Chapter 80

MILK THISTLE
[*Silybum marianum* (L.) Gaertner]

HISTORY

For over 2,000 years, milk thistle has been a treatment for hepatobiliary disease. The Roman naturalist, Pliny the Elder (AD 23–79), described this plant as "excellent for carrying off the bile." During the 16th century, milk thistle was a treatment for liver diseases. The English herbalist/physician, Nicolas Culpepper (1616–1654) recommended milk thistle for jaundice, and the Swiss physician, Albrecht von Haller (1708–1777) used milk thistle as a treatment for liver diseases. European colonists introduced milk thistle into the United States and South America. Medical herbalists (eclectics) used milk thistle for liver congestion, menstrual disorders, renal dysfunction, and varicose veins.[1]

BOTANICAL DESCRIPTION

Common Name: Milk Thistle, Blessed Milk-Thistle, Blessed Milkthistle, Spotted Thistle, Variegated Thistle

Scientific Name: *Silybum marianum* (L.) Gaertner

Botanical Family: Asteraceae (sunflowers, tournesols)

Physical Description: This annual or biennial plant reaches 3–10 ft (~1–3 m) in height with large, alternating leaves that contain spines on the edges. The veins on the leaves extrude a white, milky sap when ruptured. Single, large purple flowers with sharp spines appear at the end of each stem from June to August.

Distribution and Ecology: Milk thistle is indigenous to southern Europe, southern Russia, North Africa, and Asia Minor. This plant has naturalized to dry, rocky soils in North and South America, Australia, China, and Central Europe.

EXPOSURE

Sources

The seeds and dried fruits from milk thistle (*Silybum marianum*) are the source of the silymarin complex of flavonolignans, which are used to standardize milk thistle extract to contain 70–80% silymarin flavonolignans. The seeds and dried fruits usually contain about 1.5–3% silymarin. The typical silymarin extraction process involves the defatting of the seeds in a Soxhlet extraction with petroleum ether for 4 hours followed by a second Soxhlet extraction with methanol for 5 hours.[2] The maximum yields (mg/g seed) of flavonolignans in several samples of seeds from milk thistle using ethanol were as follows: silibinin A, 4.0; silibinin B, 7.0; silicristin (silychristin), 4.0; taxifolin, 0.6; and silidianin, 0.4.[3] The active flavonolignans in silymarin are poorly water soluble. Consequently, the extract is administered as a capsule rather than a tea, which typically contains <10% silymarin.

Medicinal Uses

Traditional

Milk thistle has been a traditional treatment of liver disease and dyspepsia since ancient times, including the

Medical Toxicology of Natural Substances, by Donald G. Barceloux, MD

treatment of gallstones and jaundice. Other traditional uses for milk thistle include amenorrhea, uterine hemorrhage, constipation, diabetes, hay fever, and varicose veins.

Current

Interpretation of the clinical trials measuring the efficacy of milk thistle extract in hepatobiliary disease is difficult because of a number of flaws in these trials including small sample size, variability in the severity and type of hepatic disease, heterogeneous doses, frequent lack of control groups, and poorly defined end points. Based on well-designed clinical trials, the use of milk thistle extracts probably does not alter the clinical course of patients with alcoholic cirrhosis or hepatitis B/C liver disease.[4] Some studies suggest, but do not prove, that milk thistle extract improves liver injury. Pooled data from case reports involving 452 patients with *Amanita phalloides* poisoning suggest a significant difference in mortality favoring the use of silibinin (mortality 9.8% vs. 18.3%, $P < 0.01$).[5] However, there are no randomized clinical trials to document the efficacy of silibinin for amanita poisoning. Silymarin is possibly efficacious as an adjuvant in the therapy of alcoholic liver disease, but the clinical data are inconsistent. A randomized trial of 200 alcoholics with cirrhosis did not demonstrate a statistically significant reduction in mortality between the silymarin and control groups during the 2.5-year observation period.[6] Additionally, a randomized-controlled clinical trial failed to detect a significant difference in serum hepatic aminotransferases between the silymarin and control groups.[7] Despite some positive results in patients with acute viral hepatitis, the value of silymarin in the treatment of these infections is unproven. A systematic review of 148 studies involving the treatment of liver disease with silymarin noted that only seven studies focused on the outcome of patients with hepatitis B, hepatitis C, or unspecified viral hepatitis.[8] These studies suggested the possibility of silymarin treatment reducing serum hepatic aminotransferases in these patients, but there was no evidence of improvement in viral load or liver histology.

Regulatory Status

The German Commission E approves the use of silymarin for the treatment of liver diseases, including hepatitis A, alcoholic cirrhosis, and chemically induced hepatitis.

PRINCIPAL INGREDIENTS

Chemical Composition

Silymarin is a mixture of flavonolignans present in milk thistle (*Silybum marianum*) seed and fruit extracts. The major constituents of the silymarin complex are the following four isomeric flavonolignans: silibinin (silybin, CAS RN: 22888-70-6), isosilibinin (isosilybin, CAS RN: 72581-71-6), silidianin (silydianin, CAS RN: 29782-68-1), and silicristin (silychristin, CAS RN: 33889-69-9) as demonstrated in Figure 80.1. There are at least two pairs of diastereoisomeric flavonolignans compounds (silibinin A and B, isosilibinin A and B).[9] These flavonolignans have phenylchromone skeletons (flavonoid moiety) with different oxidative links to coniferyl alcohols (lignan moiety).[10] Silibinin and isosilibinin occur as a pair of diastereomers, epimeric at C12 and C13. As measured by high performance liquid chromatography (HPLC) and capillary electrophoresis (CE), several samples of dried fruits from milk thistle contained about 2.5–3% weight/weight silymarin complex.[11] Silymarin accounts for about 40–80% of the bulk material for producing pharmaceutic preparations of the milk thistle, depending on the geographical source, season, and growing conditions.[12] Some, but not all, pharmaceutical preparations of milk thistle are standardized to 70% silymarin content. The principal flavonolignane in silymarin is silibinin, which comprises about 50–70% of the silymarin content. Minor flavonolignans in the silymarin complex include isosilicristin, silymonin, silandrin, 2,3-dehyrosilibinin, 2,3-dehydrosilicristin, and taxifolin.[13] The latter compound is a dihydroquercitin precursor to the flavonolignans. Remaining constituents of milk thistle extract are mostly polymeric and oxidized polyphenolic compounds that are not well delineated.[14]

Physiochemical Properties

Taxifolin (CAS RN: 480-18-2, $C_{15}H_{12}O_7$) and silicristin are more polar compounds than silibinin A and silibinin B, resulting in differences in the extraction rates for a given extraction process.[15] Degradation of flavonolignans (e.g., silibinin, silicristin) occurs at temperatures above 100 °C (212 °F).[16] Properties associated with the administration of silymarin include antioxidation, free radical scavenger, inhibition of lipid peroxidation, repletion of glutathione stores, and inhibition of phase I reactions.[17]

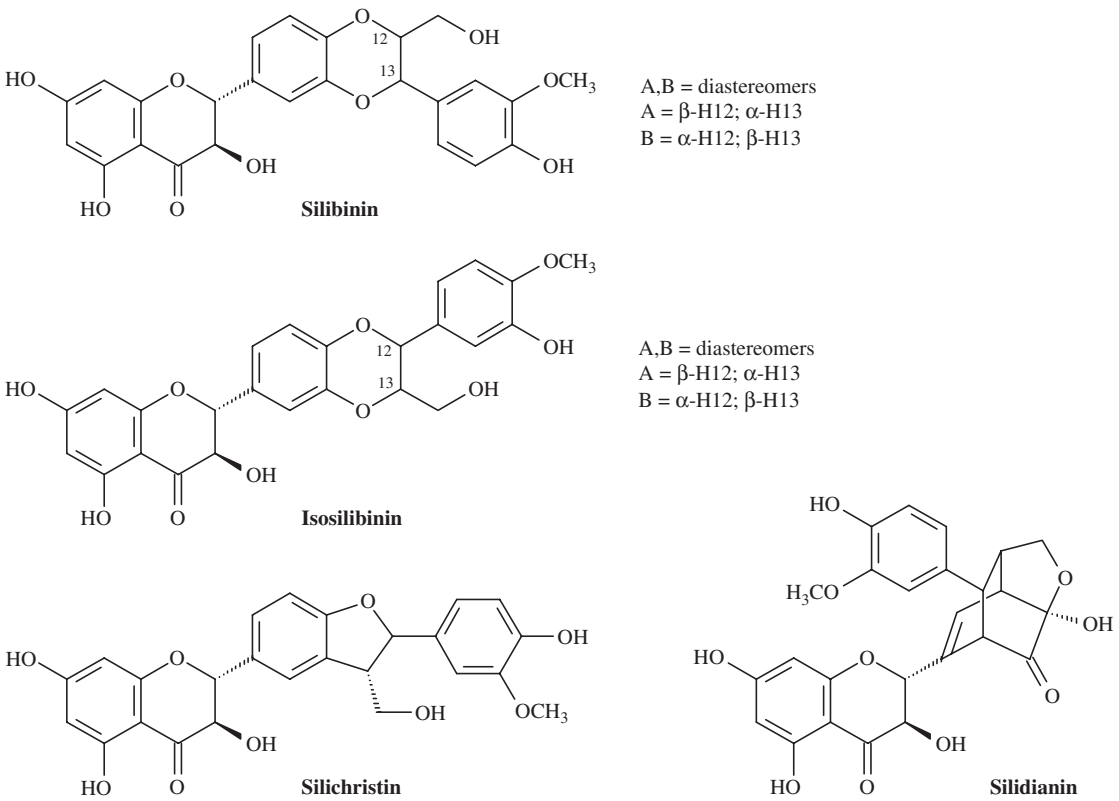

FIGURE 80.1. Chemical structures of major flavonolignans in milk thistle extract.

DOSE RESPONSE

The typical adult dose of the extract of milk thistle is 100–300 mg 3 times daily standardized to 70–80% silymarin.

TOXICOKINETICS

Kinetics

Absorption of silibinin from the gastrointestinal (GI) tract is relatively rapid with peak concentrations of free silibinin occurring about 1.5–2.5 hours after ingestion. The bioavailability of silibinin in milk thistle extract is relatively low (20–50%). The addition of phosphatidylcholine to silymarin improves the bioavailability of the flavonolignans.[18] Most (~90%) of the silibinin in plasma appears as conjugated silibinin as a result of the rapid conjugation of silibinin. The elimination half-life of total silibinin is relatively short. Following the administration of single doses ranging from 102–254 mg to six healthy volunteers, the elimination half-life of silibinin was approximately 6 hours[19] compared with about 4 hours for 12 healthy volunteers receiving a lipophilic silibinin-phosphatidylcholine complex.[20] The latter group received silipide® (IdB 1016, Inverni della Beffa Research and Development Laboratories, Milan, Italy) in a dose of 80 mg expressed as silibinin equivalents. Free silibinin is rapidly cleared from the plasma with a plasma elimination half-life of about 2 hours. The major metabolite of silibinin is a demethylated compound, while mono-hydroxy and di-hydroxy silibinin are minor metabolites.[21] The kidneys excrete <3–5% of the absorbed dose of silibinin as total silibinin (free + conjugated). Biliary excretion is a major route of silibinin elimination.[22]

Drug Interactions

In vitro studies suggest that silibinin inhibits both phase I and II reactions including CYP3A4, CYP2C9, and UGT1A1.[23] However, the clinical relevance of these effects is equivocal. A meta-analysis of three studies on the interaction of milk thistle extract on indinavir pharmacokinetics demonstrated a pooled mean difference of 1% in the $AUC_{0\text{-}8}$ (95% CI: –53–55%) of indinavir before and after the administration of milk thistle extract.[24] This difference was not statistically significant

(P = 0.97). An *in vivo* study of 12 healthy volunteers receiving 700 mg milk thistle extract daily for 28 days did not detect a statistically significant difference between the presupplementation and postsupplementation phenotypic ratios for CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity.[25] Other *in vivo* studies of volunteers receiving 900 mg standardized milk thistle extract daily for 14 days indicated that supplementation with this extract did not alter digoxin pharmacokinetics (P-glycoprotein transporter)[26] or midazolam (CYP3A4) kinetics.[27] These studies suggest that any potential CYP-mediated herb–drug interaction between milk thistle extract and drugs metabolized by these isoenzymes would be minimal.

CLINICAL RESPONSE

With the exception of anaphylaxis, the adverse reactions associated with the use of milk thistle extract are usually mild. These effects typically involve headache, GI disturbances (nausea, vomiting, diarrhea, epigastric pain), and allergic reaction (pruritus, urticaria, arthralgias).[28] A case report temporally associated the use of milk thistle capsules with intermittent episodes of nausea, vomiting, diarrhea, colicky abdominal pain, sweating, and "collapse."[29] These symptoms resolved after cessation and recurred after re-challenge with the milk thistle extract. There was no analysis of the capsules for contaminants; therefore, a causal link could not be established between silymarin from milk thistle extract and the observed clinical effects.

DIAGNOSTIC TESTING

Methods for the quantitation of flavonolignans in the silymarin complex include capillary zone electrophoresis[30] and high performance liquid chromatography with UV,[31] and liquid chromatography with electrochemical or mass spectrometric detection.[32] Stereoselective assays can quantitate free plasma (unconjugated) silibinin using column-switching HPLC with electrochemical detection and total plasma (free and conjugated) silibinin using reverse-phase HPLC with UV detection.[33] The limit of quantitation for these methods is approximately 0.25 ng/mL per diastereomer. The limits of detection and quantitation for flavonolignans by HPLC with photodiode array detector and electron spray ionization-mass spectrometry ranged from 0.5–2 ng/mL and 2.5–10 ng/mL, respectively.[34] The thermal stability of the silymarin complex is relatively low, and long-term studies indicate that the shelf-life of milk thistle tinctures (hydro-alcohol extracts) is about 3 months at 25 °C (77 °F).[35]

TREATMENT

Adverse reactions to the use of milk thistle extracts are usually mild and treatment is supportive. Gut decontamination is unnecessary. Rarely, allergic reactions including anaphylaxis may occur that requires standard care (epinephrine, antihistamines, intravenous fluids, vasopressors).

References

1. Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. Am J Gastroenterol 1998;93:139–143.
2. Wallace SN, Carrier DJ, Clausen EC. Batch solvent extraction of flavonolignans from milk thistle (*Silybum marianum* L. Gaertner). Phytochem Anal 2005;16:7–16.
3. Wallace SN, Carrier DJ, Clausen EC. Extraction of nutraceuticals from milk thistle Part II. Extraction with organic solvents. Appl Biochem Biotechnol 2003;105–108: 891–903.
4. Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases—a systematic Cochrane hepato-biliary group review with meta-analyses of randomized clinical trials. Am J Gastroenterol 2005;100:2583–2591.
5. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs 2001;61:2035–2063.
6. Pares A, Planas R, Torres M, Caballeria J, Viver JM, Acero D, 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: 615–621.
7. Lucena MI, Andrade RJ, De la Cruz JP, Rodriguez-Mendizabal M, Blanco E, Sanchez de la Cuesta F. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Ther 2002;40:2–8.
8. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. J Viral Hepatitis 2005;12: 559–567.
9. Lee DY-W, Liu Y. Molecular structure and stereochemistry of silybin A, silybin B, isosilybin A, and isosilybin B, isolated from *Silybum marianum* (milk thistle). J Nat Prod 2003;66:1171–1174.
10. Crocenzi FA, Roma MG. Silimarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. Curr Medicinal Chem 2006;13: 1055–1074.
11. Quaglia MG, Bossu E, Donati E, Mazzanti G, Brandt A. Determination of silymarin in the extract from dried *Silybum marianum* fruits by high performance liquid chromatography and capillary electrophoresis. J Pharm Biomed Anal 1999;19:435–442.

12. Wagner H, Diesel P, Seitz M. [The chemistry and analysis of silymarin from *Silybum marianum* Gaertn]. Arzneimittelforschung 1974;24:466–471. [German]
13. Kim N-C, Graf TN, Sparacino CM, Wani MC, Wall ME. Complete isolation and characterization of silybins and isosilybins from milk thistle (*Silybum marianum*). Org Biomol Chem 2003;1:1684–1689.
14. Sonnenbichler J, Zetl I. Biochemical effects of the flavonolignane silibinin on RNA, protein and DNA synthesis in rat livers. Prog Clin Biol Res 1986;213:319–331.
15. Barreto JF, Wallace SN, Carrier DJ, Clausen EC. Extraction of nutraceuticals from milk thistle. Appl Biochem Biotechnol 2003;105–108:881–889.
16. Duan L, Carrier DJ, Clausen EC. Silymarin extraction from milk thistle using hot water. Appl Biochem Biotechnol 2004;113–116:559–568.
17. Carini R, Comoglio A, Albano E, Poli G. Lipid peroxidation and irreversible damage in the rat hepatocyte model. Protection by the silybin-phospholipid complex IdB 1016. Biochem Pharmacol 1992;43:2111–2115.
18. Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E. Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet 1990;15:333–338.
19. Weyhenmeyer R, Mascher H, Birkmayer J. Study on doselinearity of the pharmacokinetics of silibinin diastereomers using a new stereospecific assay. Int J Clin Pharmacol Ther Toxicol 1992;30:134–138.
20. Gatti G, Perucca E. Plasma concentrations of free and conjugated silybin after oral intake of a silybin-phosphatidylcholine complex (silipide) in healthy volunteers. Int J Clin Pharmacol Ther 1994;32:614–617.
21. Gunaratna C, Zhang T. Application of liquid chromatography-electrospray ionization-ion trap mass spectrometry to investigate the metabolism of silibinin in human liver microsomes. J Chromatogr B 2003;794:303–310.
22. Schandalik R, Gatti G, Perucca E. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung 1992;42:964–968.
23. Sridar C, Gossen TC, Kent UM, Williams JA, Hollenberg PF. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyl transferases. Drug Metab Disp 2004;32:587–594.
24. Mills E, Wilson K, Clarke M, Foster B, Walker S, Rachlis B, et al. Milk thistle and indinavir: a randomized controlled pharmacokinetics study and meta-analysis. Eur J Clin Pharmacol 2005;61:1–7.
25. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Carrier J, 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;76:428–440.
26. Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, Yates CR, et al. Effect of milk thistle (*Silybum marianum*) and black cohosh (*Cimicifuga racemosa*) supplementation on digoxin pharmacokinetics in humans. Drug Metab Disp 2006;34:69–74.
27. Gurley B, Hubbard MA, Williams K, Thaden J, Tong Y, Gentry WB, et al. Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. J Clin Pharmacol 2006;46:201–213.
28. Wellington K, Jarvis B. Silymarin: a review of its clinical properties in the management of hepatic disorders. BioDrugs 2001;15:465–489.
29. Adverse Drug Reactions Advisory Committee (Australia). An adverse reaction to the herbal medication milk thistle (*Silybum marianum*). Med J Aust 1999;170: 218–219.
30. Kvasnicka F, Biba B, Sevcik R, Voldrich M, Kratka J. Analysis of the active components of silymarin. J Chromatogr A 2003;990:239–245.
31. Rickling B, Hans B, Kramarczyk R, Krumbiegel G, Weyhenmeyer R. Two high-performance liquid chromatographic assays for the determination of free and total silibinin diastereomers in plasma using column switching with electrochemical detection and reversed-phase chromatography with ultraviolet detection. J Chromatogr B Biomed Appl 1995;670:267–277.
32. Ding T, Tian S, Zhang Z, Gu D, Chen Y, Shi Y, Sun Z. Determination of active component in silymarin by RP-LC and LC/MS. J Pharm Biomed Anal 2001;26: 155–161.
33. Rickling B, Hans B, Kramarczyk R, Krumbiegel G, Weyhenmeyer R. Two high-performance liquid chromatographic assays for the determination of free and total silibinin diastereomers in plasma using column switching with electrochemical detection and reversed-phase chromatography with ultraviolet detection. J Chromatogr B Biomed Appl 1995;670:267–277.
34. Zhao Y, Chen B, Yao S. Simultaneous determination of abietane-type diterpenes, flavonolignans and phenolic compounds in compound preparations of *Silybum marianum* and *Salvia miltiorrhiza* by HP-DAD-ESI MS. J Pharmaceut Biomed Anal 2005;38:564–570.
35. Bilia AR, Bergonzi MC, Gallori S, Mazzi G, Vincieri FF. Stability of the constituents of calendula, milk-thistle and passionflower tinctures by LC-DAD and LC-MS. J Pharmaceut Biomed Anal 2002;30:613–624.