

Milk Thistle



Photo © Steven Foster

Silybum marianum (L.) Gaertn.

Text by Armando González Stuart, Ph.D., 2005

Botanical family: Asteraceae (Compositae).

Other common names: Marian thistle, St. Mary's Thistle.

Common names in Spanish: Cardo mariano, Cardo lechoso.

Medicinal parts: The dried, ripe fruits or achenes ("seeds").

History

The ripe fruits or achenes ("seeds") of this plant have been employed in Europe for many centuries for the treatment of liver and gall bladder dysfunctions (Schulz et al., 2004; Wichtl, 2004; Blumenthal, 2003). Originally from the European continent, this herb has been introduced to diverse parts of North America (Boon and Smith, 2004).

Active Principles

- The main active principles contained in milk thistle are silybin (silibinin), silychristin and silydianin, commonly referred to collectively as *sylimarin* (Boon and Smith, 2004; Blumenthal, 2003).

- The compounds mentioned above are phenolic compounds known as flavonolignans, which have antioxidant, anti-inflammatory, and free radical scavenging properties (Gruenwald, 2004; Tumova et al., 2004; Flora et al., 1998).
- The plant also contains fatty acids, silibonol and apigenin, as well as quercetin, taxifolin and biogenic amines (Boon and Smith, 2004; Skenderi, 2004).

Applications in Herbal Therapy

- Milk thistle is used primarily to treat various liver diseases and dysfunctions including alcoholic cirrhosis, hepatitis (due to viral infections or drug-induced), as well as hepatic problems related to diabetes (Gruenwald, 2004; Lieber et al., 2003; Jacobs et al., 2002; Blumenthal, 2000; Flora et al., 1998).
- Sylimarin has liver regenerative effects by stimulating the enzyme known as RNA polymerase in the nucleus of liver cells. This results in an increase of ribosomal protein synthesis which helps to regenerate hepatocytes. A practical application is the antidotal effect that sylimarin possesses against Amanita mushroom (death cap) poisoning. When injected intravenously, sylimarin blocks the toxic effect of the mushroom toxin alpha-amantin (Gruenwald, 2004).
- Preparations made from milk thistle have been approved by the German Commission E to treat mild gastrointestinal dysfunctions (Barrett, 2004; Blumenthal, 1998).
- Milk thistle has also been used to treat minor cases of hypotension (Skenderi, 2004).

Clinical Studies Employing Milk Thistle

- In a meta analysis of clinical trials employing milk thistle as a hepatoprotective agent, it was concluded that treatment with milk thistle appeared to be safe and well tolerated, although no reduction in mortality, no improvements in histology at liver biopsy, or in biochemical markers of liver function among patients with chronic liver disease was found (Jacobs et al., 2002).
- In another meta analysis of clinical trials evaluating sylimarin, it was concluded from the available evidence that it could be useful in the treatment of alcoholic liver cirrhosis, and that this phytochemical has a good safety record with only rare cases of gastrointestinal disturbances and allergic skin rashes having been reported (Saller et al., 2001).

- Although silymarin appears to offer a hepatoprotective effect in humans and baboons (Lieber et al., 2003), it apparently does not do so significantly in certain ruminants (Tedesco et al., 2004).
- A study was made investigating the possible modifying effect of dietary administration of the silymarin on AOM-induced colon carcinogenesis in male F344 rats. The researchers concluded that there was a clear indication of chemopreventive ability of dietary silymarin against chemically induced colon tumorigenesis. These results may provide a scientific basis for progression to clinical trials of the chemoprevention of human colon cancer (Kohno et al., 2002).
- Recent evidence that dietary silibinin can inhibit the growth of certain cancers in rodents suggests that this agent could certainly have clinical potential as an IKKbeta inhibitor. The beta subunit of the signalosome - IKKbeta, a vital catalyst of NF-kappaB activation is an obligate mediator of the disruption of insulin signaling induced by the excessive exposure of tissues to free fatty acids, as well as by adipocyte hypertrophy. For this reason, compounds which safely inhibit or suppress the activation of IKKbeta could be useful in reversing insulin resistance syndrome and help to curb type 2 diabetes. Silibinin, one of the active principles contained in milk thistle is one of the natural agents which has possesses this effect *in- vitro* (McCarty, 2005).
- A clinical trial in Germany evaluated a commercial herbal preparation containing milk thistle as well as other herbs; known as STW-5 for the treatment of dyspeptic symptoms. The results indicated that the herbal preparation was significantly better than placebo (Madisch et al., 2001).
- A review of sixteen placebo-controlled trials was undertaken related to the efficacy and safety of milk thistle in the treatment of liver dysfunctions. According to the authors, milk thistle's efficacy was not clearly established. The published evidence was clouded by poor experimental design and reporting. A possible benefit has frequently been shown, although inconsistently, for parameters such as aminotransferases, but laboratory tests are the most common outcome measure studied. Survival and other clinical outcomes have been less studied, giving mixed results. The authors concluded that future well controlled clinical studies are necessary in order to ascertain the therapeutic value of this plant and its potential effects (Mulrow et al., 2000).
- Research using various animal tumor models has shown that Silymarin possesses chemopreventive effects against chemical carcinogenesis as well as photocarcinogenesis. Topical application of silymarin inhibited 7,12-dimethylbenz(a)anthracene-initiated, as well as several tumor promoters, like 12-O-tetradecanoylphorbol-13-acetate, mezerein, benzoyal peroxide and okadaic acid, induced skin carcinogenesis in mice. Additionally, silymarin also prevented UVB-induced skin carcinogenesis. Results from various experiments suggest that silymarin could be a promising chemopreventive and safe phytochemical that

could be tested against skin cancer in humans, as well as a potential ingredient for sunscreens for protection against UV radiation (Katiyar, 2005).

- Silymarin has been evaluated for its protective effect against UV irradiation-induced apoptosis in human malignant melanoma cells (A375-S2 cells). Results from a clinical trial showed that treatment with silymarin 500 microM for 12 h significantly inhibited UV irradiation (2.4 J/cm², 5 min)-induced apoptosis in A375-S2 cells (Li et al., 2004).
- Research in vitro has shown that silibinin (one of the major constituents of silymarin) has cancer protective potential, since it down-regulates the co-activator of the androgen receptor, the prostate epithelium-derived Ets transcription factor (PDEF) and subsequently the secretion of PSA. Due to the antiproliferative potential of this phytochemical, as well as its inhibition of telomerase activity that mediates cell immortality and carcinogenesis, it may be useful therapeutically in the treatment of prostate cancer (Thelen et al., 2004^{1,2}).
- Studies in mice have shown that silibinin is efficacious in interfering with the growth of prostate cancer cells (PCA). This phytochemical compound also synergizes the therapeutic effects of doxorubicin in PCA cells, making it a potential candidate for use in combination chemotherapy (Singh and Agarwal, 2004).
- Silibinin is a natural chemopreventive agent that potentially offers the possibility of safe use in combination with chemotherapeutic agents such as doxorubicin, carboplatin or cisplatin in the treatment of breast cancer (Tyagi et al., 2004).
- Another major component of silymarin; silybin, has potent antibacterial activity against gram-positive bacteria without hemolytic activity, although it does not possess antimicrobial activity against gram-negative bacteria or fungi. Laboratory tests show that silybin inhibits RNA and protein synthesis on gram-positive bacteria (Lee et al., 2003).
- Certain anticancer agents employed in chemotherapy may induce short- and long-term toxicity to the liver. The active constituents in milk thistle may be useful in the prevention / treatment of liver dysfunction in patients currently undergoing chemotherapy (Ladas and Kelly, 2003).

Table 1. Selected Clinical Trials Employing Milk Thistle*

Reference	Plant / Plant product	Purpose of study	Number of subjects	Results
Mills et al., 2005	Milk-thistle extract capsules (450 mg) taken 3 times/day	To determine whether ingestion of milk thistle affects the pharmacokinetics of indinavir in healthy volunteers	16	The milk thistle extract did not significantly reduce levels of Indinavir
Tanamly et al., 2004	Herbal supplement containing silymarin	To evaluate silymarin, in preventing complications of chronic hepatitis C virus infection	177	Silymarin improved symptoms and general well-being, but did not have any effect upon hepatitis C virus infection, serum ALT, or serum and ultrasound markers for hepatic fibrosis. A higher dose may have been needed.
Di Cenzo et al., 2003	Silymarin (160 mg 3 times/day); Indinavir 800 mg 3 times/day	To determine if milk thistle's active principles (silymarin) alter the pharmacokinetics of indinavir	10	There was no apparent effect of silymarin on indinavir plasma concentrations.
Piscitelli et al., 2002	Milk thistle extract 175 mg (containing silymarin 153 mg)	To characterize the pharmacokinetics of indinavir in the presence and absence of milk thistle; as well as to determine the offset of any effect of milk thistle on indinavir disposition.	10	There was no interaction between milk thistle and indinavir in healthy patients.
Parés et al., 1998	Sylimarin	To determine the effect of silymarin in alcoholics with liver cirrhosis regarding survival, as well as clinical and laboratory changes	200	Silymarin did not have any significant effect on the course of the disease.
Ferenci et al., 1989	Silymarin (140 mg) three times per day	To determine the effect of silymarin on the outcome of patients	170	Effective

	with cirrhosis		
--	----------------	--	--

***Additional information about clinical trials and the products tested is available in the following publications:** Barrett, M. *Handbook of Clinically Tested Herbal Remedies* 2 Vols. New York: Haworth Herbal Press; 2004, Blumenthal, M. *ABC's Clinical Guide to Herbs*. New York: Thieme; 2003, Bratman S, Girman A. *Handbook of Herbal, Supplements and Their Therapeutic Uses*. St. Louis: Mosby; 2003, Bascom A. *Incorporating Herbal Medicine into Clinical Practice*. Philadelphia: F. A. Davis; 2002, Cassileth B, Lucarelli C. *Herb-Drug Interactions in Oncology*. London: BC Decker; 2003, Cupp M. *Toxicology and Clinical Pharmacology of Herbal Products*. Totowa, New Jersey: Humana Press; 2000 McKenna et al., *Botanical Medicines*. New York: Haworth Herbal Press; 2002, Rotblatt M, Ziment I. *Evidence-Based Herbal Medicine*. Philadelphia: Hanley and Belfus; 2002, Mahady et al., *Botanical Dietary Supplements*. The Netherlands: Swets and Zeitlinger; 2001; Ulbricht C, Basch E. *Natural Standard: Herbal and Supplement Reference*. New York: Elsevier; 2005; Werbach M, Murray M. *Botanical Influences on Illness* 2nd ed.; Tarzana CA: Third Line Press; 2000; Yarnell, E. et al., *Clinical Botanical Medicine*. New York: Mary Ann Liebert; 2003.



Safety/Precautions

- Milk thistle extracts are commonly regarded as safe, even for prolonged treatments (Mills and Bone, 2005; Gurley et al., 2004; Tanamley et al., 2004; Blumenthal, 2003, 1998; Boerth and Strong, 2002; Riley and Bhatti, 2001; Pepping, 1999).
- Only minor gastrointestinal discomfort has been experienced in rare cases (Saller et al., 2001; Blumenthal, 2000, 1998).
- Even though there are no adverse reports related to its use during pregnancy and lactation, as a precaution, consult a health professional before taking this herb if you are pregnant (Mill and Bone, 2005)
- In case of cyclopeptide mushroom poisoning, a physician should be consulted as to the possible application of the injectable preparations containing sylimarin; avoid giving milk thistle tea to any poisoned patient, as it has no therapeutic value for this purpose (Gehrmann et al., 2005).

Potential Herb/Drug Interactions

- In vivo and in vitro studies have shown that herbal products or supplements containing milk thistle seem to pose a minimal risk for CYP-mediated herb-drug

interactions in humans (Gurley et al., 2004; Patel et al., 2004; Di Cenzo et al., 2003; Zuber et al., 2002).

- Studies with healthy human subjects treated with indinavir and milk thistle extracts revealed that silymarin has no apparent effect on indinavir plasma concentrations (Di Cenzo et al., 2003).
- Studies with patients infected with the HIV virus who are currently taking antiviral medication have shown that milk thistle in commonly administered dosages apparently does not interfere with indinavir therapy (Piscitelli et al., 2002).
- One case report mentions that milk thistle may offer protection from liver toxicity caused by the pharmaceutical drug dilantin (phenytoin) (Brinker, 2001).
- Experimental studies in vitro have shown that silybin inactivated purified, recombinant cytochromes P450 (P450) 3A4 and 2C9 via a mechanism-based manner. The researchers concluded that careful administration of silybin with drugs primarily cleared by P450s 3A4 or 2C9 would be advisable, due to potential drug-drug interactions (Sridar et al., 2004)

Literature Cited

Barrett M. Handbook of Clinically Tested Herbal Remedies 2 Vols.
New York: Haworth Herbal Press; 2004; pp. 933-980.

Boerth J, Strong KM. The clinical utility of milk thistle (*Silybum marianum*) in cirrhosis of the liver. *J Herb Pharmacother.* 2002;2(2):11-7.

Boon H, Smith M. The Complete Natural Medicine Guide to the 50 Most Common Medicinal Herbs 2nd ed. Toronto: Robert Rose; 2004; pp.214-218 .

Brinker F. Herb Contraindications and Drug Interactions 3rd ed.
Sandy, Oregon: Eclectic Medical Publications; 2001.

Blumenthal, M. The ABC Clinical Guide to Herbs.
New York: Thieme; 2003; pp.285-295.

Blumenthal M. Expanded Commission E Monographs.
Boston: Integrative Medicine Publications; 2000.

Blumenthal, M. The Complete Commission E Monographs.
Boston: Integrative Medicine Publications; 1998.

DiCenzo R, Shelton M, Jordan K et al. Coadministration of milk thistle and indinavir in healthy subjects. *Pharmacotherapy*. 2003; 23(7):866-70.

Ferenci P, Dragosics B, Dittrich H et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol*. 1989;9(1):105-13.

Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol*. 1998; 93(2):139-43.

Gehrmann B, Koch W, Tschirch C, Brinkmann H. *Medicinal Herbs: A Compendium*.
New York: Haworth Herbal Press; 2005; p.133.

Gruenwald J. *PDR for Herbal Medicines 3rd ed.*
Montvale, NJ: Thomson PDR; 2004.

Gurley BJ, Gardner SF, Hubbard MA et al. In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: *Citrus aurantium*, *Echinacea purpurea*, milk thistle, and saw palmetto. *Clin Pharmacol Ther*. 2004; 76(5):428-40.

Jacobs BP, Dennehy C, Ramirez G et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med*. 2002; 113(6):506-15.

Katiyar SK. Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects (Review). *Int J Oncol*. 2005; 26(1):169-76.

Kohno H, Tanaka T, Kawabata K et al. Silymarin, a naturally occurring polyphenolic antioxidant flavonoid, inhibits azoxymethane-induced colon carcinogenesis in male F344 rats. *Int J Cancer*. 2002; 101(5):461-8.

Ladas EJ, Kelly KM. Milk thistle: is there a role for its use as an adjunct therapy in patients with cancer? *J Altern Complement Med*. 2003; 9(3):411-6.

Lee DG, Kim HK, Park Y et al. Gram-positive bacteria specific properties of silybin derived from *Silybum marianum*. *Arch Pharm Res*. 2003; 26(8):597-600.

Li LH, Wu LJ, Zhou B et al. Silymarin prevents UV irradiation-induced A375-S2 cell apoptosis. *Biol Pharm Bull*. 2004;27(7):1031-6.

Lieber CS, Leo MA, Cao Q et al., Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. *J Clin Gastroenterol*. 2003; 37(4):336-9.

Madisch A, Melderis H, Mayr G, Sassin I, Hotz J. A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study. [Article in German] *Z Gastroenterol*. 2001; 39(7):511-7.

- McCarty MF. Potential utility of natural polyphenols for reversing fat-induced insulin resistance. *Med Hypotheses*. 2005; 64(3):628-35.
- Mills E, Wilson K, Clarke M et al. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis. *Eur J Clin Pharmacol*. 2005 Jan 22; [Epub ahead of print].
- Mills S, Bone K. *The Essential Guide to Herbal Safety*. New York: Elsevier-Churchill-Livingstone; 2005; pp.594-596.
- Mulrow C, Lawrence V, Jacobs B et al. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects. *Evid Rep Technol Assess (Summ)*. 2000 ;(21):1-3.
- Patel J, Buddha B, Dey S, Pal D, Mitra AK. In vitro interaction of the HIV protease inhibitor ritonavir with herbal constituents: changes in P-gp and CYP3A4 activity. *Am J Ther*. 2004; 11(4):262-77.
- Pares A, Planas R, Torres M et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol*. 1998; 28(4):615-21.
- Pepping J. Milk thistle: *Silybum marianum*. *Am J Health Syst Pharm*. 1999; 56(12):1195-7.
- Piscitelli SC, Formentini E, Burstein AH et al. Effect of milk thistle on the pharmacokinetics of indinavir in healthy volunteers. *Pharmacotherapy*. 2002; 22(5):551-6.
- Riley TR 3rd, Bhatti AM. Preventive strategies in chronic liver disease: part I. Alcohol, vaccines, toxic medications and supplements, diet and exercise. *Am Fam Physician*. 2001; 64(9):1555-60.
- Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs*. 2001;61(14):2035-63.
- Schulz V, Hansel R, Tyler V, Blumenthal, M. *Rational Phytotherapy* 5th ed. Berlin: Springer-Verlag; 2004.
- Singh RP, Agarwal R. Prostate cancer prevention by silibinin. *Curr Cancer Drug Targets*. 2004; 4(1):1-11.
- Skenderi G. *Herbal Vade Mecum*. Rutherford, NJ: Herbacy Press; 2004; pp. 248-249.
- Sridar C, Goosen TC, Kent UM et al. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases. *Drug Metab Dispos*. 2004; 32(6):587-94.

Tedesco D, Domeneghini C, Sciannimanico D. et al. Silymarin, a possible hepatoprotector in dairy cows: biochemical and histological observations. *J Vet Med A Physiol Pathol Clin Med.* 2004; 51(2):85-9.

Tanamly MD, Tadros F, Labeeb S et al. Randomised double-blinded trial evaluating silymarin for chronic hepatitis C in an Egyptian village: study description and 12-month results. *Dig Liver Dis.* 2004; 36(11):752-9.

¹Thelen P, Jarry H, Ringert RH, Wuttke W. Silibinin down-regulates prostate epithelium-derived Ets transcription factor in LNCaP prostate cancer cells. *Planta Med.* 2004; 70(5):397-400.

²Thelen P, Wuttke W, Jarry H, Grzmil M, Ringert RH. Inhibition of telomerase activity and secretion of prostate specific antigen by silibinin in prostate cancer cells. *J Urol.* 2004 ;171(5):1934-8.

Tumova L, Gallova K, Rimakova J. *Silybum marianum* in vitro [Article in Czech] *Ceska Slov Farm.* 2004; 53(3):135-40.

Tyagi AK, Agarwal C, Chan DC, Agarwal R. Synergistic anti-cancer effects of silibinin with conventional cytotoxic agents doxorubicin, cisplatin and carboplatin against human breast carcinoma MCF-7 and MDA-MB468 cells. *Oncol Rep.* 2004; 11(2):493-9.

von Schonfeld J, Weisbrod B, Muller MK Silibinin, a plant extract with antioxidant and membrane stabilizing properties, protects exocrine pancreas from cyclosporin A toxicity. *Cell Mol Life Sci.* 1997; 53(11-12):917-20.

Wichtl M. *Herbal Drugs and Phytopharmaceuticals* 3rd ed. Boca Ratón, FL: CRC Press; 2004.

Zuber R, Modriansky M, Dvorak Z et al. Effect of silybin and its congeners on human liver microsomal cytochrome P450 activities. *Phytother Res.* 2002; 16(7):632-8.