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Advances in the Use of Milk Thistle (*Silybum marianum*)

Janice Post-White, RN, PhD, FAAN, Elena J. Ladas, MS, RD, and Kara M. Kelly, MD

Milk thistle (*Silybum marianum*) is an herbal supplement used to treat liver and biliary disorders. Silymarin, a mixture of flavanoid complexes, is the active component that protects liver and kidney cells from toxic effects of drugs, including chemotherapy. Although milk thistle has not significantly altered the course of chronic liver disease, it has reduced liver enzyme levels and demonstrated anti-inflammatory and T cell-modulating effects. There is strong preclinical evidence for silymarin's hepatoprotective and anticarcinogenic effects, including inhibition of cancer cell growth in human prostate, skin, breast, and cervical cells. Milk thistle is considered safe and well-tolerated, with gastrointestinal upset, a mild laxative effect, and rare allergic reaction being the only adverse events reported when taken within the recommended dose range. More clinical trials of rigorous methodology, using standardized and well-defined products and dosages, are needed to evaluate the potential of silymarin against liver toxicity, chronic liver disease, and human cancers.

Keywords: *milk thistle; silymarin; cancer; liver disease; mechanism; safety; efficacy*

What Is Milk Thistle?

Milk thistle is available in the United States as a dietary supplement. The fruit and seeds of the milk thistle plant have been used for more than 2000 years as a treatment for liver and biliary disorders. The seeds are the medicinal part of the plant,¹ which is indigenous to Europe but also can be found in the United States and South America.

The botanical name for milk thistle is *Silybum marianum* (L.) Gaertn., a member of the plant family Asteraceae. The active constituent of milk thistle is silymarin, a mixture of flavonolignans comprised of 4 isomers: silibinin, isosilibinin, silichristin, and silidianin. Most supplements are standardized according to their silibinin (often called silybin) content. In turn, silibinin and isosilibinin are both mixtures of 2 diastereomers, silibinin A and B and isosilibinins A and B, respectively.² Because of milk thistle's lipophilic nature, it is usually administered in capsule or tablet form rather than as an

herbal tea. Special formulations of silibinin have been developed to enhance the bioavailability of the herbal product; these forms are sold as a dietary supplement under the names Legalon, Silipide, and Siliphos. As a supplement, milk thistle is regulated as a food and has not been approved by the US Food and Drug Administration as a treatment for cancer or for any other medical condition.

History of Use of Milk Thistle

The oldest reported use of milk thistle was by Dioscorides, who recommended the herb as a treatment for serpent bites. Pliny the Elder (AD 23-79) reported that the juice of the plant mixed with honey was indicated for "carrying off bile." Milk thistle was first revered as an antidote for liver toxins in the Middle Ages^{3,4} and was later used by the British herbalist Culpepper to relieve obstructions of the liver.^{3,4} In 1898, Eclectic physicians Felter and Lloyd recognized that the herb was good for "congestion" of the liver, spleen, and kidney.^{3,4} Native Americans have used milk thistle to treat boils and other skin diseases. Homeopathic practitioners have used preparations from the seeds to treat a variety of illnesses, including jaundice, gallstones, peritonitis, hemorrhage, bronchitis, and varicose veins,⁴ and currently use milk thistle to treat liver dysfunction. The German Commission E recommends its use primarily for dyspeptic complaints and liver conditions, including toxin-induced liver damage and hepatic cirrhosis, and as a supportive therapy for chronic inflammatory liver conditions.⁵

Reasons for Milk Thistle Use Today

In the United States, milk thistle is 1 of the most frequently sold herbal products. In 2000, retail sales of

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milk thistle were \$8.9 million, a 14% increase over 1999. Patients use milk thistle in a variety of clinical settings, but it is most commonly used in gastrointestinal clinics to help treat hepatitis and cirrhosis.

Despite a paucity of clinical trials investigating the safety of milk thistle in the oncology setting, surveys have found that milk thistle is one of the most commonly prescribed hepatoprotectants among individuals with cancer. Patients and practitioners report using milk thistle to aid the liver in detoxification, anticipating that milk thistle may help clear toxins from the blood and potentially aid them in tolerating cancer therapy. This concept was initially proposed in a case study and has subsequently been supported by 1 clinical trial that was conducted among children with acute lymphoblastic leukemia.⁶

Milk thistle also may have cancer cytotoxic effects. One phase III clinical trial in adult men with prostate cancer reported delays in rising prostate specific antigen levels compared with placebo.⁷ This series will present both preclinical and clinical studies demonstrating the potential role of milk thistle as a hepatoprotectant and an anticancer agent. Although most of the cancer investigations are in the preclinical stage, phase I/II studies suggest potential efficacy and few adverse events. No other medications or supplements are currently available that preserve liver function and provide clinical benefits.

In their article in this issue, Greenlee and colleagues⁸ provide an overview of current clinical applications of milk thistle and studies supporting its use in the oncology setting. They also present rationales and preliminary studies supporting the use of milk thistle in cardiovascular, renal, and diabetic conditions.

Mechanisms of Action

Silymarin is most well known for its antioxidant and chemoprotectant effects on the liver. It is highly absorbed after oral ingestion and has a strong first-pass effect through the liver. In laboratory studies, silibinin has been found to stabilize cell membranes, thus preventing toxic chemicals from entering the cell⁹⁻¹² and exporting toxins out of the cell before damage ensues.⁹⁻¹⁵ Administration of silymarin to rats challenged with a toxin resulted in higher levels of glutathione in liver cells, decreased oxidative stress (measured by malondialdehyde concentrations), and fewer elevations in liver enzyme tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]).¹³ Silibinin also has been shown to stimulate or inhibit phase I detoxification pathways,^{16,17} stimulate phase II detoxification pathways,¹⁸ and accelerate liver cell regeneration by stimulating DNA synthesis precursors and enhancing cellular enzyme production.¹⁹⁻²²

In their article in this issue, Comelli and colleagues²³ propose a unifying mechanism of action for silymarin that demonstrates how its scavenging and antioxidant properties reduce free radical generation, inhibit nuclear factor- κ B and tumor necrosis factor induction, and balance the cascade of transcriptional processes that affect cell growth and apoptosis, thereby reducing inflammation and supporting the liver's tolerance to oxidative stress. These authors conclude that the use of silymarin before or early after a toxic insult is more likely to provide stronger protective effects than in chronic liver disease.

There is strong preclinical evidence through *in vitro* and *in vivo* models that silymarin (more specifically, the silibinin flavonoid components) interferes with promotion and progression of cancer. In preclinical studies, silymarin appeared to have direct anticancer effects against prostate, breast, and ectocervical tumor cells.^{24,25} When the silibinin flavonoid component was tested *in vitro*, it enhanced the efficacy of cisplatin and doxorubicin against ovarian, breast, and prostate cancer cells²⁶⁻²⁸ and was synergistic with vincristine, but not L-asparaginase, against CCRF-CEM T cell, acute lymphoblastic leukemia cell lines.²⁹ When tested *in vitro*, silibinin did not stimulate growth in several cancer cell lines, including leukemia, colon (Caco-2), and hepatoma (HepG2).³⁰

In their article in this issue, Deep and Agarwal³¹ describe their and others' numerous studies showing the efficacy of silymarin and its flavonoid components against skin and prostate cancer and synergistic effects with chemotherapy and their work to identify the associated molecular mechanisms. The potential clinical efficacy, along with no known negative interactions with chemotherapy agents, lack of toxicity to normal cells, and ready absorption after oral administration, suggests silymarin's potential as a chemopreventive, protective, and therapeutic agent.

One of the limitations of silymarin studies is the lack of standardization of products and components. In this issue, Kroll and colleagues³² clearly define the need to use consistent nomenclature and define the actual components and composition of products tested because each component may have different biological effects. Another limitation is the variation in doses used in clinical trials. Kroll and colleagues³² emphasize the need to conduct adequate pharmacokinetic analyses to determine pharmacological concentrations of the product that correlate with plasma and tissue concentrations and desired *in vitro* and *in vivo* effects. Although some preliminary studies of pharmacokinetics and pharmacodynamics of milk thistle extracts have been conducted, additional studies are needed to define bioavailability and concentrations required to

produce biological and clinical effects, with consideration for potential interaction with chemotherapy drugs metabolized through cytochrome P450 isoenzyme (CYP) pathways, particularly when higher dosages of milk thistle extracts are administered.

Evidence for Safety and Efficacy

Efficacy

Most early clinical trials investigated milk thistle's effectiveness in the treatment of patients with hepatitis, cirrhosis, or biliary disorders.³³⁻⁴⁰ These studies used a wide range of products and doses (120-560 mg/d) and yielded conflicting results. In one of the largest observational studies, involving 2637 patients with chronic liver disease, 8 weeks of silymarin (560 mg/d) reduced serum AST, ALT, and gamma-glutamyl-transpeptidase (a marker of bile duct disease) and decreased the frequency of palpable hepatomegaly.⁴¹ Other more recent studies have shown no effects.⁴²⁻⁴⁴ In other reports, reviewed in this issue by Greenlee and colleagues,⁸ milk thistle was used to treat hyperlipidemia, diabetes mellitus,⁴⁰ and *Amanita phalloides* mushroom poisoning.^{10,45}

In their article in this issue, Tamayo and Diamond⁴⁶ review clinical trials of milk thistle extracts conducted in the past 5 years. Although milk thistle has not significantly altered the course of chronic liver disease, it has reduced liver enzymes in some studies and exhibited select effects on anti-inflammatory measures in chronic liver disease and diabetes mellitus.^{46,47}

Milk thistle has only recently begun clinical trial testing in cancer. Two clinical trials have followed in the footsteps of 2 well-publicized case studies.^{48,49} In 50 children with acute lymphoblastic leukemia (ALL) with grade 2 or greater chemotherapy-related hepatotoxicity, milk thistle (Siliphos 5.1 mg/kg/d) was associated with a significant reduction in AST and a trend in reduction of ALT levels after 56 days.⁶ In a phase III trial of men with prostate cancer, silymarin (160 mg/d for 10 weeks), in conjunction with soy isoflavones and other antioxidants, delayed prostate specific antigen level increases, whereas the placebo group had a 2.6-fold increase.⁵⁰

Safety

Milk thistle has been used safely during pregnancy,⁵¹ in children,^{6,10} and in adults older than 75 years.⁵² There were no reported toxicities at doses of 560 mg/d for pregnant women with intrahepatic cholestasis, 20 to 50 mg/kg body weight intravenously for children with mushroom poisoning, and 420 mg/d in older adults.⁵²

One recent phase I study suggested that 13 g of Siliphos (30% silibinin) was the recommended tolerated dose, with hyperbilirubinemia observed in

higher doses (15-20 g/d).⁵³ However, as Dr. Kroll and colleagues³² address in their article, these large doses are not recommended for patients receiving cancer chemotherapy because such doses may interact with chemotherapy metabolized through CYP pathways. Although toxicities were not observed in doses up to 1200 mg/d,⁴⁴ most clinical studies continued to test smaller dose ranges of 160 to 600 mg/d, divided into 3 daily doses.⁴⁶ Absorption is rapid, with peak plasma levels occurring within a few hours and an elimination half-life of 6 hours.⁵⁴ Because of the short half-life, it is recommended that milk thistle be taken in 3 divided doses throughout the day. Silibinin is predominantly excreted in bile (80%), with the remainder secreted in the urine.

Silymarin has been shown to decrease cytochrome P450 enzyme activity, potentially affecting clearance of some chemotherapy drugs.¹⁷ However, this inhibition was not observed with oral intake of milk thistle,¹⁶ and no interference with several chemotherapy agents (cisplatin, doxorubicin, vincristine, L-asparaginase) has been shown in preclinical studies at the concentrations used.²⁶⁻²⁹ Several recent studies report no interaction with chemotherapy agents or interference with enzymes involved in metabolism of drugs (CYP3A, CYP1A2, CYP2D6, CYP2Ea, UGT1A1, P-glycoprotein) (reviewed in this issue by Tamayo and Diamond⁴⁶). These effects may be dose responsive, however, and require further study at higher dosages.³²

Adverse Events

Milk thistle is considered safe and well-tolerated, with reported adverse events similar to placebo.^{47,55,56} Although infrequent, the most commonly reported adverse events are a mild laxative effect and gastrointestinal upset.⁵⁷ Mild allergic reactions were reported at doses greater than 1500 mg/d.¹ According to the German Commission E, there are no reported side effects of milk thistle within the recommended dose range.⁵ Milk thistle appears to be safe for up to 41 months of use.⁵⁵

In a systematic review of 13 clinical trials involving 915 subjects, there were no effects on mortality or complications of alcohol-induced or virally induced chronic liver disease. Milk thistle was not associated with an increased risk of adverse events compared with placebo (3.5% vs 4.4% in placebo). The symptoms reported in both groups were pruritus, nausea and epigastric distress, and headache.⁴⁷

Research Strengths and Weaknesses

There is strong preclinical evidence through in vitro and in vivo models that silymarin protects and regenerates liver and kidney cells and interferes with promotion and progression of cancer. Some of these effects

may be dose related. Milk thistle's effect on clinical outcomes is not well established, and reported effects on liver enzyme levels are inconsistent and inconclusive. The methodological quality of the majority of the clinical trials conducted in patients with chronic liver disease is low, with most of the studies including heterogeneous populations, lacking in standardized preparations, and having poorly defined nonobjective endpoints.⁵⁸ When high-quality trials were analyzed apart from low-quality trials, the beneficial effect of milk thistle on liver enzymes was lessened,⁴⁷ suggesting either a lack of effect, sample bias, or type I error in lower quality studies. This review excluded acute liver disease, including studies of drug or mushroom toxicity. Considering that most of the reported clinical trials tested milk thistle in chronic liver disease and that the biological effects may be more active in an acute model,^{23,31} additional clinical trials are needed to test efficacy of milk thistle as a hepatoprotectant and treatment for acute liver-related disorders. Such efficacy trials should ensure sample sizes sufficient for power, randomization and inclusion of a placebo/reference group, blinding of assessors and subjects, standardized dose and product, and intention-to-treat analyses.

Oftentimes, randomized controlled trials are done under controlled and ideal conditions and may fail to account for real-life practices in which supplements are taken with many other over-the-counter and prescription medications.⁵⁹ Individual subject characteristics and practices, such as use of other herbs and supplements, should be controlled for or assessed and considered as potential covariates in the clinical efficacy trials.⁶⁰ Although systematic reviews and randomized controlled trials are considered the best evidence for practice, making clinical decisions to add milk thistle requires consideration of the quality of the studies and clinical judgment.

Summary

Silymarin functions as a potent antioxidant that stabilizes cell membranes, stimulates detoxification pathways, regenerates liver tissue, inhibits the growth of some cancer cell lines, exerts direct cytotoxic activity toward select cancer cell lines, and increases the efficacy of some chemotherapy agents. The action of silymarin involves multiple mechanisms affecting the liver and other digestive organs. Unlike other herbs, milk thistle has strong preclinical evidence for hepatoprotective and anticarcinogenic effects. It has yet to be determined, however, whether milk thistle yields better clinical outcomes. The potential of milk thistle as a hepatoprotectant and adjuvant to chemotherapy requires further clinical trial testing with standardized products and quality controls.

References

1. *PDR® for Herbal Medicines*. 3rd ed. Montvale, NJ: Medical Economics; 2004.
2. Lee DY, 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.
3. Flora K, Hahn M, Rosen H, et al. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol*. 1998; 93:139-143.
4. Foster S. *Milk Thistle: Silybum marianum*. Rev ed. Austin, Tex: American Botanical Council; 1999.
5. Blumenthal M, Busse WR, eds. *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin, Tex: American Botanical Council; 1998.
6. Ladas EJ, Cheng B, Hughes D, et al. Milk thistle (*Silybum marianum*) is associated with reductions in liver function tests (LFTs) in children undergoing therapy for acute lymphoblastic leukemia (ALL). Abstract presented at: Society of Integrative Oncology; November 11, 2006; Boston, Mass.
7. Schroder FH, Roobol MJ, Boeve ER, et al. A randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. *Eur Urol*. 2005;48:922-930.
8. Greenlee H, Abascal K, Yarnell E, Ladas E. Clinical application of *Silybum marianum* in oncology. *Integr Cancer Ther*. 2007; 6:158-165.
9. Campos R, Garrido A, Guerra R, et al. Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver. *Planta Med*. 1989;55: 417-419.
10. Hruby K, Csomos G, Fuhrmann M, et al. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol*. 1983;2:183-195.
11. Farghali H, Kameniková L, Hynic S, et al. Silymarin effects on intracellular calcium and cytotoxicity: a study in perfused rat hepatocytes after oxidative stress injury. *Pharmacol Res*. 2000; 41:231-237.
12. Lettéron P, Labbe G, Degott C, et al. Mechanism for the protective effects of silymarin against carbon tetrachloride-induced lipid peroxidation and hepatotoxicity in mice: evidence that silymarin acts both as an inhibitor of metabolic activation and as a chain-breaking antioxidant. *Biochem Pharmacol*. 1990;39: 2027-2034.
13. Campos R, Garrido A, Guerra R, et al. Acetaminophen hepatotoxicity in rats is attenuated by silybin dihemisuccinate. *Prog Clin Biol Res*. 1988;280:375-378.
14. Shear NH, Malkiewicz IM, Klein D, et al. Acetaminophen-induced toxicity to human epidermoid cell line A431 and hepatoblastoma cell line Hep G2, in vitro, is diminished by silymarin. *Skin Pharmacol*. 1995;8:279-291.
15. Valenzuela A, Guerra R, Garrido A. Silybin dihemisuccinate protects rat erythrocytes against phenylhydrazine-induced lipid peroxidation and hemolysis. *Planta Med*. 1987;53:402-405.
16. Zuber R, Modrianský M, Dvorák Z, et al. Effect of silybin and its congeners on human liver microsomal cytochrome P450 activities. *Phytother Res*. 2002;16:632-638.
17. Venkataramanan R, Ramachandran V, Komoroski BJ, et al. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures. *Drug Metab Dispos*. 2000;28:1270-1273.
18. Zhao J, Agarwal R. Tissue distribution of silibinin, the major active constituent of silymarin, in mice and its association with enhancement of phase II enzymes: implications in cancer chemoprevention. *Carcinogenesis*. 1999;20:2101-2108.

19. Sonnenbichler J, Mattersberger J, Rosen H. Stimulation of RNA synthesis in rat liver and isolated hepatocytes by silybin, an antihepatotoxic agent from *Silybum marianum* L. Gaertn. *Hoppe Seylers Z Physiol Chem.* 1976;357:1171-1180.
20. Sonnenbichler J, Zetl I. Mechanism of action of silibinin, V: effect of silibinin on the synthesis of ribosomal RNA, mRNA and tRNA in rat liver in vivo. *Hoppe Seylers Z Physiol Chem.* 1984; 365:555-566.
21. Sonnenbichler J, Zetl I. Biochemical effects of the flavonolignan silibinin on RNA, protein and DNA synthesis in rat livers. *Prog Clin Biol Res.* 1986;213:319-331.
22. Sonnenbichler J, Goldberg M, Hane L, et al. Stimulatory effect of Silibinin on the DNA synthesis in partially hepatectomized rat livers: non-response in hepatoma and other malignant cell lines. *Biochem Pharmacol.* 1986;35:538-541.
23. Comelli MC, Mengs U, Prosdociami M, Schneider C. Toward the definition of the mechanism of action of silymarin: activities related to cellular protection from toxic damage induced by chemotherapy. *Integr Cancer Ther.* 2007;6:120-129.
24. Bhatia N, Zhao J, Wolf DM, et al. Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin. *Cancer Lett.* 1999;147:77-84.
25. Zi X, Agarwal R. Silibinin decreases prostate-specific antigen with cell growth inhibition via G1 arrest, leading to differentiation of prostate carcinoma cells: implications for prostate cancer intervention. *Proc Natl Acad Sci U S A.* 1999; 96:7490-7495.
26. Scambia G, De Vincenzo R, Ranelletti FO, et al. Anti-proliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin. *Eur J Cancer.* 1996; 32A:877-882.
27. Tyagi AK, Singh RP, Agarwal C, et al. Silibinin strongly synergizes human prostate carcinoma DU145 cells to doxorubicin-induced growth inhibition, G2-M arrest, and apoptosis. *Clin Cancer Res.* 2002;8:3512-3519.
28. Dhanalakshmi S, Agarwal P, Glode LM, Agarwal R. Silibinin sensitizes human prostate carcinoma DU145 cells to cisplatin- and carboplatin-induced growth inhibition and apoptotic death. *Int J Cancer.* 2003;106:699-705.
29. Ladas EJ, Cheng B, Hughes D, et al. Milk thistle is associated with reductions in liver function tests in children undergoing therapy for acute lymphoblastic leukemia. Abstract presented at: American Society of Hematology; December 10, 2006; Orlando, Fla.
30. Duthie SJ, Johnson W, Dobson VL. The effect of dietary flavonoids on DNA damage (strand breaks and oxidised pyrimidines) and growth in human cells. *Mutat Res.* 1997;390: 141-151.
31. Deep G, Agarwal R. Chemopreventive efficacy of silymarin in skin and prostate cancer. *Integr Cancer Ther.* 2007; **ADD ISSUE AND PAGE NUMBERS**
32. Kroll DJ, Shaw HS, Oberlies NH. Milk thistle nomenclature: Why it matters in cancer research and pharmacokinetic studies. *Integr Cancer Ther.* 2007; **ADD ISSUE AND PAGE NUMBERS**
33. Vailati A, Aristia L, Sozzé E, et al. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. *Fitoterapia.* 1993;64: 219-228.
34. Salmi HA, Sarna S. Effect of silymarin on chemical, functional, and morphological alterations of the liver: a double-blind controlled study. *Scand J Gastroenterol.* 1982;17:517-521.
35. Parés 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;28:615-621.
36. Flisiak R, Prokopowicz D. Effect of misoprostol on the course of viral hepatitis B. *Hepatogastroenterology.* 1997;44:1419-1425.
37. Angulo P, Patel T, Jorgensen RA, et al. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology.* 2000;32: 897-900.
38. Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol.* 1989;9:105-113.
39. Lucena MI, Andrade RJ, de la Cruz JP, et al. 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.
40. Velussi M, Cernigoi AM, De Monte A, et al. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. *J Hepatol.* 1997;26:871-879.
41. Albrecht M, Frerick H, Kuhn U, et al. Therapy of toxic liver pathologies with Legalon®. *Z Klin Med.* 1992;47:87-92.
42. 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;36:752.
43. Strickland GT, Tanamly MD, Tadros F, et al. Two-year results of a randomised double-blinded trial evaluating silymarin for chronic hepatitis C. *Dig Liver Dis.* 2005;37:542-543.
44. Gordon A, Hobbs DA, Bowden DS, et al. 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;21:275-280.
45. Enjalbert F, Rapior S, Nouguier-Soulé J, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol.* 2002;40:715-757.
46. Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum*). *Integr Cancer Ther.* 2007;6:146-157
47. Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. *Cochrane Database Syst Rev.* 2005;(2):CD003620.
48. Invernizzi R, Bernuzzi S, Ciani D, et al. Silymarin during maintenance therapy of acute promyelocytic leukemia. *Haematologica.* 1993;78:340-341.
49. Grossmann M, Hoermann R, Weiss M, et al. Spontaneous regression of hepatocellular carcinoma. *Am J Gastroenterol.* 1995; 90:1500-1503.
50. Schroder FH, Roobol MJ, Boeve ER, et al. A randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. *Eur Urol.* 2005;48:922-930.
51. Hernandez R, Nazar E. Effect of silymarin in intrahepatic cholestasis of pregnancy. *Revista chilena de Obstetricia y Ginecologia.* 1982;47:22-29.
52. Allain H, Schück S, Lebreton S, et al. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. *Dementia Geriatr Cogn Disord.* 1999;10:181-185.
53. Flaig T, Gustafson DL, Su LJ, et al. A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. *Invest New Drugs.* 2007;25:139-146.
54. 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;9:411-416.

55. Rainone F. Milk thistle. *Am Fam Physician*. 2005;72:1285-1288.
56. Jacobs BP, Dennehy C, Ramirez G, Sapp J, Lawrence VA. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med*. 2002;113:506-515.
57. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs*. 2001;61:2035-2063.
58. Verma S, Thuluvath PJ. Complementary and alternative medicine in hepatology: review of the evidence of efficacy. *Clin Gastroenterol Hepatol*. 2007 Jan 10; [Epub ahead of print].
59. Coulter ID. Evidence summaries and synthesis: necessary but insufficient approach for determining clinical practice of integrated medicine? *Integr Cancer Ther*. 2006;5:282-286.
60. Glasgow RE, Lichtenstein E, Marcus AC. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to-effectiveness transition. *Public Health Matters*. 2003;93:1261-1267.