

LE Magazine November 2005

REPORT

A New Weapon to Fight Prostate Cancer

By Dale Kiefer



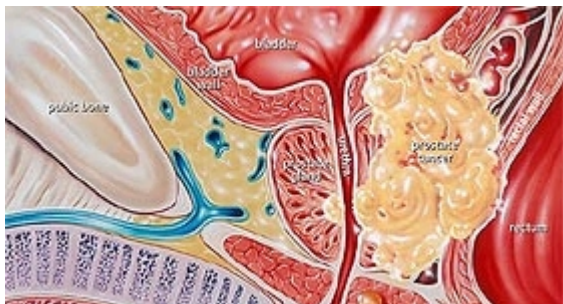
Scientists recently uncovered a novel component of milk thistle that may be a powerful new weapon for preventing and possibly even treating prostate cancer.

This phytochemical, called *isosilybin B*, potently suppresses the growth and runaway proliferation of human prostate cancer cells. Isosilybin B also suppresses the activity of a genetic factor that is expressed in most human cancers. Moreover, this potent phytonutrient inhibits the secretion of a protein that may contribute to prostate cancer progression and metastasis.

Importantly, isosilybin B is active against both hormone-dependent and hormone-independent prostate cancers. Isosilybin B may thus offer the most powerful protection against prostate malignancies of any phytonutrient yet discovered.

The beneficial effects of *silymarin* and *silibinin* extracts from the milk thistle plant have long been known. Scientists recently identified a new milk thistle extract called isosilybin B that shows remarkable effects in fighting prostate cancer via several mechanisms.

At the Research Triangle in North Carolina, scientists investigated the anti-cancer activities of milk thistle extracts and of purified milk thistle constituents against three different human prostate carcinoma cell lines: LNCaP, DU145, and PC3. These are the most commonly used laboratory models of human prostate cancer.¹



A cancerous prostate gland (light brown, center right). The gland has increased in size in a disordered growth often seen in cancer. It has invaded the bladder wall (above) and the rectal wall (at right). Also seen is the urethra (tube leading out of the bladder and down to lower left). The pubic bone is at left. [click to enlarge]

suppressor of LNCaP cells, and was also effective against the PC3 cancer cells. The researchers noted, "isosilybin B was the most potent growth inhibitory constituent of silymarin-based milk thistle extracts and was often more effective than silibinin or silymarin extracts."¹

In another experiment, the scientists examined how milk thistle constituents affect the secretion of prostate-specific antigen (PSA) by LNCaP cells. A protein synthesized in the prostate gland, PSA serves as a marker for prostate enlargement and cancer. Isosilybin B and its mirror-image isomer, isosilybin A, reduced PSA secretion, while other milk thistle constituents did not show this activity.¹ The effect of isosilybins A and B on PSA is particularly noteworthy, as emerging evidence suggests PSA itself may play a role in prostate cancer's progression and metastasis.²⁻⁴ (See "Does PSA Promote Prostate Cancer?" *Life Extension*, June 2005.) Isosilybins may thus offer a novel way to modulate PSA levels.

Continuing their investigation, the Research Triangle scientist found for the first time that milk thistle extracts suppress the activity of the DNA topoisomerase II α promoter, a genetic factor that is indispensable for cellular proliferation. A recent meta-

Examining several end points related to anti-proliferative activity against prostate cancer, the scientists found isosilybin B to be the most potent prostate cancer fighter in nearly all of the parameters studied.

First, the researchers tested individual milk thistle constituents against DU145 cells, a line of hormone-independent human prostate cancer cells. The cancer cells were exposed to varying concentrations of milk thistle compounds for three days. Isosilybin B produced significant growth inhibition of nearly 69% and was the most efficacious of all milk thistle compounds tested. By contrast, the second most effective agent inhibited cancer cell growth by only 38%, while most of the phytochemicals tested showed no activity at all.¹

Next, the investigators examined the effects of milk thistle components against hormone-dependent LNCaP prostate cancer cells and hormone-independent PC3 cells. Isosilybin B was the most effective growth

analysis found that topoisomerase IIalpha is one of the most commonly activated genes across a large majority of human cancers.¹ In DU145 prostate cancer cells, isosilybin B was the milk thistle constituent that most potently and effectively suppressed this gene promoter.¹

NEW FINDINGS, NEW PRIORITIES

These recent research findings concerning isosilybin B have significant implications for individuals and scientists interested in prostate cancer prevention and treatment.

Until recently, scientists had focused their research efforts on milk thistle components such as silymarin and silibinin, which in turn have become widely available in herbal supplements. However, as the Research Triangle team noted, “isosilybin B composes no more than 5% of silymarin, and is absent from silibinin.”¹ In other words, preparations currently sold as milk thistle extract, silymarin, or silibinin may contain little or no isosilybin B.

While the scientists reported some anti-cancer activity among other milk thistle constituents, it was necessary to apply those compounds at much higher concentrations to achieve the anti-cancer effect elicited by a relatively small dose of isosilybin B.¹ The bottom line? Isosilybin B appears to be more potent than other milk thistle isomers against prostate cancer. According to the Carolina scientists, “identification of isosilybin B as the most potent prostate carcinoma inhibitor indicates that any subsequent preclinical or phase I trials should include extracts enriched for this component.”¹



OTHER MILK THISTLE COMPONENTS

The crude extraction of milk thistle fruits or seeds yields a polyphenolic flavonoid called silymarin. Silymarin is actually a mixture of phytochemicals, the most prominent of which are silibinin (also spelled as silybin), isosilybin, silychristin, and silydianin.⁵

Most research has focused on the beneficial effects of silymarin and silibinin. Studies suggest that silymarin helps prevent the growth of human cancer cells in vitro^{6,7} and protects laboratory animals against the growth of certain tumors.⁶⁻⁸

Silibinin has shown potent antioxidant and anticarcinogenic effects,⁶ and may work synergistically with chemotherapy drugs used to treat prostate cancer.⁹ Many currently available milk thistle products contain primarily silymarin, and some are standardized in silibinin content, perhaps in light of the National Cancer Institute’s assertion that silibinin is the most active constituent of milk thistle.¹⁰

In 2003, Harvard Medical School researchers learned that the milk thistle compound isosilybin is not one, but is actually two distinct chemicals, isosilybin A and isosilybin B. Likewise, they found that silibinin comprises two chemicals, silybin A and silybin B. These closely related but distinct isomers belong to a class of plant chemicals called flavonolignans.¹¹

EFFECTS OF SILYMARIN AND SILIBININ

Isosilybin is now poised to join the ranks of the cancer-fighting milk thistle components silymarin and silibinin, two extracts whose effects already are supported by a large body of research. Indeed, numerous studies of silymarin and silibinin paved the way for further studies on milk thistle constituents.

Silymarin and silibinin appear to offer protection against prostate and other cancers. Studies have shown that both silymarin and silibinin are strong antioxidants and inhibit human carcinoma cell growth and DNA synthesis.⁶ Both compounds may help protect against skin cancer and breast cancer.^{7,8,12,13}

Silymarin and silibinin also show promise in preventing prostate cancer.

Research conducted in 2004 indicates that one or more silymarin constituents inhibit mitogenic and survival signaling by prostate cancer cells. This signaling is crucial to cancer cells’ ability to survive and thrive. “In general, advanced stage cancer cells harbor many constitutively active mitogenic signaling and anti-apoptotic mechanisms, which make them less dependent on external growth factors as well as resistant to chemotherapeutic agents,” noted University of Colorado researchers. They add, however, that silymarin’s ability to tackle cancer from a number of angles holds great promise: “In this regard, silibinin . . . has shown [multi-tasking] anti-cancer effects in different cancer cells.”¹⁴

Another research team investigated the efficacy of silibinin against prostate cancer. Based on the “strong antioxidant and

PROSTATE CANCER STATISTICS

Today, prostate cancer is the most common invasive malignancy and the second leading cause of cancer deaths in American men.^{1,6,18,19}

One in six American men will be diagnosed with prostate cancer during his lifetime.

The economic costs of prostate cancer are equally staggering. An estimated \$5.3 billion is spent on prostate cancer treatment in the United States annually.²⁰

anticarcinogenic effects of silibinin, the fact that silibinin is used clinically and marketed as a dietary supplement, and [considering] the bioavailability of silibinin in prostate after its oral administration . . . we reasoned that silibinin also could be a useful agent for the intervention of human [prostate cancer],” wrote the researchers. After conducting a variety of complex cell culture assays, they determined that “silibinin has strong potential to be developed as an antiproliferative differentiating agent for the intervention of hormone-refractory human prostate cancer.”⁶

In another 2004 report, the University of Colorado research team noted that silymarin and silibinin inhibit the secretion of pro-angiogenic factors from tumor cells, which are necessary for tumor cells to recruit the blood supply required for their continued growth. Furthermore, silymarin and silibinin inhibit the growth of cancer cells in culture, while inducing programmed cell death, or apoptosis. Silibinin may also work synergistically with the chemotherapy drug doxorubicin to help kill cancer cells, making it a strong candidate for combination therapy.⁹

Silibinin has even exerted cancer-fighting effects against an advanced form of prostate cancer. Adding silibinin to the diet of mice that had received a surgical graft of advanced human prostate tumor cells resulted in decreased proliferation and increased programmed cell death of the cancer cells.¹⁵

Animal and human studies alike have shown milk thistle to be non-toxic. “At high doses . . . a laxative effect is possible due to increased bile secretion and flow,” noted a report published in *Alternative Medicine Review*. “Mild allergic reactions have also been noted but were not serious.”¹⁶ However, as one researcher noted regarding milk thistle’s use as a pharmaceutical in Belgium, “The drug has a general safety pattern comparable to placebo.”¹⁷

Combining the wisdom of the ancients with cutting-edge medical technology, science is discovering exciting new applications for milk thistle in the fight against prostate cancer. Isosilybin B, a previously little-known constituent of milk thistle extract, appears to hold great potential for preventing this much-dreaded malady.

ADDITIONAL BENEFITS OF MILK THISTLE

In addition to being a potentially important therapeutic tool in preventing and managing prostate cancer, milk thistle offers a host of other health benefits. Numerous scientific studies and clinical experience suggest that milk thistle may have great value in protecting the liver, treating liver disease, managing elevated cholesterol, and preventing skin cancer.

- **Protecting the liver.** Extracts of milk thistle have been reported to protect the liver against a wide variety of toxins, including acetaminophen, ethanol, and carbon tetrachloride. Furthermore, milk thistle has been shown to guard liver cells against ischemic injury, radiation, and iron toxicity. In Europe, milk thistle extract is used to treat people poisoned by the liver-toxic *Amanita* mushroom.²¹

Several mechanisms of action may account for milk thistle’s liver-protective effects. Silymarin from milk thistle has been reported to possess antioxidant effects and protect against depletion of glutathione, one of the liver’s most important antioxidants. Silymarin has also been found to inhibit the pro-inflammatory enzyme lipooxygenase. Other findings suggest that milk thistle extracts suppress the formation of fibrotic scar tissue in the liver that can occur with certain liver diseases, and that it may help to stimulate the regeneration of liver tissue.²¹

Milk thistle extracts appear to have several strong anti-inflammatory effects on liver tissue. Specifically, silymarin may help to stabilize mast cells and inhibit neutrophil migration, Kupffer cells, and the formation of inflammatory prostaglandins and leukotrienes.²¹

- **Treating liver disease.** Milk thistle extracts have been found to be effective in treating both acute and chronic hepatitis. In patients with acute viral hepatitis, treatment with silymarin helped to shorten treatment time and improve several markers of liver health, including bilirubin and the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In those with chronic hepatitis, six months of daily silymarin supplementation yielded similar improvement in liver enzymes.¹⁶

Milk thistle also benefits liver health in people with cirrhosis and alcoholic liver disease. When administered to individuals with alcoholic liver disease, silymarin helped to lower elevated bilirubin and liver enzymes to normal levels. Milk thistle extract also helped improve liver tissue cells, as determined by liver biopsy histology. Long-term supplementation with milk thistle over three years helped to improve survival rates in patients with cirrhosis of the liver.¹⁶

• **Managing cholesterol.** An animal study provides intriguing evidence that milk thistle may help promote healthy cholesterol levels. When rats with diet-induced elevated cholesterol levels consumed silymarin from milk thistle, their levels of beneficial high-density lipoprotein (HDL) rose, while their levels of total and biliary (liver) cholesterol diminished. Studies in humans are indicated to further investigate milk thistle's role in managing cholesterol.¹⁶

• **Skin cancer prevention.** One of the most exciting findings of recent years concerns the potential skin-protective effect of milk thistle extracts. Researchers found that topically applied milk thistle extract protects the skin of mice exposed to chemical carcinogens from skin tumor formation.⁷ Further studies in mice demonstrated that topically applied milk thistle extract protects the skin of mice against ultraviolet light-induced skin cancer.²² Further studies are indicated to explore the potential skin cancer-protective effects of topical application and internal consumption of milk thistle in humans.



REPORT

A New Weapon to Fight Prostate Cancer

By Dale Kiefer

MORE RESEARCH NEEDED

Despite the impressive findings showing that isosilybin B inhibited prostate cancer cell growth by 69%, no human studies have been conducted to validate whether prostate cancer patients would see these same kinds of benefits.

Scientists have shown that milk thistle extracts possess anti-cancer actions on human prostate carcinoma in vitro and in vivo. Many of the mechanisms by which silymarin compounds interfere with prostate cancer progression have been identified. The scientists who conducted the most recent study stated that, in addition to isosilybin B, there might be other silymarin compounds that are effective as well. These scientists concluded their presentation of this study by noting that:

“these findings are suggestive that (silymarin) extracts enriched for isosilybin B, or isosilybin B alone, might possess improved potency in prostate cancer prevention and treatment.”

Since silymarin compounds cannot be patented, the National Cancer Institute should sponsor clinical studies in prostate cancer patients to clarify whether these compounds are clinically important in humans. An ideal study would be to evaluate PSA progression (using PSA doubling time values and PSA velocity values) and then institute isosilybin B to see the effect on these biologic parameters. Patients undergoing radical prostatectomy could also be treated prior to surgery with isosilybin B to see the effect on PSA, free PSA, and the histological findings on specimens obtained from tissues removed during the radical prostatectomy procedure.



Colored urogram of the pelvis of a 60-year-old man with prostate gland cancer. The prostate is below the bladder and should be clear, but due to the presence of a tumor it appears cloudy. The urethra shows narrowing caused by the pressure from the tumor. [click to enlarge]

References

1. Davis-Searles PR, Nakanishi Y, Kim NC, et al. Milk thistle and prostate cancer: differential effects of pure flavonolignans from *Silybum marianum* on antiproliferative end points in human prostate carcinoma cells. *Cancer Res.* 2005 May 15;65(10):4448-57.
2. Gallardo-Williams MT, Maronpot RR, Wine RN, Brunssen SH, Chapin RE. Inhibition of the enzymatic activity of prostate-specific antigen by boric acid and 3-nitrophenyl boronic acid. *Prostate.* 2003 Jan 1;54(1):44-9.
3. Cohen P, Graves HC, Peehl DM, et al. Prostate-specific antigen (PSA) is an insulin-like growth factor binding protein-3 protease found in seminal plasma. *J Clin Endocrinol Metab.* 1992 Oct;75(4):1046-53.
4. Cohen P, Peehl DM, Graves HC, Rosenfeld RG. Biological effects of prostate specific antigen as an insulin-like growth factor binding protein-3 protease. *J Endocrinol.* 1994 Sep;142(3):407-15.
5. Wang P, Cong R, Wang J, Zhang L. Determination of the active flavonoids in silymarin. *Se Pu.* 1998 Nov;16(6):510-2.
6. 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 USA.* 1999 Jun 22;96(13):7490-5.
7. Lahiri-Chatterjee M, Katiyar SK, Mohan RR, Agarwal R. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. *Cancer Res.* 1999 Feb 1;59(3):622-32.
8. Katiyar SK, Korman NJ, Mukhtar H, Agarwal R. Protective effects of silymarin against photocarcinogenesis in a mouse skin model. *J Natl Cancer Inst.* 1997 Apr 16;89(8):556-66.
9. Singh RP, Agarwal R. Prostate cancer prevention by silibinin. *Curr Cancer Drug Targets.* 2004 Feb;4(1):1-11.

10. Available at: <http://www.nci.nih.gov/cancertopics/pdq/cam/milkthistle/HealthProfessional/page2>. Accessed August 24, 2005.
11. 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 Sep;66(9):1171-4.
12. Zi X, Feyes DK, Agarwal R. Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468: induction of G1 arrest through an increase in Cip1/p21 concomitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins. *Clin Cancer Res*. 1998 Apr;4(4):1055-64.
13. Tyagi AK, Agarwal C, Chan DC, Agarwal R. Synergistic anti-cancer effects of silibinin with conventional cytotoxic agents doxorubicin, cisplatin and carboplatin against human breast carcinoma MCF-7 and MDA-MB468 cells. *Oncol Rep*. 2004 Feb;11(2):493-9.
14. Singh RP, Agarwal R. A cancer chemopreventive agent silibinin, targets mitogenic and survival signaling in prostate cancer. *Mutat Res*. 2004 Nov 2;555(1-2):21-32.
15. Singh RP, Sharma G, Dhanalakshmi S, Agarwal C, Agarwal R. Suppression of advanced human prostate tumor growth in athymic mice by silibinin feeding is associated with reduced cell proliferation, increased apoptosis, and inhibition of angiogenesis. *Cancer Epidemiol Biomarkers Prev*. 2003 Sept;12(9):933-9.
16. Anon. *Silybum marianum* (milk thistle). *Altern Med Rev*. 1999 Aug;4(4):272-4.
17. Laekeman G, De Coster S, De Meyer K. St. Mary's Thistle: an overview. *J Pharm Belg*. 2003;58(1):28-31.
18. Wingo PA, Landis S, Ries LA. An adjustment to the 1997 estimate for new prostate cancer cases. *CA Cancer J Clin*. 1997 Jul;47(4):239-42.
19. Available at: <http://apps.nccd.cdc.gov/uscs/GraphV.asp?group=3f&Year=2001&Gender=MAL&Var1=United+States&TableType=INCI>. Accessed August 24, 2005.
20. Available at: <http://prg.nci.nih.gov/snapshots/Prostate-Snapshot.pdf>. Accessed August 24, 2005.
21. Luper S. A review of plants used in the treatment of liver disease: part 1. *Altern Med Rev*. 1998 Dec;3(6):410-21.
22. Mallikarjuna G, Dhanalakshmi S, Singh RP, Agarwal C, Agarwal R. Silibinin protects against photocarcinogenesis via modulation of cell cycle regulators, mitogen-activated protein kinases, and Akt signaling. *Cancer Res*. 2004 Sep 1;64(17):6349-56.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.