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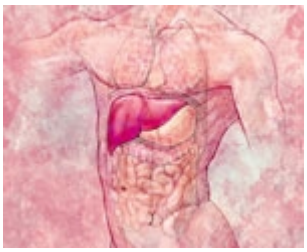
COVER STORY



Liver And Kidney Protection - Courtesy of Silibinin

The liver is one of the largest organs in the body, and its chief detoxifier. We tend to take the liver for granted, but we shouldn't. Today's environment places the liver under unprecedented stress. If you live in a large city, drive a lot, use dry cleaning, live or work in a building that has been freshly painted, take prescription drugs, drink alcohol, smoke, eat processed food, and/or use pesticides and herbicides in your backyard, you have plenty of reasons to give your liver some help. The liver is especially vulnerable to toxic overload, with harmful consequences for our health and longevity.

Silymarin and its chief active ingredient, silibinin, help prevent toxic liver damage; if such damage is done, silymarin and silibinin help the liver regenerate faster. Silymarin and silibinin actually accelerate the rate of protein synthesis in the liver, leading to faster cell regeneration (Sonnenbichler 1986, Valenzuela 1994). Silymarin and silibinin act in the ribosomes, special cellular organelles where protein synthesis takes place. It was discovered that silibinin can bind to the receptor for an important enzyme called DNA-dependent RNA polymerase I. This brings an increase in ribosomal RNA, which then leads to more protein synthesis.

A German study (Sonnenbichler 1999) discovered that silibinin also protects the kidneys from toxic injury, and produces similar accelerated regeneration in the kidneys after toxic damage (with agents such as chemotherapy drugs, for instance). Since the kidneys are often damaged by analgesics, chemotherapy drugs and other toxic agents, the finding that silibinin helps protect them and even stimulates their regeneration is of great clinical interest.

It should be noted that this ability to stimulate new cell growth in the liver and kidneys pertains only to normal cells; silymarin and silibinin have no such stimulatory effect on cancer cells. This is of enormous importance: Silibinin can apparently selectively stimulate the growth of certain types of normal cells while inhibiting the growth of malignant cells. Likewise, the very fact that silibinin raises glutathione levels in the liver serves as a safeguard against cancer since higher glutathione levels produce a shift in the immune function toward better anti-cancer and anti-viral defenses.

Silibinin appears to reduce the liver damage induced by alcohol and also to prevent the development of fibrosis by keeping the hepatic stellate cells normal. Hepatic stellate cells, also called fat-storing cells, become activated under inflammatory conditions. They increase dramatically in size and transform themselves into myofibroblasts, which generate increased collagen deposition leading to fibrosis. In addition, myofibroblasts secrete various cytokines and growth factors that induce even more stellate cells to transform into myofibroblasts. Silibinin inhibits the transformation of stellate cells into myofibroblasts (Fuchs 1997). Thus, silibinin can also be called an antifibrogenic agent. Fuchs and her colleagues theorize that with prolonged treatment silibinin accumulates in the target cells and downregulates the expression of the gene for the transforming growth factor-beta 1 (TGF-beta 1). Since this growth factor has the ability to induce its own production, silibinin breaks the so-called fibrogenesis loop, or the self-perpetuation of hepatic fibrosis.

The users of acetaminophen can also profit from taking silibinin. Acetaminophen (commonly known by its most common brand name, Tylenol) is regarded as damaging to the liver and the kidneys. Garrido (1991), however, obtained some interesting results showing synergy in antioxidant action between acetaminophen and silibinin. The fascinating finding is that acetaminophen is actually a phenolic antioxidant; it is not acetaminophen, but its toxic metabolite, a benzoquinone acting as a potent free radical, that produces glutathione depletion in the liver. Based on his in vitro findings, Garrido suggests that silibinin, like flavonoids in general, inhibits the cytochrome P-450 system, so less of the toxic metabolite is produced. At the same time, the antioxidant action of unconverted acetaminophen synergizes with the antioxidant action of silibinin. Thus, the use of acetaminophen together with silibinin actually results in a surprising side benefit.

In addition, silibinin strongly inhibits the production of production of leukotrienes, inflammatory compounds that produce liver damage and are also involved in cholestasis, a technical term for partial or total suppression of bile flow (Dehmlow 1996). In fact, inhibition of leukotriene production is one of the strongest protective effects of silymarin and silibinin, and is seen even at fairly low concentrations, achievable at the clinical dose range. This helps account for the traditional use of silymarin as a remedy against insufficient bile flow.

In summary, the centuries-old practice of using milk thistle for a variety of liver problems has been validated by modern research. Silymarin and its most active ingredient, silibinin, have been found to help prevent glutathione depletion and lipid peroxidation in the liver, stabilize cell membranes, normalize the cells (anti-fibrotic action), decrease inflammation and improve various markers of liver function. Thus, multiple studies have shown that silymarin and silibinin provide effective protection to the liver, the kidneys and other organs.

Accumulation of toxins

The FDA has found the level of chlorinated pesticides in food to be alarming (Total Diet Survey). DDE was found in 63% or more of the 42 food samples, although DDT and DDE have been banned for use in this country since 1972. Unfortunately, toxic chemicals used all over the world move easily around the globe with the winds.

There is enough evidence today of a connection between chemical exposure and chronic health problems to understand that our herbicides, pesticides, household chemicals, food additives, etc., create a serious health problem.

Now, what happens when the liver's detoxification system is overloaded? The answer is simple. When the liver cannot do its work, the toxins that we are exposed to accumulate in the body and make us sick in various ways. They have damaging effects on many body functions, particularly the immune system, and cause many chronic health problems. An overburdened and undernourished liver is actually known to be a root cause of many chronic diseases.

A majority of cancers are thought to be due to the effects of environmental carcinogens (cigarette smoke is one of them), particularly if combined with deficiencies of nutrients that are needed for optimal functioning of the detoxification and immune systems. So a well functioning detoxification system is especially important in the prevention of cancer. It was recently demonstrated in a study of chemical plant workers in Turin, Italy, that people with the poorest detoxification systems were the ones who developed bladder cancer. (Talska G et al. 1994)

What does the liver do?

The liver is a remarkable organ with multiple functions. Weighing about four pounds, it is one of the largest organs of the body, located on the right side in the upper abdomen. The liver quietly does an extraordinary job in keeping us alive and healthy by metabolizing the food we eat, i.e. breaking it down to useful parts and protecting us from the damaging effects of the numerous toxic compounds that we are exposed to on a daily basis. It has impressive restorative capabilities and will regenerate itself when part of it is damaged.

This regeneration capacity is one of the intriguing survival mechanisms of the body and very fortunate for us, as our health to a large extent depends on a well-functioning liver. While being exposed to a tremendous amount of potential damage, the liver is responsible for a multitude of essential functions related to metabolism, filtration, bile production, detoxification and immune function.

The metabolic functions of the liver are countless, as the liver is intricately involved in carbohydrate, fat and protein metabolism, in storage of vitamins and minerals and in many essential physiological processes. So, for example, the liver is involved in several regulatory mechanisms that control blood sugar levels and hormone levels. It synthesizes proteins (such as plasma albumin, fibrinogen and most globulins), lipids and lipoproteins (phospholipids, cholesterol) as well as bile acids that are excreted in the detoxification process.

Detoxification is an essential part of the human body's metabolism, and the liver plays a key role in this process. Toxic chemicals, both of internal and external origin, are constantly bombarding the liver. Our normal everyday metabolic processes actually produce a wide range of toxins that need to be taken care of by neutralizing mechanisms in the liver. Nutritional deficiencies and imbalances add to the production of toxins, as do alcohol and many prescription drugs, which increases the stress on the liver by requiring a strong detoxification capacity. Even unprocessed organic foods, however, have naturally occurring toxic components and require an effective detoxification system.

It is our external environment, however, that contributes the most to the load of toxins that the liver has to detoxify. The burden on the liver today is heavier than ever before in history. Toxic chemicals are found in the food we eat, in the water we drink and the air we breathe, both outdoors and indoors. Chemicals such as p-xylene, tetrachloroethylene, ethylbenzene and benzene were documented as "everywhere present" in the air in a study by the Environmental Protection Agency (EPA) (Wallace LA et al., 1989). Others listed as "often present" were chloroform, carbon tetrachloride, styrene and p-dichlorobenzene. A visit to the gas station or the dry cleaner as well as smoking resulted in elevated breath levels of toxins.

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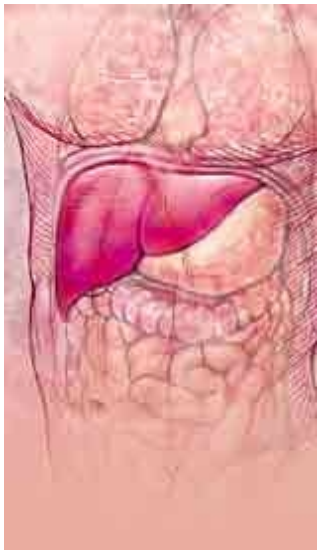

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Liver detoxification

The liver has three main detoxification pathways: 1) Filtering of the blood to remove large toxins; 2) breaking down enzymatically unwanted chemicals, which usually occurs in two steps: Phase I modifies the chemicals to make them an easier target for the Phase II enzyme systems; 3) synthesizing and secreting bile for excretion of fat-soluble toxins and cholesterol.

Filtering of the blood is one of the liver's primary functions. Approximately two quarts of blood pass through the liver every minute to be detoxified. This is critical, as the blood is loaded with bacteria, endotoxins and antigen-antibody complexes and various other toxic substances from the intestines. A healthy liver clears almost 100% of the bacteria and toxins from the blood before it joins the general circulation.

The liver's second main role in detoxification involves an enzymatic process in two steps for the neutralization of unwanted chemical compounds, such as drugs, pesticides and enterotoxins from the intestines. Even normal body compounds such as hormones get eliminated this way. Phase I enzymes directly neutralize some of these chemicals, but many others are converted to intermediate forms that are then processed by phase II enzymes. These intermediate forms are often much more chemically active and therefore more toxic than the original substance, so if the Phase II detoxification systems aren't working adequately, these intermediates linger and cause damage.

Phase I detoxification involves a group of 50 to 100 enzymes called the cytochrome P450 system. These enzymes play a central role in the detoxification of both exogenous (such as drugs and pesticides) and endogenous (such as hormones) compounds and in the synthesis of steroid hormones and bile acids.

A side effect of this metabolic activity is the production of free radicals, which are highly reactive molecules that will bind to cellular components and cause damage. The most important antioxidant for neutralizing these free radicals is glutathione, which is needed both for Phase I and Phase II. When exposure to high levels of toxin produce so many free radicals from Phase I detoxification that all the glutathione is used up, Phase II processes dependent on glutathione stop. This causes an imbalance between Phase I and Phase II activity, which results in severe toxic reactions, due to buildup of toxic intermediate forms.

Phase II detoxification involves conjugation, which means that a protective compound becomes bound to the toxin. Besides glutathione conjugation there are essentially five other pathways: amino acid conjugation, methylation, sulfation, sulfoxidation, acetylation and glucuronidation. These enzyme systems need nutrients and metabolic energy in order to work. If the liver cells are not functioning properly, phase II detoxification slows down and increases the toxic load by allowing the buildup of toxic intermediates.

The third major role of the liver is synthesis and secretion of bile. The liver manufactures approximately one quart of bile every day, which serves as a carrier for toxic substances to be effectively eliminated from the body. In addition, the bile emulsifies fats and fat-soluble vitamins in the intestine, improving their absorption. When the excretion of bile is inhibited (cholestasis), toxins stay in the liver longer with damaging effects.

Cholestasis has several causes, one of which is obstruction of the bile ducts by the presence of gallstones. Bile flow can also be impaired within the liver itself. By far the most important cause of cholestasis and impaired liver function in the United States is the consumption of alcohol. Other common causes are viral hepatitis and side effects from various drugs, particularly steroidal hormones including estrogen and oral contraceptives.

These conditions often cause alterations of liver function tests indicating cellular damage. In the initial stages of liver dysfunction, however, standard tests (serum bilirubin, alkaline phosphatase, SGOT, LDH, GGTP, etc.) are usually not sensitive enough to be of value. The measurement of serum bile acids, on the other hand, has proven to be a safe and sensitive test to determine the functional capacity of the liver.

Symptoms that may indicate reduced liver function are general malaise, fatigue and digestive disturbances including constipation, allergies and chemical sensitivities. Generalized pruritus, and nausea and vomiting during pregnancy can also be a result of impaired hepatofunction.

In conclusion

We live in an age of toxic overload. Silibinin, the chief active ingredient in milk thistle extract, is one of our best defenses against

this constant chemical assault. Silibinin is highly effective at protecting the liver, the pancreas and the kidneys from toxic damage, an ever-increasing danger due to our exposure to harmful chemicals. In addition, silibinin has been shown to have various other health benefits, including cancer prevention. The right dosage is extremely important for effectiveness. People who complain that herb products do not deliver as promised typically use products that contain only ineffective, miniscule doses of the main active ingredient. Fortunately, more and more herbal extracts, including silibinin, are now available in guaranteed potency form, and in sufficient dosage to produce results.

References

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References for Silibinin Articles

Altorjay I et al. The effect of silibinin on the free radical scavenger mechanisms of human erythrocytes in vitro. Acta Physiol Hung 1992;80:375-80.

Bialecka M. The effect of bioflavonoids and lecithin on the course of experimental atherosclerosis in rabbits. Ann Acad Med Stetin 1997;43:41-56.

Bindoli A et al. Inhibitory action of silymarin on lipid peroxide formation in rat liver mitochondria and microsomes. Biochem Pharmacol 1977;26:2405-9.

Boigk G et al. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. Hepatology 1997;26:643-9.

Bokemeyer C et al. Silibinin protects against cisplatin-induced nephrotoxicity without compromising cisplatin or ifosfamide anti-tumor activity. Br J Cancer 1996;74:2036-41.

Chen H et al. Protective effects of silibinin and tetrandrine on the outcome of spontaneously hypertensive rats subjected to acute coronary artery occlusion. Int J Cardiol 1993;41:103-8.

Dehmlow C et al. Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells. Life Sci 1996;58:1591- 1600.

Dehmlow C et al. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. Hepatology 1996;23:749-54.

Di Giulio AM et al. Inhibition of high glucose-induced protein mono-ADP-ribosylation restores neuritogenesis and sodium-pump activity in SY5Y neuroblastoma cells. J Neurosci Res 1999;57:663-9.

Feher J et al. Effect of silibinin on the activity and expression of superoxide dismutase in lymphocytes from patients with chronic alcoholic liver disease. Free Rad Res Commun 1987;3:373-7.
Feher J et al. Liver cell protection in toxic liver lesions. Acta Physiol Hung 1989;73:285-91.

Feher J et al. Liver-protective action of silymarin therapy in chronic alcoholic liver disease. Orv Hetil 1989;130:2723-7.

Ferenci P et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver.
J Hepatol 1989;9:105-13.

Fuchs E et al. Effects of silibinin and of a synthetic analogue on isolated rat heptatic stellate cells and myofibroblasts. Drug Res 1997;47:1383-7.

Geller LI et al. Treatment of fatty hepatosis in diabetics. Probl Endokrinol (Mosk) 1993;39:20-2.

Germani E et al. Progressive and selective changes in neurotrophic factor expression and substance P axonal transport induced by perinatal diabetes: protection action of antioxidant treatment. J Neurosci Res 1999;57:521-8.

Gershbein LL. Action of dietary trypsin, pressed coffee oil, silymarin, and iron salt on 1,2-dimethylhydrazine tumorigenesis by gavage. Anticancer Res 1994;14:1113-6.

Gorio A et al. Endogenous mono-ADP-ribosylation in retina and peripheral nervous system. Adv Exp Med Biol 1997;419:289-95.

Gower JD et al. Prevention by antioxidants of oxidative damage to rabbit kidneys subjected to cold ischemia. Biochem Pharmacol 1989;38:213-15.

Kim DH et al. Silymarin and its components are inhibitors of beta-glucuronidase. Biol Pharm Bull 1994;17:443-5.

Kreeman V et al. Silymarin inhibits the development of diet-induced hypercholesterolemia in rats. Planta Med 1998;64:138-42.

Lahiri-Chatterjee M et al. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. Cancer Res 1999;59:622-32.

Locher R et al. Inhibitory action of silibinin on low density lipoprotein oxidation. Drug Res 1998;48:236-9.

Manna SK et al. Silymarin suppresses TNF-induced activation of NF-kappaB, c-Jun N-terminal kinase, and apoptosis. J Immunol 1999;163:6800-9.

Mira L et al. Scavenging of reactive oxygen species by silibinin dehemisuccinate. Biochem Pharmacol 1994;48:753-9.

Mowrey D. Guaranteed Potency Herbs: Next Generation Herbal Medicine. Keats Publishing, 1990.

Onat D et al. Effect of alpha-tocopherol and silibinin dihemisuccinate on the proliferation of human skin fibroblasts. Biotechnol Appl Biochem 1999;29:213-15.

Pietroangelo A et al. Antioxidant activity of silibinin in vivo during long-term iron overload in rats. Gastroenterology 1995;109:1941-9.

Rui YC et al. Effects of silibinin on production of oxygen free radical, lipoperoxide and leukotrienes in brain following ischemia and reperfusion. Chung Kuo 1990;11:418-21.

Saliou C et al. Selective inhibition of NF-kappaB activation by the flavonoid hepatoprotector silymarin in HepG2. Evidence for different activating pathways. FEBS Lett 1998;440:8-12.

Sanhuenza J et al. Changes in the xanthine dehydrogenase/xanthine oxidase ratio in the rat kidney subjected to ischemia-reperfusion stress: preventive effect of some flavonoids. Res Commun Chem Pathol Pharmacol 1992;78:211-8.

Scambia G et al. Antiproliferative effect of silibinin on gynecological malignancies: synergism with cisplatin and doxorubicin. European J Cancer 1996;32A:877-82.

Schonfeld J et al. Silibinin, a plant extract with antioxidant and membrane stabilizing properties, protects exocrine pancreas from cyclosporin A toxicity. CMLS Cell Mol Life Sci 1997; 53:917-20.

Schriewer H, Rauen HM. The effect of silibinin dihemisuccinate on cholesterol biosynthesis in rat liver homogenates. Arzneimittelforschung 1977;27:1691-4.

Skottova N, Krecman V. Silymarin as a potential hypocholesterolemic drug. Physiol Res 1998;47:1-7.

Skottova N, Krecman V. Dietary silymarin improves removal of low density lipoproteins by the perfused rat liver. Acta Univ Palacki Fac Med 1998;141:39-40.

Skottova N et al. Activities of silymarin and its flavolignans upon low density lipoprotein oxidizability in vitro. Phytother Res 1999; 13:535-7.

Sonnenbichler J et al. Biochemical effects of the flavonolignan silibinin on RNA, protein, and DNA synthesis in rat livers. Progress Clin Biol Res 1986;213:319-31.

Sonnenbichler J et al. Stimulatory effects of silibinin and silichristin from the milk thistle Silybum marianum on kidney cells. J Pharmacol Exp Ther 1999;290:1375-83.

Strauber RE, Stindl G. Protective effect of silibinin against ethanol-induced cytotoxicity in HepG2 cells. J Hepatol 1999;30 (Suppl):277.

Soto CP et al. Prevention of alloxan-induced diabetes in the rat by silymarin. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1998;119:125-9.

Tang ZJ. Alterations in insulin receptor in injured rats and the effects of dexamethasone and silibinin. Chung Hua 1991;7:214-7.

Valenzuela A et al. Selectivity of silymarin on the increase of glutathione content in different tissues of the rat. Planta Med 1989;55:420-2.

Valenzuela A et al. Effect of silibinin dihemisuccinate on the ethanol metabolizing systems of the rat liver. Cell Biochem Funct 1989;7:173-8.

Valenzuela A, Garrido A. Biochemical bases of the pharmacological action of the flavonoid silymarin and its structural isomer silibinin. Biol Res 1994;27:105-12.

Velussi M et al. Long-term (12 months) treatment with antioxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde in cirrhotic diabetic patients. J Hepatol 1997;26:871-9.

Zhao J, Agarwal R. Tissue distribution of silibinin, the major active constituent of silymarin, in mice and its association with enhancement of phase II enzymes: implications in cancer chemoprevention. Carcinogenesis 1999;20:2101-8.

Zhao J et al. Significant inhibition by the flavonoid antioxidant silymarin against 12_Otetradecanoylphorbol 13-acetate-caused modulation of antioxidant and inflammatory enzymes, and coclooxygenase 2 and interleukin-1 alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumor promotion. Mol Carcinog 1999;26:321-33.

Zi X et al. Novel cancer chemopreventive effects of silymarin: inhibition of mRNA expression of an endogenous tumor promoter TNF alpha. Biochem Biophys Res Commun 1997;239:334-9.

Zi X et al. Anticarcinogenic effect of a flavonoid antioxidant, silymarin, in human breast cancer cells MDA-MB 468; induction of G1 arrest through an increase in Cip1/p21concommitant with a decrease in kinase activity of cyclin-dependent kinases and associated cyclins. Clin Cancer Res 1998;4:1055-64.

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;96:7490-5.

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