

## **Milk Thistle – A Multi-Talented Plant**

### **Narda G. Robinson, DO, DVM, MS**

When Pliny the Elder prescribed milk thistle two thousand years ago, he did so for a variety of health concerns, including serpent bites, melancholy, plague, and milk production, in addition to “carrying off bile”.<sup>i</sup> <sup>ii</sup> Now, the popularity of milk thistle is soaring, not only for treating chronic liver problems for which it is best known, but also for its ability to protect other organs from the damaging effects of radiation, chemotherapy, other xenobiotics, and chronic disease. <sup>iii</sup> For example, its antioxidant actions decrease gentamicin-induced nephrotoxicity in dogs;<sup>iv</sup> milk thistle also promotes kidney function in patients with end-stage diabetic nephropathy.<sup>v</sup>

### **What’s in It**

“Milk thistle extract”, the first substance extracted from the crushed seeds, contains up to 80% silymarin, the main active constituent.<sup>vi</sup> In contrast, the silymarin content of unprocessed seeds may fall as low as 4% silymarin. <sup>vii</sup> Some manufacturers standardize the silymarin content to ensure equivalence between batches. Silibinin (also called silybin), a semipurified fraction of silymarin, acts as an important marker for research in order to track pharmacokinetics and ensure adequate plasma and/or target tissue concentrations.<sup>viii</sup> Monitoring pharmacokinetics becomes especially important when studying phytomedicinals exhibiting poor or erratic bioavailability, as do the flavonolignans comprising silymarin. Complexing silibinin with phosphatidylcholine dramatically improves oral availability; manufacturers may also add vitamin E and zinc to further manage liver dysfunction; doing so does not attenuate bioavailability<sup>ix</sup>.

### **Working for the Liver**

The plant stimulates liver repair and detoxification through four main avenues: 1) antioxidation, free radical scavenging, and glutathione regulation; 2) stabilization of cell membranes and permeability, which limits hepatotoxin entry into hepatocytes; 3) ribosomal RNA synthesis promotion, stimulating liver regeneration; and 4) slowing transformation of stellate hepatocytes into myofibroblasts, slowing the onset of cirrhosis arising through collagen deposition.<sup>x</sup>

### **New Applications for Cancer**

Probably the most salient new applications for milk thistle arise in its role as an adjunct for cancer chemoprevention, treatment, and in order to reduce side effects of treatment.<sup>xi</sup> <sup>xii</sup> Specifically, silymarin has led to reductions in tumor incidence and number of chemically-induced tumors in rat models for colon, tongue, and bladder cancer. It has also held back the growth of human prostate cancer and lung cancer xenografts in mice bred as immunodeficient.<sup>xiii</sup> Milk thistle derivatives protect the kidneys from radiation injury and cisplatin nephrotoxicity<sup>xiv</sup> <sup>xv</sup> and may protect the heart from doxorubicin-induced lipid peroxidation. When combined with omega-3 fatty acids, milk thistle has reduced the number of radionecrosis sites in cancer patients and prolonged survival.<sup>xvi</sup> Milk thistle potentiated antitumor effects of drugs like cisplatin in both *in vivo* and *in vitro* studies.<sup>xvii</sup>

## Drug-Herb Interactions

The risk of herb-drug interactions appears to be low, but not non-existent. Milk thistle may inhibit certain isoforms of the cytochrome P450 family, namely CYP3A4 and CYP2C9. This becomes significant when combined with agents that depend on CYP3A4 for metabolism, raising concerns about adding milk thistle for “liver protection” during chemotherapy, especially at high doses.<sup>xviii</sup> Silymarin has potentiated chemotherapy toxicity in at least one study.<sup>xix</sup> However, a recent investigation testing its effects on the disposition of irinotecan as a model drug indicated that milk thistle poses little risk of interfering with agents of similar metabolic profile.<sup>xx</sup> Still, evaluating clinically significant interactions for each target species will likely prove necessary, given the large interspecies differences in cytochrome P450-mediated metabolic activities between humans, horses, dogs, and cats.<sup>xxi</sup>

## Adverse Effects

Milk thistle’s ability to promote liver regeneration could conceivably stimulate tumor growth in cases of hepatocellular carcinoma,<sup>xxii</sup> but one study showed that milk thistle demonstrated strong anticancer (i.e., pro-apoptotic and growth-inhibiting) activity against human hepatocellular carcinoma cells.<sup>xxiii</sup>

On the other hand, silymarin/silibinin promoted mammary tumor growth in two rodent models. This likely occurred through stimulation of estrogen receptor signaling by silymarin.<sup>xxiv</sup> This raises caution about its safety in cases of breast cancer.

Overall, the majority patients tolerate even high doses of milk thistle; as with most herbs, adverse effects typically involve gastrointestinal upset.

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<sup>i</sup> Mulrow C, Lawrence V, Jacobs B, et al. Milk thistle: effects on liver disease and cirrhosis and clinical adverse effects. *Evid Rep Technol Assess*. 2000. Chapter 1. Introduction. Obtained on 1-26-08 at <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.section.29172>.

<sup>ii</sup> Post-White J, Ladas EJ, and Kelly KM. Advances in the use of milk thistle (*Silybum marianum*). *Integrative Cancer Therapies*. 2007;6(2):104-109.

<sup>iii</sup> Greenlee H, Abascal K, Yarnell E, and Ladas E. Clinical applications of *Silybum marianum* in oncology. *Integrative Cancer Therapies*. 2007;6(2):158-166.

<sup>iv</sup> Varzi HN, Esmailzadeh S, Morovvati H, et al. Effect of silymarin and vitamin E on gentamicin-induced nephrotoxicity in dogs. *J Vet Pharmacol Therap*. 2007;30:477-481.

<sup>v</sup> Greenlee H, Abascal K, Yarnell E, and Ladas E. Clinical applications of *Silybum marianum* in oncology. *Integrative Cancer Therapies*. 2007;6(2):158-166.

<sup>vi</sup> Kroll DJ, Shaw KS, and Oberlies NH. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies. *Integrative Cancer Therapies*. 2007;6(2):110-119.

<sup>vii</sup> Greenlee H, Abascal K, Yarnell E, and Ladas E. Clinical applications of *Silybum marianum* in oncology. *Integrative Cancer Therapies*. 2007;6(2):158-166.

<sup>viii</sup> Kroll DJ, Shaw KS, and Oberlies NH. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies. *Integrative Cancer Therapies*. 2007;6(2):110-119.

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- <sup>xiv</sup> Greenlee H, Abascal K, Yarnell E, and Ladas E. Clinical applications of *Silybum marianum* in oncology. *Integrative Cancer Therapies.* 2007;6(2):158-166.
- <sup>xv</sup> Gaedeke J, Fels LM, Bokemeyer C, et al. cisplatin nephrotoxicity and protection by silibinin. *Nephrol Dial Transplant.* 1996;11(1):55-62.
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