odds ratio (OR) 0.75 (0.5 - 1.1)]; but that, on the other hand, the use of silymarin leads to a significant reduction in liver-related mortality of -7% [OR: 0.54 (0.3 - 0.9); $p < 0.01$]. An individual trial reported a reduction in the number of patients with encephalopathy of -8.7% ($p = 0.06$). In one study of patients with cirrhosis-related diabetes mellitus, the insulin requirement was reduced by -25% ($p < 0.01$). We conclude that available evidence suggests that silymarin may play a role in the therapy of (alcoholic) liver cirrhosis. Silymarin has a good safety record and only rare case reports of gastrointestinal disturbances and allergic skin rashes have been published. This review does not aim to replace future prospective trials aiming to provide the 'final' evidence of the efficacy of silymarin.

Flora K, Hahn M, Rosen H, Benner K. Milk thistle (Silybum marianum) for the therapy of liver disease. Am J Gastroenterol 1998 Feb;93(2):139-43 . Silymarin, derived from the milk thistle plant, *Silybum marianum*, has been used for centuries as a natural remedy for diseases of the liver and biliary tract. As interest in alternative therapy has emerged in the United States, gastroenterologists have encountered increasing numbers of patients taking silymarin with little understanding of its purported properties. Silymarin and its active constituent, silybin, have been reported to work as antioxidants scavenging free radicals and inhibiting lipid peroxidation. Studies also suggest that they protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumor promoters, stabilize mast cells, chelate iron, and slow calcium metabolism. In this article we review silymarin's history, pharmacology, and properties, and the clinical trials pertaining to patients with acute and chronic liver disease.

Clinical Trials in cattle

Vojtisek B, Hronova B, Hamrik J, Jankova B. [Milk thistle (*Silybum marianum*, L., Gaertn.) in the feed of ketotic cows] [Article in Czech] *Vet Med (Praha)* 1991 Jun;36(6):321-30. Two comparative trials were performed, each with 16 cows which in the period of 2-6 weeks after parturition had 7.9 mg and more acetone in 1 litre of milk. The cows, crossbreds of the Czech Red-Pied cattle with the Holstein cattle, were divided into control and test groups, eight in each using the system of pairs. The cows of test groups were given for a fortnight feed rations containing a meal of milk thistle (*Silybum marianum*, L., Gaertn.) seeds, at a rate of 0.3 kg per head/day with the contents of 2.34% silybin and silydianin (substances of the so called silymarin complex of the flavonolignane group). In comparison with the control cows, in the blood and milk of the former ones a decrease was demonstrated in the sum of acetone + acetoacetic acid (up to P less than 0.01) and beta-hydroxybutyric acid in the blood (up to P less than 0.05). The ketonuria degree dropped remarkably. Although there were not observed any differences in the parameters of acid-base metabolism in the blood (pH, PCO₂, BE, SB, BB), the pH values and net acid-base output in urine were higher in these cows. Milk production in the cows of control groups was decreasing during the trial (up to P 0.01), but in the test cows it was higher by 7.7% (trial 1) and by 3.4% (trial 2), in comparison with the milk yield at the beginning of the trials. Differences in metabolism parameters and milk production in favour of the cows which were given milk thistle in their feed rations were observed even in a fortnight after the diet stopped to contain this ingredient.

Experimental trials in dogs

Vogel G; Tuchweber B; Trost W; Mengs U: Protection by silibinin against *Amanita phalloides* intoxication in beagles. *Toxicol Appl Pharmacol* 1984 May;73(3):355-62. A single oral dose of the lyophilized deathcap fungus *Amanita phalloides* (85 mg/kg body wt) caused gastrointestinal signs of diarrhea, retching, and vomiting in beagles after a latent period of 16 hr. The pathologic lesions; the increases in serum transaminase (GOT, GPT), alkaline phosphatase, and bilirubin, as well as the fall in prothrombin time all indicated that liver damage was maximal at about 48 hr after poisoning. Four of twelve dogs given *A. phalloides* died with signs of hepatic coma within 35 to 54 hr with the biochemical values in the survivors reverting to normal by the ninth day. Silibinin administration (50 mg/kg) 5 and 24 hr after intoxication suppressed the serum changes and the fall in prothrombin time. The degree of hemorrhagic necrosis in the liver was markedly reduced, and none of the silibinin-treated dogs died.

Desplaces A; Choppin J; Vogel G; Trost W: The effects of silymarin on experimental phalloidine poisoning. *Arzneimittelforschung* 1975 Jan;25(1):89-96. The hepatoprotective action of silymarin, the active principle extracted from the fruit of *Silybum marianum* (L.) Gaertn., in animals (dogs, rabbits, rats, mice) intoxicated with phalloidine is evident, both after protective and curative treatment. A dose of 15 mg/kg of silymarin protects every animal when given 60 min before the toxin. When injected 10 min after phalloidine, a dose of 100 mg/kg of silymarin again provides total protection. However, as the time span between administration of the toxic substance and start of treatment increases, so the efficacy of silymarin decreases; after 30 min its curative effect is negligible. The histochemical and histoenzymological studies show that during intoxication of the mice by phalloidine, silymarin inhibits the effect of the toxic substance and regulates the functions of the hepatocyte, when given either 60 min before or 10 min after phalloidine.

Floersheim GL; Eberhard M; Tschumi P; Duckert F: Effects of penicillin and silymarin on liver enzymes and blood clotting factors in dogs given a boiled preparation of *Amanita phalloides*. *Toxicol Appl Pharmacol* 1978 Nov;46(2):455-62.

Paulova J; Dvorak M; Kolouch F; Vanova L; Janeckova L: [Verification of the hepatoprotective and therapeutic effect of silymarin in experimental liver injury with tetrachloromethane in dogs]: Overeni hepatoprotektivniho a terapeutickeho ucinku silymarinu pri experimentalnim poskozeni jater tetrachlormetanem u psu. *Vet Med (Praha)* 1990 Oct;35(10):629-35. The efficiency of preventive administration of silymarin and of silymarin medication were tested in dogs suffering from CCl₄ intoxication of liver. Sixteen dogs of the Beagle breed at the age of 8 to 10 months and of the weight 11.5 to

14.0 kg were divided into four groups with four animals each. Those groups were administered per os a single dose of CCl₄, 0.35 ml per kg liveweight contained in sunflower oil. The intact control groups was given sunflower oil free of any additive. Silymarin was administered per os in the form of suspension in the Dorfman reagent twice a day at the dose of 100 mg per kg. Silymarin was administered to the animals of the treated group four days after intoxication, to those of the preventively treated group four days before intoxication. The intact control group and the CCl₄ intoxicated control were administered the pure Dorfman reagent. Pure CCl₄ induced a significant increase in the AST and ALT activity in 12 and 24 hours after administration, and histological lesions in the liver--vacuolization of hepatocytes and necrobiosis of nuclei. The curative effects of silymarin on these changes were low. The protective effects of silymarin were manifested by the significantly lower AST and ALT activities in the 12th and 24th hour of the trial and by the insignificantly lower extent of lesions in liver parenchyma if compared with the control CCl₄ intoxicated group.

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