

COVER STORY

**Can Silibinin Arrest Cancer Cells Growth?**

The last decade has brought many discoveries about the natural ways to prevent breast cancer and prostate cancer. Certain supplements, such as potent extracts of green tea, have been shown to be effective in lowering cancer risk, and even in fighting cancer, particularly when used together with other therapeutic agents. Since flavonoids of various kinds have antiproliferative properties, they have emerged in a starring role. Epidemiological studies have confirmed that diets rich in flavonoids appear to lower the risk of many kinds of cancer, including breast and prostate cancer.

A recent in vitro study by Zi and Agarwal (1999) found that silibinin was able to arrest cell growth in prostate cancer lines, probably through inhibiting various kinase enzymes. Silibinin helped arrest cell growth in the early phase of the cell cycle, known as G1. The researchers found a 20% increase in G1 cell population when the culture was treated with silibinin. It is well known that potent flavonoids have an antiproliferative effect on tumor tissue, so this was not surprising. But this is not the end of the story. It turned out that the growth arrest did not lead to apoptosis (programmed cell death), but to cell differentiation. As the authors put it:

"The silibinin-treated [cancer] cells that are unable to grow follow a differentiation pathway as evidenced by neuroendocrine-like morphology, elevated prostate tissue differentiation markers... and altered cell-cycle regulatory molecules."

Differentiated cells are the mature cells that perform specialized tasks appropriate to the organ. In this study, silibinin transformed a significant proportion of malignant cells to normal, differentiated prostate cells. Silibinin treatment also resulted in a large decrease in PSA secretion. The authors conclude that silibinin "has strong potential to be developed as an antiproliferative differentiating agent for the intervention of hormone-refractory human prostate cancer."

Another study found that silibinin inhibits proliferation in both drug-sensitive and drug-resistant breast cancer and ovarian cancer lines. The suggested mechanism of action involves silibinin's ability to bind to nuclear type II estrogen receptors, which are thought to mediate the antiproliferative effects of flavonoids (Scambia 1996). Comparing the properties of silymarin and silibinin, two investigators, Zhao and Agarwal (1999) state:

"Studies from our laboratory have shown that silibinin, the major active constituent of silymarin, has comparable [to silymarin] inhibitory effects towards human prostate, breast and cervical carcinoma cell growth, DNA synthesis and cell viability, and is as strong an antioxidant as silymarin."

Silibinin also showed synergy with two common chemotherapy drugs, cisplatin and doxorubicin. By arresting tumor cell division at a vulnerable stage, silibinin can apparently make tumor cells more sensitive to chemotherapy. Because of its effectiveness, silibinin is now in phase I clinical trials in patients with advanced ovarian cancer (Scambia 1996).

Likewise, silibinin has been shown to protect the kidneys during chemotherapy with certain extremely toxic drugs such as cisplatin (Bokemayer 1996). This is also fairly typical for effective alternative therapies for cancer: They often synergize with the mainstream treatment, and at least partly protect against its devastating effects on normal tissue. Thus, there is much to say for the combination of mainstream treatment with potent flavonoids such as silibinin.

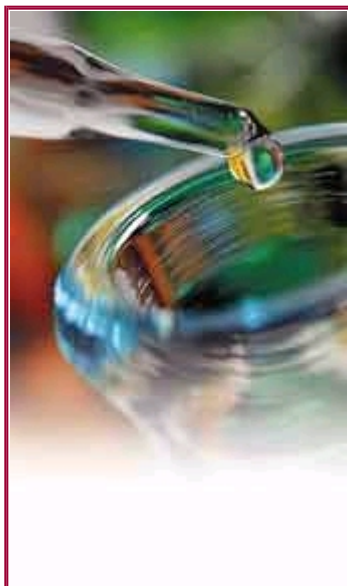
Can silibinin slow aging?

Startling new discoveries about a popular herb

In February 1991, The Life Extension Foundation introduced a German drug called silymarin to its members. The primary known benefit of silymarin at the time was to protect the liver. Since 1991, a plethora of newly published research reveals additional life-saving benefits that can be attributed to this herbal extract from milk thistle.

One of these new discoveries has prompted The Life Extension Foundation to participate in an investigation to ascertain whether a silymarin concentrate called silibinin is effective in the treatment of prostate cancer. In this article, we present some startling new findings about this herbal extract that is sold in Europe

The authors of a recent study (Onat 1999) concluded that silymarin's and silibinin's antiproliferative mechanism of action is not yet fully known, but it may involve modulating signal transduction pathways. These signaling pathways are involved in aging, atherosclerosis and cancer. Compounds that can inhibit excess proliferation involved in aging-related disorders are of great clinical interest. Onat found that both alpha tocopherol and silibinin had a similar inhibitory action on the proliferation of skin fibroblasts. Insofar as excess fibroblast proliferation is one of the phenomena of aging, silibinin could become one of the agents used to slow the aging of the skin.



What is silibinin?

Standardized milk thistle extract usually consists of a minimum 35% silibinin (by HPLC analysis). Silibinin is regarded as the most biologically active ingredient of silymarin. A new pharmaceutical concentrate contains a minimum of 80% silibinin, thus ensuring a higher concentration of silymarin's most potent component to the body. Being able to obtain enough silibinin is of particular importance for those who need to ensure effective dosage for the treatment of various diseases.

important supplement for the prevention of atherosclerosis.

Silibinin may also prove useful as a drug helping the survival of hypertensive patients who suffer a heart attack. In a rat model of acute coronary artery blockage combined with hypertension, intravenous administration of silibinin was found to reduce blood pressure and arrhythmias, decrease ventricular hypertrophy, and reduce mortality (Chen 1993). Fewer heart cells died in the silibinin-treated hypertensive rats. The finding that silibinin was able to reduce the size of the infarct zone is especially important, since the extent of heart cell death is an important predictor of mortality or subsequent congestive heart failure.

One of the ways in which silibinin protects against the development of cancer is by enhancing the activity of protective Phase II enzymes, glutathione transferase and quinone reductase. These two extremely important enzymes detoxify the various pro-carcinogenic metabolites that result from the initial stage of detoxification. Zhao and Agarwal (1999) found that in mice the activity of glutathione transferase in particular was enhanced by oral treatment with silibinin. This enhancement was especially evident in the small bowel, but was found also in liver, lungs, stomach, skin and prostate. Garrido's earlier finding in relation to acetaminophen indicates that silibinin can also inhibit the cytochrome P-450 system, which constitutes the main group of Phase I enzymes (Garrido 1991). This suggests that silibinin lowers the levels of toxic metabolites through a mechanism that may involve the inhibition of certain Phase I enzymes, and simultaneous enhancement of Phase II enzymes.

Silibinin and silymarin have also been shown to inhibit an enzyme called beta-glucuronidase, which catalyzes the breakdown of glucuronides, compounds created in the liver for the purpose of safely disposing of various toxic chemicals. Liver damage causes an increase in beta-glucuronidase; it has been suggested that it is a factor in liver cancer. Toxins such as carbon tetrachloride increase serum beta-glucuronidase. Likewise, our intestinal bacteria produce this enzyme; scientists suspect that it is related to colon cancer. Kim (1994) found that both silymarin and silibinin inhibited beta-glucuronidase to a similar degree in rats treated with carbon tetrachloride. The potential for reducing the risk of colon cancer and liver cancer is worth further exploration.

Cardiovascular health and the brain

An early German study (Schriewer and Rauen 1977) showed that silibinin dose-dependently inhibits the biosynthesis of cholesterol in vitro. This has been confirmed by more recent studies (reviewed by Skottova 1998). Another interesting effect is faster removal of low-density lipoproteins by the liver in the presence of silymarin. Studies have also shown that silymarin and silibinin inhibit the development of diet-related excess cholesterol levels in rats. Supplementing the diet with silymarin or silibinin resulted in an increase in HDL levels and a decrease in liver cholesterol content.

A recent study by Skottova (1999) compared the effectiveness of silymarin with that of silibinin in inhibiting copper-induced oxidation of low-density lipoproteins in vitro.

Silymarin and silibinin were found to be equally effective in prolonging the initial "lag phase" (the stage of oxidation when the process is proceeding slowly). In Skottova's study, silichristin and silidianin appeared to act instead as pro-oxidants when tested at the same concentrations as silibinin. Consequently, Skottova concludes, "silibinin is the most important compound of silymarin in protecting the LDL from oxidation."

Another in-vitro study of copper-induced oxidation of LDLs found that silibinin could prolong the lag phase by more than 50%. The authors suggest that silibinin binds to LDL particles and prevents the oxidation of polyunsaturated fatty acids (Locher 1998). Altogether, silibinin shows a potential for being used as an effective hypocholesterolemic and anti-atherogenic agent. It may yet emerge as an

as a prescription drug. We will restrict the information in this report to the effects of silymarin/silibinin outside the liver and kidneys. For those concerned about liver/kidney health, the article that follows this report will review the effects of silymarin/silibinin on various hepatic and renal diseases.

Of related interest is the ability of silibinin to protect the brain under conditions of ischemia (insufficient oxygen). Here the chief mechanisms of action include the scavenging of free radicals and the inhibition of lipoxygenase pathways, lowering the production of cell-damaging leukotrienes (Rui 1990). This is no surprise, considering that silibinin has been shown to help protect the liver and the kidneys from ischemic damage, including ischemia due to exposure to low temperatures (Gower 1989), and has been shown to be an effective inhibitor of leukotriene production. The potential of silibinin as adjuvant therapy for stroke remains to be explored. At The Life Extension Foundation's Critical Care Research Facility in Southern California, silymarin is one component of a neuro-protective "cocktail" used to successfully protect against experimentally induced ischemia.

Silibinin may also help counteract the greater oxidative stress in pregnant diabetic women, which threatens the normal development of the fetus, particularly in regard to the cardiovascular and nervous system. When pregnant diabetic rats were given silibinin, markers of neural development showed considerable normalization (Germani 1999).

Silibinin's effect on diabetes

Silibinin is of considerable interest in the treatment of diabetes, since preliminary evidence indicates that it may prove helpful in normalizing the action of insulin. A Chinese study found that rats subjected to heat injury (scalding) showed elevated blood glucose and high insulin levels due to stress-induced insulin resistance. The function of insulin receptors in the liver was shown to be impaired. Treatment with silibinin significantly enhanced the binding of insulin to the receptors (Tang 1991).

Silibinin was also found to help normalize pancreatic function in the presence of cyclosporin A, an immunosuppressive drug that is damaging to the pancreas (Schonfeld 1997). This included a lowering of insulin secretion without raising serum glucose, possibly indicating that silibinin improves insulin sensitivity.

Schonfeld and colleagues suggest that silibinin should be investigated as a potential treatment for Type II diabetics, who overproduce insulin due to insulin resistance. The authors also suggest that the protective effect of silibinin on the pancreas is non-specific, and is probably due to its antioxidant and membrane-stabilizing properties. Very likely, silibinin protects the pancreas not only against cyclosporin A, but also against alcohol and other toxins, and against free radicals in general.

Glycation, or the damage of proteins by simple sugars, is one of the greatest problems in diabetes. Glycation is a major causal factor leading to diabetic retinopathy, a frequent cause of blindness, and diabetic neuropathy (peripheral nerve degeneration, leading to axon atrophy and eventual loss of sensation). One of the simple sugars involved in this damage is ribose. Exposure to high glucose levels induces increased ribosylation of at least five proteins. It also suppresses the sodium-pump activity (an active transport of sodium ions across cell membranes in exchange for potassium ions) and the maintenance of neural tissue.

A recent in vitro study showed that silibinin can normalize the degree of ribosylation and the sodium pump activity even in the presence of abnormally high glucose levels (Di Giulio 1999). A similar protective effect of silibinin against ribosylation was found in the retina (Gorio 1997). Thus, silibinin may be able to decrease the extent of diabetic neuropathy and retinopathy, two extremely serious complications of diabetes. Considering that silibinin has also been shown to protect the kidneys, another organ seriously damaged by glycation (kidney failure is a frequent cause of death in diabetics), silibinin should be seriously explored as an adjunct treatment in diabetes.

A potent antioxidant

It has been established that silibinin is an effective scavenger of various free radicals, including hydroxyl and peroxy radicals, and the hypochlorite ion that originates in neutrophils (Mira 1994). While it constitutes an important antibacterial defense, the hypochlorite radical is also extremely damaging to normal cells, and must be quickly "disarmed." Unchecked, the hypochlorite ion can even chlorinate DNA bases. In the presence of iron, it creates the hydroxyl radical, which can also directly attack DNA. The presence of powerful flavonoids such as silibinin helps prevent the damage from this "friendly fire."

Silibinin has been found to protect red blood vessels and stabilize their membranes through inhibition of lipid peroxidation. In addition, silibinin increases the activity of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase in human red blood cells (Altorjay 1992). Another study found that silymarin normalized low SOD activity and altered immunoreactivity in the lymphocytes (a common type of white blood cell) of patients with alcoholic liver cirrhosis (Feher 1989).

Finally, silibinin has been found to protect against iron-mediated tissue damage. Iron overload is a dangerous condition, since iron catalyzes various free radical reactions with resulting lipid peroxidation in the membranes. The liver is a primary site of iron-induced damage. Silibinin's antioxidant activities help protect against iron toxicity. In addition, there is evidence suggesting silibinin acts as an iron chelator, binding the free iron for safe excretion in the bile (Pietrangelo 1995; Mira 1994). Thus, iron overload states are another condition during which treatment with silibinin might be helpful. Pietrangelo points out that in fact the high antioxidant activity of flavonoids might be partly due to their ability to form inactive iron chelates, thus reducing the formation of peroxides. Pietrangelo and colleagues found that silibinin was able to protect the rat liver mitochondria against abnormalities caused by iron-induced oxidative stress, such as lipid peroxidation, ATP depletion and abnormal calcium cycling.

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Can Silibinin Arrest Cancer Cells Growth?

Flavonoids, lignans and the importance of glutathione

The extract of milk thistle seed is commonly referred to as silymarin. Silymarin is a collective name for a mixture of flavonoids or, more technically, flavolignans. Both flavonoids and lignans are often loosely grouped together with isoflavonoids (soy), phytosterols and coumestans into a category of compounds known as phytoestrogens. Structural and chemical similarities between flavonoids and human steroid hormones, and thyroid hormone are particularly intriguing. Molecular biologists have begun studying the complex hormone-like actions of flavonoids, including the modulation of various enzyme activities and signaling pathways. Eventually this may lead to a fuller understanding of how diets rich in phytoestrogens help protect against a variety of cancers, including breast cancer, prostate cancer and colon cancer.

Lignans have potent hormone-like properties and are now beginning to be studied in relation to cancer and immunomodulation. The most commonly used natural sources of lignans are flaxseed and stinging nettle (*Urtica dioica*). Flavonoids are part of a larger group of important compounds known as polyphenols, widely distributed in the plant world. Together with chlorophyll and carotenoids, flavonoids are the most common pigments in plants. The reason that vegetables, fruit (especially berries), and beverages such as tea and wine are so protective against cancer, cardiovascular disease and many other disorders of aging is due in large part to their content of flavonoids.

More than 4000 flavonoids have been identified so far.

Depending on molecular structure, all flavonoids show various degrees of antioxidant activity. Some are in fact very powerful antioxidants, more potent by far than vitamins C or E. Potent flavonoids such as proanthocyanidins in grape seed extract, quercetin and various other compounds in ginkgo or catechins in green tea enter our antioxidant network to regenerate vitamin C and glutathione to their antioxidant status (for more information on antioxidant networks, see Dr. Lester Packer's excellent recent book, *The Antioxidant Miracle*). By restoring ascorbic acid and glutathione to the reduced (antioxidant) state, flavonoids greatly potentiate the action of these primary antioxidant compounds.

Dr. Lester Packer states that all flavonoids are antioxidants; their antioxidant potency depends on their molecular structure. Those flavonoids that are strong antioxidants can quench the particularly dangerous hydroxyl radical. Flavonoids stabilize cell membranes, probably thanks to their ability to protect lipids against peroxidation. Typically, flavonoids also decrease the production of nitric oxide. In excess, nitric oxide promotes chronic inflammation and the generation of more free radicals.

There is also evidence that indicates that certain flavonoids (including those found in wine, tea, and coffee) can chelate iron, which can act as a powerful catalyst of free radical induced damage. The ability to chelate iron further enhances the ability of flavonoids to decrease oxidative stress.

Taking a variety of flavonoids is a must for life extensionists. Because they lower oxidative stress and inflammation, two conditions very prominently associated with aging, flavonoids have the potential to retard the aging process. The most potent flavonoids may even extend life span. Very likely, their mechanism of action extends beyond the scavenging of free radicals and reducing inflammation. It may involve an inhibition of certain genes that affect aging.

Milk thistle through the ages



Milk thistle (*Silybum marianum*) is a member of the aster family, which also includes the artichoke, a close relative. A handsome plant with milky white veins on spiky leaves, milk thistle is native to the Mediterranean region, but it is now widely grown for medicinal use in the United States, Africa and South America. Its extract has been used as folk medicine for more than 2000 years. It was first mentioned in writing by the ancient Greek scholar Theophrastus (372-287 B.C.). Interestingly, the physicians of the ancient world recommended milk thistle root mixed with honey as a cough medicine. Medieval monks and nuns spread the use of milk thistle throughout Europe; it was one of the most common herbs grown in cloister gardens, and was known as Heal Thistle or Saint Mary's Thistle. Various parts of the plant were used for medicinal extracts, including flowers and leaves. Mystical properties were ascribed to the Heal Thistle; it is one of

Because of their hormone-like character, flavonoids affect many fundamental aspects of our physiology. We have barely begun to investigate these amazingly potent compounds. Evolved by plants for their own protection against DNA damage, viruses and bacteria, flavonoids have turned out to be effective guardians of human health as well, indicating an essential commonality of biological mechanisms at the molecular level.

One of the primary anti-aging properties of flavonoids is their ability to boost the levels of glutathione, our main endogenous antioxidant and detoxifier. It is present in all cells, but particularly abundant in the liver. Liver poisons act chiefly by depleting glutathione. When glutathione is essentially used up due to toxic overload, and the levels of glutathione in the liver fall below a certain threshold, glutathione-dependent detoxification cannot proceed, and toxins accumulate. It has been shown that silymarin can raise the levels of glutathione in a rat liver by as much as 35%, and that this glutathione-raising action is selective for the liver, intestine and stomach.

Simply raising glutathione levels produces a whole cascade of physiological benefits. But this is not the end of the story. Flavonoids also modulate the action of various enzymes, such as lipoxygenase, which catalyzes the oxidation of polyunsaturated fatty acids, leading to the production of harmful inflammatory compounds known as leukotrienes. Some flavonoids slow the activity of the main Phase I enzymes, the Cytochrome P-450 system. This means a slower conversion of various pro-carcinogens into carcinogenic metabolites. Since these metabolites need to be detoxified by glutathione, slowing down their production prevents rapid glutathione depletion. At the same time, certain potent flavonoids, including silymarin and its chief ingredient silibinin, induce the detoxifying Phase II enzymes, glutathione peroxidase and quinone reductase.

Taking various methylating agents, lipoic acid (which has also been shown to raise glutathione levels) and a mix of various antioxidants are all important ways of helping the liver in its huge task of detoxification. We should try to keep liver glutathione levels as high as possible-and this is where silymarin and silibinin appear to be particularly effective.

In addition to their well-known role in promoting liver health, silymarin (milk thistle extract) and silibinin have now joined grape seed extract, green tea extract, bilberry and ginkgo as phytonutrients that provide a wide range of antioxidant, anti-inflammatory, anticarcinogenic and cardiovascular benefits.

Anti-inflammatory properties

Like many other flavonoids, silibinin can also inhibit the production of nitric oxide (Dehmlow 1996). Excess nitric oxide can be very destructive. It triggers chronic inflammation and promotes the generation of more free radicals.

Silibinin's anti-inflammatory properties are also of great interest. Silibinin can inhibit the formation of pro-inflammatory prostaglandins (PGE-2), but there is some evidence that in the liver this takes place only at very high concentrations. On the other hand, silibinin excels at inhibiting the lipoxygenase pathway, thus reducing the generation of harmful inflammatory compounds called leukotrienes (Dehmlow 1996). The inhibition was remarkably strong. At higher concentrations, silibinin lowered the leukotriene levels to 28% of the control values.

The powerful reduction of leukotriene levels by silibinin is of great clinical interest in the treatment of inflammatory disorders. The commonly used non-steroidal anti-inflammatories (NSAIDs) reduce the production of inflammatory prostaglandins, but are notoriously ineffective at controlling leukotrienes. Leukotrienes are a major culprit in inflammation-induced damage to the tissues. The fact that even low concentrations of silibinin strongly inhibits leukotriene production is potentially of great clinical importance in preventing gallstone formation, as well as tissue damage in liver and kidneys.

the symbolic plants that appear in medieval paintings. The use of milk thistle for bronchitis persisted for many centuries; only in the fifteen hundreds it became known that milk thistle was an excellent detoxifier. It was also established that the seed had the most potent medicinal properties, and that the extract of crushed milk thistle seeds was effective in many cases of indigestion, liver problems and toxic liver damage. Later milk thistle was recommended as a remedy against gallstones, jaundice and spleen disorders. Modern science has validated many of these medicinal uses. The active ingredients of milk thistle extract were identified in 1960. The main active ingredient, silibinin, was extracted in 1980, making higher doses more affordable. As potent antioxidants and anticarcinogens, milk thistle extract (silymarin) and silibinin are now attracting more and more attention as effective adjuvant therapy for various liver disorders, including cirrhosis and hepatitis C. In Germany, where herbal products are required to be tested for effectiveness, milk thistle extract has been officially approved for the treatment of both chronic and acute liver disorders by the world-renowned Commission E. Some American alternative clinicians favor the standardized German product for the treatment of hepatitis and cirrhosis. Research on silibinin, however, seems to confirm that silibinin is



Silibinin inhibits the production of nitric oxide, a destructive

compound that can trigger chronic inflammation

In skin cells, the flavonoids in silymarin appear to inhibit the cyclooxygenase-2 enzyme, thus leading to a lower production of inflammatory prostaglandins (Zhao 1999). COX-2 inhibitors are gaining more and more attention in cancer prevention and therapy, especially in the prevention of stage I tumor promotion. Demlow, on the other hand, stresses that in the liver at least, selective lowering of leukotrienes may be one of silibinin's main hepatoprotective properties, since in the liver prostaglandins are essentially protective, and silibinin has little effect on prostaglandin production in the liver.

Demlow also found that silibinin is a potent scavenger of the hypochlorite ion. She concludes, "The deleterious effects of [hypochlorite] that can lead to cell death, and those of leukotrienes that are especially important in inflammatory reactions, can be inhibited by silibinin in concentrations that are reached in vivo after the usual clinical dose. Silibinin is thought not only to display hepatoprotective properties but might also be cytoprotective in other organs and tissues."

Summary

"Toxic overload" is one way to describe our modern environment. If you are worried about the health of your liver, chemical allergies, carcinogen-induced cancer, pancreas health and blood sugar, there is good news: silibinin, the main active ingredient of milk thistle, an herb used since ancient times can help protect you and keep your vital organs in top shape. It can even reverse liver damage. And the most recent research findings broaden silibinin's range of potential applications to include cancer, cardiovascular disease, kidney and pancreatic health, and other age-related conditions.

Recent research has shown that silymarin and silibinin should be rightfully placed with ginkgo, green tea and grape seed extract as an indispensable anti-aging herbal supplement.

The following article discusses the effects of silymarin-silibinin on liver and kidney function and also provides suggested doses to prevent or treat various diseases.

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approximately equivalent to silymarin in effectiveness. The ability of milk thistle extract and silibinin to protect organs other than liver, especially the kidneys and the pancreas, against toxic and ischemic damage is now well documented. More recently, both silymarin and silibinin have also emerged as promising natural agents in the prevention and treatment of cardiovascular disorders, diabetes, and cancer, including breast and prostate cancer. One exciting discovery is that milk thistle appears to be a "smart herb," able to enhance new cell growth where needed for repair, but arresting cell division in tumor tissue; likewise, it can enhance the activity of certain enzymes, but inhibit others. The flavonoids in milk thistle seem to have special affinity for Type II estrogen receptors. There is also emerging evidence that milk thistle extract is a COX-2 inhibitor-another example of its "smart," selective action. We are discovering more and more about the multiple benefits of this ancient healing herb.

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