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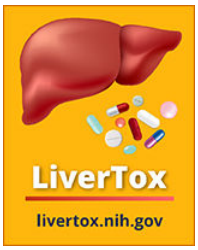

Milk Thistle

Updated: January 21, 2020.

OVERVIEW

Introduction

Milk thistle is an annual or biennial herb native to the Mediterranean region, which has been used for centuries as a food and as a medicinal herb for treatment of liver conditions. Milk thistle has not been implicated in causing liver injury and is still used widely as a liver tonic in patients with acute and chronic liver diseases.

Background

Milk thistle (Silybum marianum) is an herb native to Europe, Asia Minor and Northern Africa that has been used widely to treat liver disease. Extracts of milk thistle seeds contain multiple flavanolignans, known collectively as silymarin, consisting largely of silybinin, silychristin and silydianin. In cell culture and animal models, silymarin has been shown to prevent or ameliorate acute liver injury due to many toxins including acetaminophen and Amanita phalloides. Human studies of silymarin in patients with chronic liver disease have been promising but inconclusive. Controlled trials of silymarin in chronic hepatitis C and nonalcoholic fatty liver disease found little or no evidence of benefit in ameliorating disease activity or in slowing disease progression. Milk thistle is marketed as capsules or tablets containing ethanol extracted silymarin in amounts of 250 to 750 mg and is purported to be beneficial for liver disease, including alcoholic and viral liver disease. The daily dosage varies but it is typically taken 2 to 3 times daily. Intravenous preparations of purified silybinin are approved in Europe for therapy of Amanita phalloides mushroom poisoning. No prospective controlled trials of intravenous silybinin have been published. Oral silymarin has few if any adverse side effects and is well tolerated even in high daily doses.

Hepatotoxicity

Despite its wide spread use in patients with and without liver disease, milk thistle has not been implicated in causing serum enzyme elevations or clinically apparent acute liver injury. While silymarin has effects on cytochrome P450 enzymes and hepatic transporters in vitro, there is little evidence that it causes clinically significant herb-drug interactions.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Other Names: Silybin, Silybum, Silymarin, Marian thistle

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Milk Thistle – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

Fact Sheet at National Center for Complementary and Integrative Health, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Milk Thistle	84604-20-6	Herbal mixture	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 21 January 2020

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; milk thistle is not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS] mentions that silymarin is used to treat liver disease but evidence for its benefit is contradictory).

Milk thistle. In, PDR for herbal medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 578-83.

(Compilation of short monographs on herbal medications and dietary supplements).

Flora K, Hahn M, Rosen H, Benner K. Milk thistle (Silybum marianum) for the therapy of liver disease. Am J Gastroenterol. 1998;93:139–43. PubMed PMID: 9468229.

(Review of the evidence of hepatoprotective activities of milk thistle based upon its antioxidants and ability to scavenge free radicals and inhibit lipid peroxidation, but evidence in human trials has been inconclusive; intravenous silymarin protects laboratory animals exposed to Amanita phalloides and open label studies in humans have reported higher than expected survival rates).

Stedman C. Herbal hepatotoxicity. Semin Liver Dis. 2002;22:195–206. PubMed PMID: 12016550.

(Review and description of patterns of liver injury due to herbals, including discussion of potential risk factors, and herb-drug interactions; milk thistle is not discussed).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis. 2003;7:453–73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity; milk thistle is not listed as causing hepatotoxicity).

Gordon A, Hobbs DA, Bowden DS, Bailey MJ, Mitchell J, Francis AJ, Roberts SK. Effects of Silybum marianum on serum hepatitis C virus RNA, alanine aminotransferase levels and well-being in patients with chronic hepatitis C. J Gastroenterol Hepatol. 2006;21:275–80. PubMed PMID: 16460486.

(17 patients with chronic hepatitis were treated for 12 weeks with silymarin or placebo in a cross over study; there were no significant changes in HCV RNA or ALT levels and adverse events were similar in the two groups).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl. 2004;10:1018–23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, none attributed to milk thistle).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008; 100: 688-95. Spanish. PMID: 19159172

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, but none attributed to milk thistle).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, milk thistle is not listed).

Ferenci P, Scherzer TM, Kerschner H, Rutter K, Beinhardt S, Hofer H, Schöniger-Hekele M, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. Gastroenterology. 2008;135:1561–7. PubMed PMID: 18771667.

(Intravenous infusion of silibinin daily for 7 days led to rapid and marked fall in serum HCV RNA levels in 30 patients with chronic hepatitis C, the decrease starting within one day, ranging from 1 to 5 log[10] IU/mL, being dose dependent and usually followed by a rise once infusions were stopped).

Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Cochrane Database Syst Rev. 2007;(4):CD003620. PubMed PMID: 17943794.

(Systematic review concluded that milk thistle had no significant effects on mortality in patients with alcoholic liver disease or chronic hepatitis B or C and was not associated with an increased risk of adverse events).

El-Kamary SS, Shardell MD, Abdel-Hamid M, Ismail S, El-Ateek M, Metwally M, Mikhail N, et al. A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis. Phytomedicine. 2009;16:391–400. PubMed PMID: 19303273.

(Controlled trial of 4 week course of silymarin vs placebo in 105 patients with acute viral hepatitis found no differences in outcome, but minimally faster resolution of dark urine and jaundice; there were no serious adverse events and side effects were uncommon and similar in frequency between the two groups).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis. 2009;29:373–82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; milk thistle is not listed as a potentially hepatotoxic botanical).

Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. Phytother Res. 2010;24:1423–32. PubMed PMID: 20564545.

(Review of the history, active components, mechanism of action, in vitro and in vivo studies of activity and clinical efficacy and safety of milk thistle; the active component is found in lipophilic extracts of the plant seeds and is composed of flavonolignands, silybin, silydianin and silychristin, collectively known as silymarin, which acts as an antioxidant, antifibrotic and toxin blockading agent).

Wagoner J, Negash A, Kane OJ, Martinez LE, Nahmias Y, Bourne N, Owen DM, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. Hepatology. 2010;51:1912–21. PubMed PMID: 20512985.

(Silymarin inhibited hepatitis C virus replication in cell culture systems, inhibiting virus entry, viral RNA and protein production and production of infectious virus).

Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, Kelly KM. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Cancer. 2010;116:506–13. PubMed PMID: 20014183.

(Among 50 children receiving induction chemotherapy for acute leukemia who were treated with milk thistle [5 mg/kg] or placebo by mouth daily for 28 days, there were no differences in mean changes in ALT, AST, or serum bilirubin, although there was "a trend" for lower levels of liver toxicity with silymarin).

Payer BA, Reiberger T, Rutter K, Beinhardt S, Staettermayer AF, Peck-Radosavljevic M, Ferenci P. Successful HCV eradication and inhibition of HIV replication by intravenous silibinin in an HIV-HCV coinfected patient. J Clin Virol. 2010;49:131–3. PubMed PMID: 20709593.

(27 year old woman with chronic hepatitis C and HIV infection was treated with two weeks of daily intravenous silibinin overlapping by one week with 16 weeks of peginterferon and ribavirin, and had a sustained HCV and transient HIV virological response).

Schrieber SJ, Hawke RL, Wen Z, Smith PC, Reddy KR, Wahed AS, Belle SH, et al. Differences in the disposition of silymarin between patients with nonalcoholic fatty liver disease and chronic hepatitis C. Drug Metab Dispos. 2011;39:2182–90. PubMed PMID: 21865319.

Pharmacokinetic and safety study of escalating doses of silymarin in 18 patients with hepatitis C and 12 with nonalcoholic fatty liver found no evidence of toxicity when given in high doses of up to 8 days).

Loguercio C, Festi D. Silybin and the liver: from basic research to clinical practice. World J Gastroenterol. 2011;17:2288–301. PubMed PMID: 21633595.

(Review of the chemical structure, mechanisms of action, and clinical efficacy of silybin, a component of milk thistle; no discussion of safety and no mention of hepatotoxicity).

Choi YH, Chin YW, Kim YG. Herb-drug interactions: focus on metabolic enzymes and transporters. Arch Pharm Res. 2011;34:1843–63. PubMed PMID: 22139685.

(Summary and review of in vitro and clinical evidence of herb-drug interactions).

Fried MW, Navarro VJ, Afdhal N, Belle SH, Wahed AS, Hawke RL, Doo E, et al. Silymarin in NASH and C Hepatitis (SyNCH) Study Group. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: a randomized controlled trial. JAMA. 2012;308:274–82. PubMed PMID: 22797645.

(Controlled trial of 6 month course of two doses of silymarin vs placebo in 154 patients with chronic hepatitis C found no effect on ALT or HCV RNA levels, and side effects were similar in the silymarin and placebo treated groups).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, 15 of which were attributed to a herbal or dietary product, but none specifically to milk thistle).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to milk thistle or other herbal products).

Gores KM, Hamieh TS, Schmidt GA. Survival following investigational treatment of amanita mushroom poisoning: thistle or shamrock? Chest. 2014;146:e126–e129. PubMed PMID: 25288004.

(71 year old man developed acute liver failure 2 days after consuming wild mushrooms [bilirubin 1.5 mg/dL, ALT 2730 U/L, INR 1.3] and was treated experimentally with intravenous silymarin [but only after 4 days when laboratory results were already improving] and recovered rapidly).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148(7):1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 145 [16%] were attributed to herbal and dietary supplements, but none specifically to milk thistle).

Zhang S, Pan H, Peng X, Lu H, Fan H, Zheng X, Xu G, Wang M, Wang J. Preventive use of a hepatoprotectant against anti-tuberculosis drug-induced liver injury: A randomized controlled trial. J Gastroenterol Hepatol. 2016;31:409–16. PubMed PMID: 26243373.

(Among 379 adults being treated for tuberculosis who were given S. marianum or vitamin C as a hepatoprotectant, clinically apparent liver injury occurred in 1 of the silymarin- but none of the vitamin C-treated controls, and rates of ALT elevations were somewhat higher with silymarin [44% vs 36%]).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: A tabular listing and clinical characteristics. Int J Mol Sci. 2016;17:E537. pii. PubMed PMID: 27070596.

(Listing of names of herbal and dietary supplements implicated in published cases of liver injury does not list or mention silymarin or milk thistle).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol. 2017;107(Pt A):472–501. PMID: 27402097

(In a comprehensive online compendium of names of herbal and dietary supplements implicated in cases of liver toxicity, milk thistle is not listed).

Abenavoli L, Izzo AA, Milić N, Cicala C, Santini A, Capasso R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother Res. 2018;32:2202–2213. PubMed PMID: 30080294.

(Review of the chemistry, pharmacology, clinical efficacy and safety of milk thistle concludes that despite the antiinflammatory, antioxidant and antifibrotic properties observed in animal studies of milk thistle, its efficacy in patients with liver disease "is not fully compelling").

Navarro VJ, Belle SH, D'Amato M, Adfhal N, Brunt EM, Fried MW, Reddy KR, et al. Silymarin in NASH and C Hepatitis (SyNCH) Study Group. Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled trial. PLoS One. 2019;14:e0221683. PubMed PMID: 31536511.

(Among 78 adults with nonalcoholic fatty liver disease treated with silymarin [420 or 700 mg] or placebo 3 times daily for 48 weeks, there were no differences in ALT or AST levels or liver histological changes among the 3 treatment groups and no differences in adverse event rates despite the high levels of silymarin used).

Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. Phytother Res. 2019;33:1627–38. PubMed PMID: 31069872.

(Review of the safety of silymarin mentions that it was found to have no toxicity in animals and to be safe in humans even when used in high doses [2.1 gm daily] or in patients with liver disease, the usual reported adverse events being mild and transient nausea and diarrhea).