

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

Part 1—Treating Cancer and Hyperlipidemia and Restoring Kidney Function

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Milk thistle (*Silybum marianum*) seed is a very popular and widely used “liver herb” that is frequently prescribed for treating such disorders as viral hepatitis and alcoholic cirrhosis and for preventing liver damage from toxic mushrooms. Clinical studies tend to confirm the validity of these uses and the German Commission E approves of using standardized extracts to treat toxic liver damage and as a supportive treatment for inflammatory liver disease and hepatic cirrhosis.¹ The Commission E also approves of using crude milk thistle seed tea for treating dyspepsia.

This picture strongly suggests that milk thistle acts solely on the liver but existing research and historical use suggest otherwise. Milk thistle is not simply a hepatic trophorestorative but also provides benefits for many other systems. In fact, the potential nonhepatic clinical uses of milk thistle are so extensive that a two-part article is necessary to analyze them fully. In part 1, we review milk thistle’s history, its value for treating cancer and hyperlipidemia, and its use as a kidney trophorestorative. In part 2, we will discuss additional clinical uses, the plant’s safety profile, and potential interactions with other drugs as well as covering various ways to dispense milk thistle.

History

Milk thistle is native to the Mediterranean region. The plant’s leaves and seeds have been used continuously since at least Greco-Roman days for treating many ailments, particularly those that affect the liver. Similar folk uses remain. For instance, the Basque people today use a decoction of milk thistle seeds as a digestive aid, aperient, anti-inflammatory, antineoplastic, hypotensive, general tonifier, venous tonifier, styptic, and diuretic.²

Milk thistle traveled with European emigrants to the United States and became naturalized in North America. The American Eclectic physicians used a “strong tincture” of milk thistle for treating congestive conditions of the splenic circulation; congestion of the liver, spleen, or kidneys; gallstones; vomiting in pregnancy; amenorrhea; uterine hemorrhaging; hematuria; and painful dysuria.³ The herb was considered to be specific for treating indi-

viduals with splenic, hepatic, and renal congestion; sallow faces; capricious appetites; nervous irritability; despondency; physical debility; pain in either hypochondrae; congestion of organs supplied by the celiac axis; and nonmalarial spleen hypertrophy.

In 1929, scientists began researching milk thistle, inspired by its continued use by German physicians as a treatment for jaundice and liver disorders. In the late 1950s, silymarin was isolated. Silymarin is a complex of flavonolignans including silybin (also known as silybinin, silibin, or silibinin), silydianin, and silychristin. Milk thistle seed usually contains 4–6 percent silymarin. Nearly all of the milk thistle research concerns the properties of either silymarin or silybin. As a result, milk thistle today is usually dispensed in capsule form with a standardized, concentrated content of 70–80 percent silymarin.

Milk Thistle and Cancer

Silymarin shows strong potential as a preventative and adjunct treatment in many types of cancer. The herb may also potentiate some chemotherapy drugs and prevent resistance to such drugs. There are, unfortunately, no clinical trials on milk thistle or silymarin in patients with cancer. Trials are urgently needed to validate the large amount of promising, preclinical research—especially because milk thistle is a widely used supplement.

Prostate Cancer Studies

Silybin, at concentrations achievable through diet, strongly inhibited the growth of advanced human prostate-cancer cells grafted to mice, reducing tumor volume by 53–64 percent.⁴ Silymarin and silybin both induced growth inhibition and apoptosis in rat prostate carcinoma cells and highly inhibited cell growth and DNA synthesis in different prostate human carcinoma cell lines in vitro.^{5,6} Silymarin had an antiproliferative effect on androgen-stimulated cell proliferation and secretion of prostate-specific antigen.⁷ This substance’s anticarcinogenic effect is likely to be caused by impairing an adapter protein signaling pathway and causing a G1 arrest in the cell cycle.⁸ In vitro studies have suggested that silybin may be a useful agent for treating hormone-refractory human prostate cancer and may enhance the effectiveness of tumor necrosis factor (TNF)- α -based chemotherapy in advanced prostate cancer.^{9,10}

Skin Cancer Studies

Silymarin fed to mice (0.5 percent of diet) inhibited growth and caused regression of skin tumors.¹¹ Silymarin had a rapid and significant inhibitory effect on the secretion of the primary angiogenic cytokine by cancer epithelial cells, potentially stopping tumor growth before metastasis occurred.¹² Topical silymarin provided highly significant protection against induced skin tumors in mice and caused significant anti-inflammatory responses.¹³ In another study, topical silymarin provided “extremely” high protection against induced skin tumor promotion in mice, inhibiting promoter-induced edema, hyperplasia, proliferation index, and oxidant state.¹⁴

Silymarin’s antitumor-promoting effect is primarily targeted against stage I tumor promotion in mouse skin.¹⁵ A single topical application of silymarin inhibited 76–95 percent of drug-induced skin edema and inhibited cyclo-oxygenase-2 and interleukin-1 tumor promotion in mice. As in prostate cancer, silymarin’s effect on skin cancer involves an inhibition of activation of the signaling protein erbB1 as well as other antiproliferative and apoptotic effects, even when used topically.¹⁶

Low concentrations of silymarin significantly inhibited NF-kappaB activation in cells exposed to a solar ultraviolet (UV) light simulator.¹⁷ Skin tumor promoters, such as UV-B radiation, activate epidermal growth factor receptor (EGFR) in mouse skin and cell culture. Treatment with silymarin resulted in significant inhibition of activation of EGFR in vitro.¹⁸ Topical silymarin provided substantial protection against different stages of UV-B–induced carcinogenesis in mice, prevented UV-B–induced immunosuppression, and significantly reduced UV-B–induced hydrogen peroxide-producing cells and inducible nitric oxide synthase–expressing cells. These results support the theory that silymarin can prevent photocarcinogenesis in mice.^{19,20}

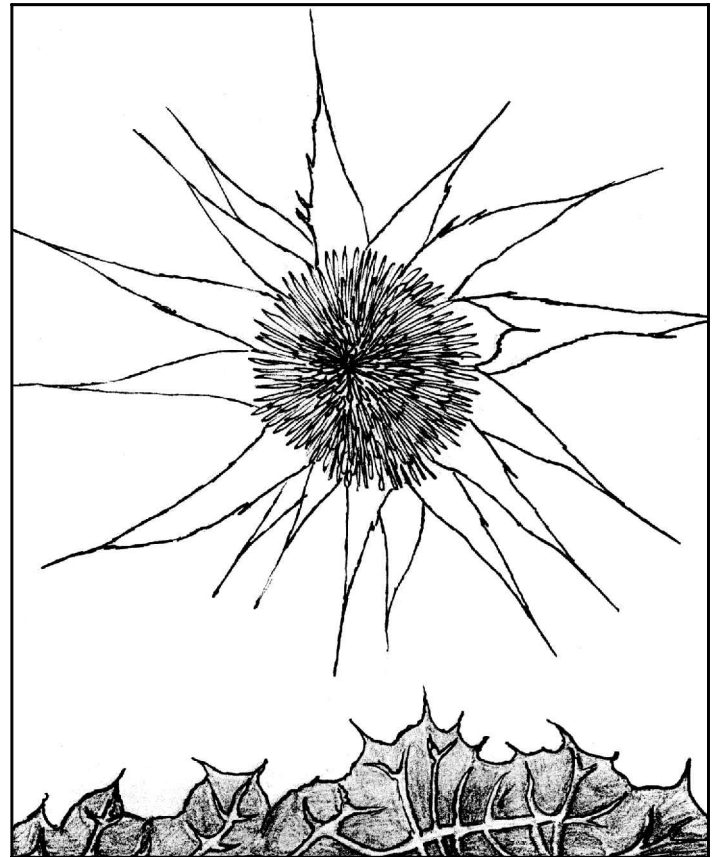
Topical silymarin appears to be a beneficial supplement to sunscreen protection for increasing anticarcinogenic protection and working to prevent other UV-mediated damage.^{21–23} Topical silymarin significantly reduced UV-induced erythema in humans. Researchers considered silymarin to be an important candidate for preventing and/or treating skin cancer or cancers of epithelial origin in humans.²⁴

Other Cancers

The responses of many other types of cancer to silymarin have also been investigated. Two studies showed that dietary feeding of silymarin inhibits the induction of tongue squamous-cell cancer.^{25,26} Animals who were fed silymarin at the initiation or postinitiation phase of tumor induction had significantly decreased incidences of bladder neoplasms and preneoplastic lesions.²⁷

Silymarin and its constituent silybin highly and significantly inhibited both cell growth and DNA synthesis in different breast and cervical human-carcinoma cells in vitro.²⁸

Silymarin induced G1 growth arrest in breast-cancer cells in vitro via similar mechanisms to those seen in prostate-cancer cells.²⁹ Silymarin inhibited the formation of mammary lesions in organ culture when applied after carcinogenic substances.³⁰



Silybum marianum (milk thistle). Drawing ©2003 by Kathy Abascal, B.S., J.D., Herbalist.

Inhibition of tyrosine phosphorylation of erbB1 (primary growth pathway signal inhibited) → Lack of activation of SHC → Further lack of signal propagation → Kip1:p27 ratio increase (Cip1:p21 ratio increase occurs via separate undetermined pathway) → Cyclin-dependent kinase inhibitor-to-cyclin-dependent kinase activity ratio increase → Lack of cyclin-related kinase activity → G1 cell arrest (no growth)

Figure 1. Proposed mechanisms of inhibition of cancer by silymarin.

Drug-induced adenocarcinoma frequencies of the colon, both total and occurrence in the proximal and distal portions, were significantly decreased in rats who were fed silymarin.^{31,32} Silybin inhibited cellular proliferation and induced cellular differentiation in leukemia HL-60 cells in vitro.³³

Thus, the antineoplastic effects of milk thistle are not limited to any one particular type of cancer (see Figure 1).

Optimizing Chemotherapy and Radiation Therapy

Besides inhibiting or killing cancer cells directly, milk thistle and its constituents may have a role to play in combination with standard allopathic cancer therapies. We addressed the growing problem of drug-resistant cancer and the general issue of using herbs to combat this problem in a previous article.³⁴ Here, we focus only on milk thistle and silymarin.



Milk thistle.

Silybin inhibited the growth of drug-resistant ovarian- and breast-cancer cells in vitro, showing that its antineoplastic effects are at least partially distinct from those of many chemotherapy agents.³⁵ Silymarin increased daunomycin accumulation and potentiated doxorubicin toxicity in cancer cells expressing P-glycoprotein and inhibited cellular efflux of these drugs.³⁶ Silymarin and its constituents protected rat heart microsomes and mitochondria against doxorubicin-induced lipid peroxidation, suggesting that the herb may prevent doxorubicin-mediated damage to the heart.³⁷

Silybin potentiated the antitumor action of cisplatin in vivo and in vitro and reduced recovery time in mice who were given cisplatin.³⁸ Another study showed that the herb potentiated the effect of cisplatin and doxorubicin against various breast and ovarian cancer cell lines in vitro.³⁵ Although in vitro silybin was not synergistic with cisplatin or ifosfamide against testicular-cancer cells, silybin did prevent the renal damage for which these drugs are notorious in a rat testicular-cancer model.³⁹ Silybin also prevented renal damage caused by cisplatin in otherwise healthy rats.⁴⁰

A case study showed milk thistle's potential use in conjunction with chemotherapy.⁴¹ A male patient with acute myelocytic leukemia suffered from severe liver damage, necessitating a reduction in chemotherapy doses and an intermittent administration schedule. After nearly 2 years of intermittent, reduced-dose chemotherapy, 80 mg of silymarin was finally added to this patient's regimen. For 4 months, he was able to tolerate full chemotherapy doses with no signs of liver damage. He then stopped all chemotherapy drugs and was apparently free of cancer. Clinical trials are definitely warranted to determine the clinical benefit of milk thistle as an adjunct to chemotherapy.

Milk thistle may also be of benefit to patients who undergo radiation therapy. Patients (n = 405) with brain metastases, who were given omega-3 fatty acids and milk thistle before stereotactic radiotherapy, had improved survival times and decreased numbers of radionecroses.⁴² Silymarin administered 1 hour before gamma irradiation moderated radiation-induced changes in target organs, spleens, livers, and bone marrow in animals.⁴³ Milk thistle is a very safe botanical and studies have suggested that it is potentially beneficial for treating a wide variety of cancers. In addition, milk thistle may ameliorate and potentiate various chemotherapies, help to prevent the development of resistance to chemotherapy drugs, and prevent some side-effects of radiation therapy. Milk thistle, used topically, also appears to have a strong ability to prevent UV-B-damage to skin. Practitioners should include standardized milk thistle products in their cancer treatment regimens, particularly when there is liver or renal damage related to chemotherapy or potential for such damage.

Hypolipidemic and Cardiovascular Effects

Treating patients who have cancer is a relatively specialized area. Helping people to deal with atherosclerosis and its risk factors is much more common for practitioners who work with a general population of patients. Milk thistle may also be beneficial in this area.

Milk thistle seed oil fed to rats reduced serum total cholesterol and triglyceride levels (84 percent and 60 percent, respectively).⁴⁴ More research on milk thistle oil would be likely to yield interesting results if this study is any indication of what this oil can do; it is surprising that more information on milk thistle oil is not available. Unfortunately, these constituents (and other milk thistle constituents) seem to have been ignored, creating the misimpression that the plant's action is solely the result of its beneficial flavonolignans.

Silymarin protected rabbits effectively against liver damage induced by a high-fat diet.⁴⁵ Silymarin increased high-density lipoprotein (HDL) cholesterol, decreased liver cholesterol content, and prevented a diet-induced decrease in glutathione in rats who were on a high-cholesterol diet.⁴⁶ Silymarin may inhibit cholesterol synthesis directly in the liver. However, silymarin administered to rats on a high-cholesterol diet mildly increased the rats' HDL but did not reduce serum total cholesterol levels.⁴⁷⁻⁴⁹ In other animal studies, silymarin and silybin reduced serum total cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein while enhancing HDL in hyperlipidemic rats.⁵⁰ A fraction of silymarin fed to rats who were on a high-fat diet for 3 weeks modified the animals' lipoprotein profiles positively and counteracted the development of fatty livers.⁵¹ Silymarin added to LDL showed a positive effect via an index used to measure the susceptibility of LDL to oxidation.⁵²

Silybin (300 mg/kg per day, for 8-12 days) reduced mortality in spontaneously hypertensive rats compared to controls and reduced blood pressure and the incidence of postocclusion arrhythmias in spontaneously hypertensive rats to the same extent as tetrandrine (a constituent found in *Stephania*

tetrandra).⁵³ This study implied that silybin may be beneficial when used in hypertensive patients who develop acute myocardial infarctions.

Silymarin (80 mg) or silybin (60 mg) decreased in vitro aggregation of rat platelets.⁵⁰ Intravenously, silybin lowered the amplitude and duration of diastolic blood pressure without changing the aortic blood flow, cardiac contractility, or electrocardiogram in open-chest cats; these changes were changes deemed to be beneficial in coronary heart disease.

Although it is unclear whether milk thistle will have a beneficial impact on the serum lipid profile, the herb should be considered for treating hyperlipidemic patients who are unable to modify their diets because it appears to offset some of the risks of a high-cholesterol diet. Milk thistle also appears to affect HDL levels beneficially, thereby decreasing the risk of atherosclerosis. Thus, this herb should be considered for patients with adverse HDL/LDL ratios and has potential use as a cardioprotectant for patients with hyperlipidemia. One study indicated that milk thistle seed oil reduces serum lipid levels, suggesting that patients with hyperlipidemia may benefit from adding ground milk thistle seeds to their diets.

Kidney Regeneration

Milk thistle's effects on the kidney closely mirror the herb's effects on the liver and milk thistle's utility in nephrology is supported by some intriguing clinical research. One clinical trial found that patients with end-stage diabetic nephropathy had significant thiol deficiency that was directly correlated with significantly diminished T-lymphocyte activation and increased synthesis of TNF- α . Treatment with silymarin restored thiol status to normal within 72 hours in vivo and in vitro. Similarly, T-cell activation increased and TNF- α release was reduced, showing a normalizing effect on immunoregulatory defects.⁵⁴

During continuous ambulatory peritoneal dialysis, macrophages are highly compromised, possibly the result of a thiol-disulfide imbalance. Peritoneal macrophages treated with silymarin or silybin stabilized cellular thiol status with a resulting improvement of phagocytosis.⁵⁵

Silymarin stimulates RNA polymerase I in kidney epithelium, leading to increased protein synthesis and cellular regeneration, exactly as it does in the liver.⁵⁶ Silybin and silichristin are believed to be mostly responsible for these effects while silidianin produces little effect. This work suggests that silymarin may be particularly useful in situations in which renal epithelium is becoming necrotic.

Silymarin, administered orally before exposure to γ radiation, had significant protective effects on urea and creatinine serum levels in an animal model.⁵⁷ In vitro experiments with monkey

kidney cells damaged by paracetamol, cisplatin, and vincristine showed that treatment with silybin before or after chemically induced injury can lessen or prevent the nephrotoxicity of these drugs.⁵⁸ And, as discussed above, silymarin protected the kidneys from chemotherapy-induced damage.

Silybin decreased cyclosporin-induced lipid peroxidation in the rat kidney without a protective effect on glomerular filtration rate.⁵⁹ Silymarin inhibited xanthine oxidase in vitro. Xanthine oxidase converts hypoxanthine to xanthine and xanthine to uric acid.⁶⁰ Xanthine oxidase is implicated in renal tissue oxidative injury after ischemia-reperfusion. Silymarin prevents the decrease in dehydrogenase/xanthine oxidase ratio that results in tissue injury.⁶¹

Silymarin had a moderate diuretic effect in isotonic saline-loaded rats. However, silymarin caused a marked decrease in potassium excretion, suggesting that this constituent is a potassium-sparing diuretic.⁶²

Milk thistle should be used as a renal protectant as well as a liver protectant. It should be prescribed to counter the adverse effects of any drug or treatment modality that may damage the kidneys. Milk thistle should also be considered for treating patients with acute tubular necrosis or in other situations in which epithelial-cell loss is occurring, based on the renal regenerative effects of the herb.

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Conclusions

Milk thistle has a well-established role as a hepatoprotectant. It should also be considered as a renal protectant and shows strong potential as a component of cancer treatment regimens and as an adjunct support to chemo- and radiation therapy. Unfortunately, clinical studies validating these uses are lacking. However, because of milk thistle's high safety profile (which will be addressed in Part 2), practitioners should not wait for definitive research before expanding their clinical use of this remarkable plant. □

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