

# The Many Faces of *Silybum marianum* (Milk Thistle)

## Part 2—Clinical Uses, Safety, and Types of Preparations

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In Part 1 of this article, we reviewed the evidence supporting milk thistle's use in cancer, as a renal protectant, and its ability to be of benefit to patients with hyperlipidemia and other circulatory problems. Part 2 covers other potential clinical uses of milk thistle, its safety profile, and types of preparations that can be dispensed to patients.

### Hepatic Diabetes

Given the well-established efficacy of milk thistle for treating liver disease, a trial was conducted in people with diabetes secondary to alcoholic cirrhosis. In a 12-month unblinded, controlled study of 60 insulin-treated diabetic patients who were also alcohol abusers, 600 mg of silymarin per day significantly decreased fasting glucose levels, mean daily glucose levels, daily glucosuria, and hemoglobin A1c (HgA1c) levels after 4 months of treatment.<sup>1</sup> There was also a significant decrease in fasting insulin levels and mean exogenous insulin requirements while the nonsilymarin-treated control group experienced significant increases in both parameters. Basal and glucagon-stimulated C-peptide levels decreased in the treated group and increased significantly in the control group.

In a randomized, controlled trial, 60 patients with diabetes who were alcohol abusers were given 600 mg of silymarin daily for 6 months.<sup>2</sup> Mean levels of fasting blood glucose, daily blood glucose, daily glycosuria, glycosylated hemoglobin, daily insulin need, fasting insulinemia, blood malondialdehyde, and basal- and glucagon-stimulated C peptide were all significantly lower than both baseline and in the controls. The researchers concluded that silymarin may reduce lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and decreasing the need for exogenous insulin administration.

In another trial, silybinin inhibited glucose-stimulated increase *in vitro* but did not affect blood-glucose concentration *in vitro*, indicating a potential benefit in treating noninsulin-dependent diabetes mellitus.<sup>3</sup>

Alloxan produces necrosis of pancreatic beta cells and is used to induce diabetes in animals. In one study, silymarin fully prevented deleterious changes in plasma glucose and pancreatic cell damage 120 hours after the first silymarin dose when given concomitantly with alloxan.<sup>4</sup> Similar results have been obtained in mice.<sup>5</sup> In other studies of animals with diabetes, silybinin did not affect hyperglycemia but prevented the onset of diabetic neuropathy.<sup>6</sup> Silybinin also prevented deleterious changes in the retinas of rats with diabetes.<sup>7</sup>

Clinical studies have also indicated that milk thistle may have positive effects on diabetes caused by alcoholic liver cirrhosis. This type of diabetes shares features with the diabetes that typically arises in pancreatic cancer. Milk thistle may diminish the tissue insulin resistance in these types of diabetes and may also prevent diabetic sequelae, such as neuropathy and retinopathy. In our opinion, milk thistle should be prescribed routinely for patients with these types of disorders.

### Neuroprotectant Effects of Silymarin

Silymarin had a neuroprotective effect on microglial cell cultures and appears to inhibit nitric oxide production and iNOS gene activation.<sup>8,9</sup> An extract of milk thistle enhanced neurite outgrowth in culture, prolonged neurite survival, and protected cultured rat hippocampal neurons against oxidative stress-induced cell death.<sup>10</sup> Silymarin inhibited C6 glial cell monamine oxidase enzyme production *in vitro*, which has been implicated as contributing to the neuronal damage associated with various neurodegenerative diseases.<sup>11</sup> *In vitro* studies have also suggested that silybinin can inhibit the activity of 5-lipoxygenase in the cerebral blood vessels and may protect the brain from ischemia.<sup>12</sup>

Milk thistle's potential as a neuroprotectant is based entirely on *in vitro* studies. It is particularly difficult to assess the clinical value where information on whether the constituents reach the brain in sufficient concentrations *in vivo* is lacking. As a result, we cannot make a strong recommendation for using milk thistle to treat neurodegenerative diseases. However, clinical herbalists frequently report that milk thistle has a positive clinical effect on carpal tunnel syndrome, myalgias, and multiple sclerosis,<sup>\*,13</sup> and we would include milk thistle in our treatment for a variety of nerve and brain disorders if other, better-understood therapies were ineffective.

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## Fetal Alcohol Syndrome

Animal studies consistently show that milk thistle protects the rat fetus against the detrimental effects of ethanol. The progeny of pregnant rats on an ethanol diet (35 percent) supplemented with silymarin performed better in maze tests and were more able to form memories than controls.<sup>14,15</sup> Their fetuses had normal levels of gamma glutamyl transpeptidase activity in brain and liver tissue while the fetuses of the controls had elevated levels.<sup>16,17</sup>

When pregnant patients are unable or unwilling to avoid alcohol, and although results can only be extrapolated from animal research at present, milk thistle should be prescribed because it may prevent some of the deleterious effects of alcohol on the unborn fetus. Milk thistle should never be used to promote or sustain alcohol abuse. It is unlikely that milk thistle will prevent all aspects of fetal alcohol syndrome; the herb may only mitigate some of the damage.

## Inflammation

Many lines of evidence support the idea that milk thistle and silymarin produce anti-inflammatory activity. All of this work is preclinical, however. At low doses, silymarin has suppressed T-lymphocyte function in mice but it stimulated inflammatory processes at higher doses.<sup>18</sup> Silymarin also had significant anti-inflammatory and antiarthritic activities in rats.<sup>19</sup> Orally administered silymarin reduced carrageenan-induced paw edema in rats and topically reduced ear mouse inflammation that had been induced; the effects of the herb were comparable to indomethacin.<sup>20</sup>

Transcription factor NF-kappa-B is a key regulator in inflammatory and immune reactions. In vitro silymarin suppresses NF-kappa-B in a potent manner but does not affect TNF[(tumor necrosis factor)-alpha-induced NF-kappa-B activation.<sup>21</sup> At doses achievable by oral supplementation, silybinin significantly inhibited leukotriene formation by Kupffer cells in vitro by inhibiting the 5-lipo-oxygenase pathway.<sup>22</sup> Other studies support the inhibitory effects of silymarin and its flavanolignan constituents inhibit lipoxygenase and prostaglandin synthetase in vitro.<sup>23,24</sup>

Milk thistle obviously has an anti-inflammatory action. However, there are many botanicals with more thoroughly established actions for this purpose, such as turmeric (*Curcuma longa*). We do not prescribe milk thistle as a first-line, general anti-inflammatory but would consider its use in this manner if other agents failed and, of course, for patients with hepatic inflammation. However, some practitioners use the herb consistently to treat inflammation of the joints, particularly the wrists.<sup>13</sup>

## Biliary Obstruction

Milk thistle's effects on the bile ducts and hepatic-bile synthesis may be clinically important. Silymarin (420 mg per day, for 30 days) has reduced biliary cholesterol concentrations with a significant decrease in the bile saturation index in 15

cholecystectomized patients compared to placebo controls, probably by decreasing the synthesis of liver cholesterol.<sup>25</sup>

In another year-long study of patients with primary biliary cirrhosis, oral silymarin (140 mg, 3 times per day) failed to produce significant changes in alkaline phosphatase activity, total bilirubin, aspartate transaminase, and albumin levels.<sup>26</sup> At doses of 420 mg per day, silymarin improved indices of liver function (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and bilirubin) in patients with liver disease of various etiologies, including patients who were exposed to toxic levels of toluene or xylene.<sup>27</sup> Silymarin has also alleviated the pruritus, but not the biochemical alterations that accompany it, in pregnancy-related intrahepatic cholestasis.<sup>28</sup>

Silymarin improved the antioxidant capacity of the liver, diminished direct bilirubin concentration, and caused an increase of liver enzyme activities in rats with ligated bile ducts compared to controls.<sup>29</sup> Silymarin administered orally to rats with extrahepatic biliary obstruction reduced thiobarbituric acid reactive substances (oxidized lipids) production significantly (50–70 percent) and clearly reduced lipid peroxidation in the liver.<sup>30</sup> Silymarin ameliorated hepatic collagen accumulation, even in advanced biliary fibrosis, in rats. Silymarin protected against ethinyl estradiol-induced cholestasis by normalizing the bile salt pool size and HCO<sub>3</sub> output in rats.<sup>31</sup>

Silymarin has not been shown to offset the negative parameters of biliary obstruction conclusively. However, based on existing research and the herb's long history of use, we would prescribe milk thistle to patients with biliary obstruction, and consider the herb to be potentially useful for addressing obstruction secondary to pancreatic disorders, such as pancreatic cancers.

## Safety

The toxicity of silymarin is very low. Numerous double-blind and postmarketing studies have shown minimal adverse effects with only occasional loose stools occurring with any regularity.<sup>32</sup> The oral LD<sub>50</sub> in rats was 10,000 mg/kg with a maximum tolerated dose of 300 mg/kg in dogs. The herb is devoid of embryotoxicity as far as is known.<sup>33</sup>

Silymarin, and to a greater degree silydianin and silychristin, have been protective against cytotoxicity in human hepatocytes; silybinin and isosilybin were less effective. The two latter compounds were cytotoxic at higher concentrations and longer incubation, while the former constituents produced no cytotoxicity.<sup>34</sup>

In another study, low concentrations of silymarin and silybin inhibited cell attachment to the matrix and eventually resulted in cell damage. The research indicates that the negative effect on cultured cells should be considered when silymarin is prescribed for long-term use and that, perhaps, this isolated constituent group is not entirely benign.<sup>35</sup>

## Drug Interactions

A number of studies have assessed the ability of milk thistle or silymarin standardized extracts to reduce the hepatotoxicity of various drugs. A double-blinded, placebo-controlled study of

**Table 1. Miscellaneous Additional Research on Milk Thistle**

| Condition                       | Research Support   |
|---------------------------------|--|
| Toxic liver disease             | In patients suffering from toxic liver diseases (n = 2637) who took Legalon 70 for 8 weeks, subjective complaints decreased, clinical findings by physicians and serum levels of liver enzymes improved significantly. <sup>a</sup> Eighty-eight (88) percent of physicians rated the treatment as satisfactory to very good.    |
| Protectant against toxins       | Blue-green algae secrete a cyclic heptapeptide that causes severe hepatocellular necrosis and hemorrhage. Pretreatment of rats or mice with a single dose of silymarin completely abolished the lethal effects, pathologic changes and significantly decreased levels of serum enzyme induced by this heptapeptide. <sup>b</sup> |
| Protectant against toxins       | Silymarin has been shown to protect liver, kidney, erythrocytes and platelets from the toxic effects of ethanol, carbon tetrachloride, cold ischemia and drugs. In rats, silymarin prevented cyclosporin-induced pancreatic toxicity. <sup>c</sup>   |
| Protectant against toxins       | Silybin administered before a dose of phalloidin prevented toxin-induced morphologic liver changes and significantly reduced serum liver enzyme activity. <sup>d</sup> When administered without the toxin, silybin had no effect on serum liver enzymes.  |
| Protectant against toxins       | Silymarin (25 mg/kg body weight/day, orally), given 6 weeks after aflatoxin administration, had a curative effect on lipid peroxide levels in liver and kidney compared to controls. <sup>e</sup>  |
| Protectant against toxins       | Silybinin prevented cyclosporin A–induced pancreatic toxicity but did not affect cholecystokin-stimulated amylase secretion from the isolated perfused pancreas. <sup>c</sup> Its effect indicates that it may protect the exocrine pancreas against other noxious insults, such as alcohol.                                     |
| Protectant against toxins       | Silybin protects against iron-induced hepatic toxicity in vivo in rats. <sup>f</sup>   |
| Malaria                         | Silymarin protected rats infected with <i>Plasmodium bergheii</i> from hepatic damage and prevented deleterious changes in lipoprotein, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase and bilirubin at a dose of 5 mg/kg body weight. <sup>g</sup>                                       |
| Cooley's anemia                 | Silybin binds Fe <sup>3+</sup> , even at an acidic pH, showing a possible role in chelation therapy for chronic iron overload, as in the treatment of Cooley's anemia. <sup>h</sup>  |
| Immunomodulator                 | Silybinin enhanced the motility of polymorphonuclear leukocytes immobilized by various means. In human volunteers, silybinin enhanced the spontaneous motility of leukocytes. <sup>i</sup>   |
| Immunomodulator                 | Silymarin had a strong stimulatory effect on lymphocytes in vitro. <sup>j</sup>  |
| Fatty-acid composition in liver | Silymarin fed to chickens corrected adverse changes in the fatty-acid composition of the liver of chickens who were given estradiol benzoate and increased the percentage of unsaturated fatty acids in the liver. <sup>k</sup>  |
| Viral infection                 | Silybinin did not affect the morphology of normal cells but delayed pathologic changes of virus infected cells. <sup>l</sup>   |
| Allergic asthma                 | Silymarin showed a protective effect on bronchoconstriction in the early phase of allergic asthma in guinea pigs. <sup>m</sup>   |
| Acute colitis                   | Silymarin (50 mg/kg) attenuated macroscopic colonic damage and reduced colonic myeloperoxidase activity in a rat model of acute colitis. <sup>n</sup>  |

<sup>a</sup>Albrecht M, Frerick H, Kuhn U, Strenge-Hesse A. Therapy of toxic liver disease with Legalon [in German]. *Zeitschrift für Klinische Medizin Berlin* 1992;47:87–88, 90–92; <sup>b</sup>Mereish KA, Bunner DL, Ragland DR, Creasia DA. Protection against microcystin-LR-induced hepatotoxicity by silymarin biochemistry histopathology and lethality. *Pharm Res* 1991;8:273–277; <sup>c</sup>Ref. 3; <sup>d</sup>Tuchweber BR, Sieck R, Trost W. Prevention by silybin of phalloidin induced acute hepatotoxicity. *Toxicol Appl Pharmacol* 1979;51(2); <sup>e</sup>Rastogi R, Srivastava AK, Rastogi AK. Long term effect of aflatoxin B1 on lipid peroxidation in rat liver and kidney: Effect of picroliv and silymarin. *Phytother Res* 2001;15:307–310; <sup>f</sup>Pietrangelo A, Borella F, Casalgrandi G, et al. Antioxidant activity of silybin in vivo during long-term iron overload in rats. *Gastroenterology* 1995;109:1941–1949; <sup>g</sup>Chander R, Kapoor NK, Dhawan BN. Hepatoprotective activity of silymarin against hepatic damage in *Mastomys natalensis* infected with *Plasmodium bergheii*. *Ind J Med Res: Sect B* 1989;90:472–477; <sup>h</sup>Borsari M, Gabbi F, Ghelfi F, et al. Silybin, a new iron-chelating agent. *J Inorg Biochem* 2001;85(2–3):123–129; <sup>i</sup>Kalmar L, Kadar J, Somogyi A, et al. Silybinin Legalon-70 enhances the motility of human neutrophils immobilized by formyl-tripeptide calcium ionophore lymphokine and by normal human serum. *Agents Actions* 1990;29(3–4):239–246; <sup>j</sup>Amirghofran Z, Azadbakht M, Karimi MH. Evaluation of the immunomodulatory effects of five herbal plants. *J Ethnopharmacol* 2000;72(1–2):167–172; <sup>k</sup>Sanchez GJA, Santiago LD. Action of silymarin on the fatty-acid composition of liver fats of estrogen treated chickens [in Spanish]. *Arch Farmacol Toxicol* 1981;7:143–150; <sup>l</sup>Ref. 12; <sup>m</sup>Breschi MC, Martinotti E, Apostoliti F, Nieri P. Protective effect of silymarin in antigen challenge and histamine-induced bronchoconstriction in vivo guinea pigs. *Eur J Pharmacol* 2002;437(1–2):91–95; <sup>n</sup>Cruz T, Glavez J, Crespo E, et al. Effect of silymarin on the acute stage of trinitrobenzenesulphonic acid model of rat colitis. *Planta Med* 2001;67:94–96.

60 patients on chronic psychotropic drug therapy showed that silymarin (800 mg per day) reduced the lipoperoxidative hepatic damage associated with treatment with butyrophenones or phenothiazines.<sup>36</sup> Silymarin extracts (420 mg per day) also prevented liver damage caused by general anesthetics in patients who were undergoing major surgeries in controlled clinical trials.<sup>37</sup>

Silymarin extracts (420 mg daily) did not prevent serum liver enzyme level elevations in patients with Alzheimer's disease who were treated with tacrine in a double-blinded trial.<sup>38</sup> However, the extract was more effective than placebo for reducing nausea and anticholinergic adverse effects. The extract also prevented the most serious indications of liver damage (e.g., eleva-

tion of serum liver enzymes significantly better than placebo (more than fivefold). Thus, silymarin may reduce some adverse effects of tacrine.

Silybinin, silydianin, and silycristin have inhibited CYP2D6, CYP2E1, and CYP3A4 dose dependently in vitro.<sup>39</sup> However, the concentrations necessary to achieve these effects are not reached during clinical use of silymarin supplements.

Silymarin has significantly reduced the activity of CYP3A4 enzyme (50–100 percent) in cultured hepatocytes and also reduced mitochondrial respiration.<sup>40</sup> Because of the potential for interactions, some researchers recommend caution in combining silymarin with drugs that are metabolized by CYP3A4, such as the protease inhibitors indinavir and nevirapine.<sup>41</sup> However, in a

clinical trial of 10 healthy volunteers who took milk thistle (175 mg, containing 153 mg of silymarin three times per day, for 3 days) with indinavir, milk thistle did not interfere with the indinavir therapy.<sup>42</sup>

Silybinin, administered orally to mice, induced phase II enzymes in liver, lung, stomach, skin, and small-bowel tissue.<sup>43</sup> Silybinin had little effect on the metabolism of erythromycin (CYP3A4), chlorzoxazone (CYP2E1), S-mephenytoin (CYP2C19), caffeine (CYP1A2), or coumarin (CYP2A6) in one study but “clearly” inhibited dinitronifedipine oxidation (CYP3A4) and warfarin hydroxylation (CYP2C9) in vitro. The researchers in this study stated that metabolic interactions with xenobiotics that are metabolized by CYP3A4 and CYP2C9 could not be excluded based on their research, especially if taken orally with medications because of the higher potential concentration of silybinin in the gut.<sup>44</sup>

However, another meticulous study of silymarin flavonolignans in human microsomes concluded that silymarin did not inhibit CYP3A4 and 2D6 isoforms (responsible for the biotransformation of more than 67 percent of drugs known to be transformed in the liver) and that no drug interactions should be expected when using therapeutic doses of silymarin.<sup>39</sup> These researchers analyzed the earlier study, noting that the concentrations needed for interference could not be attained at recommended oral doses of milk thistle. The investigators also noted that the enzyme activity recorded in the first study perhaps was an artifact induced by the use of dimethylsulfoxide (DMSO) in the experiment. In response, one of the researchers, Uwe Fuhr, M.D., agreed that drug interactions were unlikely at therapeutic doses, especially if care is taken not to administer milk thistle at the same time as drugs such as warfarin.<sup>†</sup> However, he disagreed that DMSO created artifacts in his study.

It has been theorized that the alcohol-inducible cytochrome P450 2E1 is involved in the hepatoprotective mechanism of silymarin but in vitro studies have shown no evidence of such an interaction.<sup>45</sup> It appears that milk thistle may not act by interfering with the CYP2E1 metabolism of ethanol but instead produces a protective effect by scavenging hydroxyethyl radicals derived from the ethanol metabolism.<sup>46</sup>

Milk thistle appears to be a very safe botanical, and is unlikely to alter the metabolism of prescription medications. When clinically indicated, milk thistle preparations providing a daily dose of 200–400 mg of silymarin can be prescribed without hesitation. The preparation should be combined with hepatotoxic drugs to help optimize therapy with them.

Some caution may still be warranted when using newer extracts with drugs. The current trend in research is to modify

silymarin constituents to increase their bioavailability. The conclusion that silymarin will not cause drug interactions via the P450 system is based on current therapeutic doses of silymarin. This recommendation may not hold if significantly higher amounts of silybinin are delivered and absent solid evidence, practitioners should not automatically assume that more silybinin is better for the conditions discussed in this article. This is especially true as silybinin has been shown to have some cytotoxic effects in vitro. Finally, milk thistle should not be taken concurrently with prescription medications to avoid the possibility that higher flavonolignans concentrations in the gut might interfere with the medications.

## Types of Preparations

Almost all of the research on milk thistle involves its isolated flavonolignans, principally silymarin. There is an assumption in the literature that these are the only active components of milk thistle. However, while the beneficial effects of silymarin appear to be stellar, there is no evidence proving that milk thistle's without concentrated amounts of silymarin lacks clinical efficacy. Much emphasis is placed on the fact that silymarin is both poorly soluble in water and poorly absorbed into the body. However, many studies suggest

that silymarin provides benefits at very low levels and *no* research has been done comparing various doses and types of preparations, other than to show that various proprietary formulations are more bioavailable than others without showing that this has led to superior clinical results.

Milk thistle has been used as a decoction for treating almost all of the conditions discussed in this article for at least 2000 years. In addition, physicians in the late 1800s reported good success using tinctures of milk thistle; these were preparations that contained at most 3–6 percent silymarin.

There are a few studies indicating that milk thistle itself has medicinal value. For instance, an infusion of milk thistle seed administered to mice before methoxsalen protected against the hepatotoxicity caused by this agent.<sup>47</sup> An abstract of a Russian article indicated that adding milk thistle seed to bread products effectively acted as a restorative in humans, increasing overall vitality.<sup>48</sup>

Mice who were fed milk thistle seed oil had increased body weight without any microscopic pathologic changes in their livers, kidneys, stomachs, or intestines.<sup>49</sup> A similar animal study was mentioned previously regarding the beneficial effect of milk thistle seed oil on lipid profiles in animals. A petroleum ether extract of milk thistle seeds significantly reduced serum levels of alkaline phosphatase and arginase in hepatotoxic animals.<sup>50</sup> A milk thistle seed extract showed a free-radical-scavenger activity equivalent to superoxide dismutase in a rat paw edema test using doxorubicin as the phlogistic agent.<sup>51</sup>

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*Milk thistle appears to be a very safe botanical and is unlikely to alter the metabolism of prescription medications.*

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<sup>†</sup>Personal communication with Uwe Fuhr, M.D., Köln, Germany.

Further investigations into the properties of milk thistle itself are definitely needed. Because the long-term effects of silymarin have not been studied in healthy humans, we prefer to follow the historical clinical experience, and typically recommend that patients who wish to use milk thistle as a generic hepatoprotectant or liver cleanser use either ground milk thistle seed (12–15 g per day), an infusion, or a fluid extract (1:1, 3–8 mL, three times per day). Studies and historical usage indicate that this is entirely safe, effective, and, in our opinion, is preferable to capsules with concentrated amounts of silymarin absent a specific disease state or toxin exposure. Length of use should be determined by the patient's condition and desired outcome.

## Conclusions

There are a number of conclusions that can be drawn from the existing research on milk thistle. First, in vitro and animal studies show a strong, beneficial action in a wide variety of disorders. Logically, clinical studies of milk thistle's potential benefit should be made a priority. Second, given the safety profile of the herb, clinicians would be well-advised to expand their use of this plant although clinical studies are lacking. Third, milk thistle as a food (ground or seed oil), as a tea, and as preparations without concentrated amounts of silymarin appear to be beneficial and are, perhaps, the preferable forms for use in addressing nonspecific disease states. Capsules containing concentrated amounts of silymarin can be reserved for treating for the specific conditions (such as cancer, liver-related diabetes, etc.) discussed in this article. □

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