

## **Phytotherapeutic properties of milk thistle seeds: An overview**

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### **ABSTRACT:**

Milk thistle (*Silybum marianum*, Asteraceae) seeds have been used for over 2000 years as remedy for several diseases especially for liver and still widely used. The active constituents of milk thistle seed are three flavonolignans viz. silibinin, silychristin, and silidianin collectively known as silymarin extracted from milk thistle seeds, available commercially as standardized extract. Milk thistle seed extract (silymarin) and its constituents (mainly silibinin) act as antioxidant and hepatoprotective; effective in treating toxin poisoning, hepatitis, cirrhosis, fibrosis of liver; stimulate liver regeneration. However, human studies regarding management of alcoholic cirrhosis and hepatitis are equivocal. Milk thistle seed has anti-inflammatory, immunomodulatory, lipid and biliary effects. It also has antiviral, antitumor and other therapeutic properties. Milk thistle preparations are safe, well tolerated and cause no serious side effects except mild gastrointestinal and allergic reactions. Milk thistle seed is a very promising herbal drug. More research is warranted to substantiate its broad ranging phytotherapeutic effects.

**Key words:** Milk thistle, *Silybum marianum*, hepatoprotective, silymarin, seeds, antioxidant.

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### **INTRODUCTION:**

Milk thistle (*Silybum marianum* L. Gaert., Asteraceae) seeds have been used for centuries as herbal medicine mainly for the treatment of liver diseases. The common name, milk thistle, is derived from the 'milky white' veins on the leaves, which, when broken open, yield a milky sap. The therapeutically active constituents of milk thistle seeds are three isomeric flavonolignans namely silibinin (silybin), silychristin, and silidianin collectively known as silymarin extracted from the dried milk thistle seeds. Silibinin is the most biologically active. The seeds also contain other flavonolignans, betaine, apigenin, silybonol, proteins, fixed oil and free fatty acids, which may contribute to the health giving effects of milk thistle seeds. [1, 2] Present review

attempts to provide a brief overview of the recent advances in the pharmacological and therapeutic aspects of milk thistle seeds.

### **Botanical descriptions**

Milk thistle is an annual or biennial plant. It is erect, stout, 5-10 feet tall with large prickly leaves, large purple flowering heads and strongly spinescent stems (Fig. 1). When broken the leaves and stems exude a milky sap. The glabrous leaves are dark green, oblong, sinuate-lobed or pinnatifid with spiny margins. The leaves have milk-white veins. White veins give the leaves, which initially form a flat rosette, a diffusely mottled appearance. During flowering season, from June to September each stem bears a terminal head containing a single, large, purple, slightly fragrant flower ending in sharp spines. The reddish purple flowers are ridged with sharp spines. The achenes, 6-7 mm in length and transversely wrinkled, are dark in colour, grey flecked with a yellow ring at the apex. Attached to the achene is a long white pappus. The fruits are glossy brown or grey with spots. [2]



**Figure 1: Milk thistle (*Silybum marianum*) flowering head.**

### **Traditional cultivation and usage**

Milk thistle was once cultivated in Europe as vegetable. The de-spined leaves were used in salads and as spinach. The stalk, root and flowers were also consumed. He roasted seeds were used as coffee substitute. Preparations of milk thistle seeds have been used medicinally from as early as fourth century B.C. and first reported by Theophrastus. Traditionally the seeds have been used in Europe as galactagogue in nursing mothers, bitter tonic, and antidepressant, in liver complications (including gallstones), dyspepsia, splenic congestions, varicose veins, diabetes, amenorrhea, uterine hemorrhage and

menstrual problems. Its use as liver protectant can be traced back to Greek and Roman references of first century A.D. [1, 3]

#### **Present day cultivation and usage**

Milk thistle is indigenous to Kashmir (India), Southern Europe, Southern Russia, North Africa, and Asia Minor. It was introduced to most areas of Europe, North and South America and Southern Australia and cultivated mainly in dry rocky soils of European countries, Australia, Canada, China, North and South America as medicinal plant. It is also grown widely as ornamental plant for its attractive foliage. The seeds are collected ripe during late summer. Presently milk thistle seed, its purified extracts and its active constituents are mainly used in liver diseases. It is the most widely used hepatoprotective agent, in chronic inflammatory hepatic disorders including hepatitis, jaundice, alcohol abuse, fibrosis, cirrhosis and fatty infiltration; in hepatotoxicity by mushroom poisoning and by industrial pollutants. It is also widely used as nutraceuticals agent. In homoeopathy the seed tincture has been used in liver disorders, jaundice, gall stones, peritonitis, haemorrhage, bronchitis and varicose veins. Extracts, tablets or capsules containing standardized extract of milk thistle seeds are available commercially. [1, 3]

#### **Phytotherapeutic applications**

The seeds of milk thistle can be consumed raw (usually freshly milled), made into a tea or used as a hydro-alcoholic extract for medicinal use. Silymarin is included in the pharmacopoeia of many countries. Average adult dose of powdered seed is 12-15 g/day; as dry standardized seed extract (silymarin): 200-400 mg/day; as liquid seed extract: 4-9 ml/day. Silymarin is very poorly soluble in water, so milk thistle seed is not much effective in the form of tea. Extracts from the seed are generally marketed as tablet and encapsulated form for oral use, usually containing concentrated seed extract standardized to 70-80 % of silymarin. Silymarin is also administered by parenteral route. [4] The effects of silymarin (the standardized extract from milk thistle seed) are discussed below.

Milk thistle seed's therapeutic and health promoting efficacy involves a variety of molecular mechanisms. Its primary activities are of use as antioxidant and hepatoprotective.

**Antioxidant:** Silymarin has been reported to act as an excellent antioxidant, scavenging free radicals (reactive oxygen species) and inhibiting lipid peroxidation thereby protecting cells against oxidative stress. It augments the non-enzymatic and

enzymatic antioxidant defense systems of cells involving reduced glutathione, superoxide dismutase and catalase. It can protect the liver, brain, heart and other vital organs from oxidative damage for its ability to prevent lipid peroxidation and replenishing the reduced glutathione levels. Silibinin exhibits membrane protective properties and it may protect blood constituents from oxidative damage. [5,6]

**Hepatoprotection:** Use of milk thistle seeds as liver protectant dates back to the first century. Antioxidant activity is one of the important factors in hepatoprotection.

*Antihepatotoxic potential:* Silymarin protects liver cells against many hepatotoxins in humans and animals. Some mushrooms (e. g. *Amanita phalloides*, the death cup fungus and *A. virosa*) contain two toxins: phalloidine and  $\alpha$ -amanatine which destroy hepatocyte cell membrane and block hepatic protein synthesis leading to severe liver damage and death. Silymarin effectively prevents both of these effects by blocking the toxin's binding sites, increasing the regenerative capacity of liver cells. Silibinin was found to be an effective measure against liver damage if it is administered intravenously within 24 hours after mushroom ingestion. In one study, 60 patients with severe *Amanitia* poisoning were treated with infusions of 20 mg/kg of silybinin with excellent results showing no death of the patients treated. Silymarin is often used as supportive therapy in food poisoning due to fungi. [7, 8]

Silymarin also offers liver protection against tetracycline, d-galactosamine and thallium-induced liver damage and erythromycin estolate, amitriptyline, nortriptyline and tert-butyl hydroperoxide exposure of neonatal hepatocytes. It reduces liver damage due to long term treatment with phenothiazine or butyrophenone. Silibinin significantly inhibits concanavalin A-induced liver disease. It also provides hepatoprotection against poisoning by phalloidin, halothane, thioacetamide, acetaminophen and carbon tetrachloride. It also protects liver from ischaemic injury, iron overload and radiation. [1, 6]

Silymarin is used for the treatment of several liver diseases characterized by degenerative necrosis and functional impairment including chronic liver disorders. The German Commission E endorses use silymarin for the treatment of liver diseases, including hepatitis A, alcoholic cirrhosis, and chemically induced hepatitis. [3]

*Alcoholic liver disease/cirrhosis:* Ethanol metabolism involves formation of free radicals leading to oxidative stress in liver. Silymarin successfully opposes alcoholic cirrhosis with its antioxidant and hepatoprotective mechanisms restoring the normal liver biochemical parameters. Silymarin also ameliorates cytolysis in active cirrhosis patients. However use of silymarin is inadvisable in decompensated cirrhosis. [9]

*Hepatitis:* In patients with acute viral hepatitis, silymarin shortens treatment time and shows improvement in serum bilirubin, and serum liver enzymatic levels. Biochemical values are restored to normal sooner in silymarin-treated patients. In chronic active hepatitis silymarin treatment improves liver function tests. Histological improvement is observed in silymarin-treated patients with chronic hepatitis. Silymarin causes stable remission of alcoholic hepatitis normalizing the liver biochemical parameters. [10]

*Liver fibrosis:* Liver fibrosis can result in remodeling of liver architecture leading to hepatic insufficiency, portal hypertension and hepatic encephalopathy. The conversion of hepatic stellate cells into myofibroblast is considered as central event in fibrogenesis. Silymarin treatment markedly inhibits this process in liver fibrosis patients showing antifibrotic potential. [6]

*Liver tissue regeneration:* Silymarin stimulates liver tissue regeneration by increasing protein synthesis in the injured liver. In *in vivo* and *in vitro* experiments performed in the liver of rats from which part of the organ (liver) was removed, silibinin produces a significant increase in the formation of ribosomes and in DNA synthesis, as well as an increase in protein synthesis. Interestingly, the increase in protein synthesis is induced by silibinin only in injured livers, not in healthy ones [6].

There are a number of systematic reviews regarding the applications of milk thistle seeds in liver diseases but most of the human studies done to date are of such variable design, quality and results that no definitive conclusions about degrees of effectiveness in the treatment or prevention of alcoholic cirrhosis and hepatitis can yet be made. Better quality clinical trials are necessary. [1,11]

**Anti-inflammation:** Milk thistle seed and its active extract silymarin have anti-inflammatory and anti-arthritis effects due to excellent antioxidant property, scavenging free radicals which act as pro-inflammatory agents. Silymarin was found to be more effective in cases of developing arthritis compared to developed arthritis. Silymarin and silibinin hinder inflammatory process by inhibiting neutrophil migration and Kupffer cell inhibition. They also inhibit the formation of inflammatory mediators viz. prostaglandins and leukotrienes especially (by inhibiting 5-lipoxygenase pathway) and release of histamine from basophils. Therefore, milk thistle seed may possess anti-allergic and anti-asthmatic activities. [12,13]

**Immunomodulation:** Silymarin's immunomodulatory activity in liver disease patients may also be involved in its hepatoprotective action. Silymarin protects experimental rodents from ultraviolet radiation-induced immunosuppression. [14] Silibinin inhibits activation of human T-lymphocyte, human polymorpho-nuclear leucocyte. Silymarin

significantly suppresses the inflammatory mediators, expression of histocompatibility complex molecules and nerve cell damage. Long term administration of silymarin improves immunity by increasing T-lymphocytes, interleukins and reducing all types of immunoglobulins. Silymarin can be useful in development of therapeutic adjuvant in which immunosuppression is required including autoimmune and infectious diseases. [1, 5]

**Liver lipidaemic control:** It was found that silymarin and silibinin reduce the synthesis and turnover of phospholipids in the liver. Silibinin neutralizes ethanol-induced inhibition of phospholipids synthesis and the reduction in glycerol incorporation into lipids of isolated hepatocytes. Furthermore, silibinin stimulates phosphatidylcholine synthesis and increases the activity of choline phosphate cytidyltransferase in rat liver both in normal conditions and after galactosamine intoxication. Silymarin significantly inhibits hepatic lipid peroxidation and may diminish triglyceride synthesis in liver. Impairments in the liver lipid profile caused as a result of prolonged effect of ethanol, anti-tubercular drugs (isoniazid, rifampacin), and liver toxicants (acetaminophen, halothane, microcystin) are effectively improved by silymarin. [4,6]

**Blood (plasma) lipidaemic control:** Administration of silymarin to type II hyperlipidemic patients resulted in slightly decreased total cholesterol and high-density lipoprotein levels in blood plasma. Silymarin reduces plasma levels of cholesterol and low-density lipoprotein levels in hyperlipidaemic rats, whereas silibinin does not reduce plasma levels of cholesterol in normal rats; however, it reduces total phospholipid levels. Biliary cholesterol and phospholipid concentrations in rats are also slightly reduced. Silymarin-induced reduction of biliary cholesterol and phospholipids in both rat and human may be in part due to decreased liver cholesterol synthesis. Silymarin could represent a novel agent in the prevention and therapy of hypercholesterolemia and atherosclerosis. [6,15]

**Biliary effect:** Silymarin undergoes excessive enterohepatic circulation, which allows a continuous loop between intestine and liver. It prevents the disturbance of bile secretion, thereby increasing bile secretion, cholate and bilirubin excretion. [1]

**Anti-viral effect:** Although silymarin does not affect viral replication it has beneficial role in viral hepatitis by its inhibitory action on inflammatory and cytotoxic processes induced by viral infection. Silibinin strongly inhibits growth of both HepG2 (hepatitis B

virus negative; p53 intact) and Hep3B (hepatitis B virus positive; p53 mutated) cells with relatively more cytotoxicity in Hep3B cells which is associated with apoptosis induction. Silymarin also showed inhibitory activity against other viruses in different cell lines. [5]

**Antitumor and anticarcinogenic effects:** Silymarin significantly inhibits tumor growth and also cause regression of established tumors. It is associated with *in vitro* anti-proliferative, pro-apoptotic and anti-angiogenic efficacy in prostate tumor. Silymarin feeding during the promotion phase of 4-nitroquinoline-1-oxide-induced rat tumorigenesis exerts chemopreventive activity against tongue squamous cell carcinoma. The cancer chemopreventive and anticarcinogenic effects of silymarin in long term animal tumorigenesis models and in human prostate, breast, and cervical carcinoma cells are also reported. Treatment with silibinin results in a highly significant inhibition of both cell growth and DNA synthesis with loss of cell viability in case of cervical carcinoma cells. [5,13]

It is well demonstrated that ultraviolet light-induced immunosuppression and oxidative stress play an important role in the induction of skin cancers. Topical or dietary administration of silymarin to mouse skin prevents photocarcinogenesis by significantly inducing apoptosis, increase in catalase activity and induction of cytochrome P-450 and ornithine decarboxylase activity. Similar results are also obtained in other chemical-induced skin carcinogenesis models. Prevention of ultraviolet light-induced immunosuppression and oxidative stress by silymarin may be associated with the prevention of photocarcinogenesis. [16]

Silibinin significantly induces growth inhibition, a moderate cell cycle arrest and a strong apoptotic cell death in small cell and non-small cell human lung carcinoma cells. Silibinin inhibits the growth of human prostate cancer cells both *in vitro* and *in vivo*. Silymarin and silibinin have strong anti-angiogenesis effect on the colon cancer cell line and effective against chemical-induced bladder carcinogenesis in mice and hepatocellular carcinoma in rats. [5]

**Neuroprotection:** Silymarin was found to be useful in prevention and treatment of neurodegenerative and neurotoxic processes due to its antioxidant effects. Silymarin can effectively protect dopaminergic neurons against lipopolysaccharide-induced neurotoxicity in brain [17].

**Cardioprotection:** During cancer therapy, the use of certain chemotherapeutic agents like doxorubicin is limited by cardiotoxicity that is known to be mediated by oxidative

stress and apoptosis induction. Silibinin has such cardioprotective properties due to its antioxidant and membrane protective actions. [18]

**Miscellaneous effects:** Silymarin helps to maintain normal renal function. Silibinin reduces oxidative damage to kidney cells *in vitro*. In rats, silibinin prevents cisplatin-induced nephrotoxicity, but does not prevent cyclosporine-induced glomerular damage. As an antioxidant, silymarin can protect the pancreas against certain forms of damage. In a controlled trial of human diabetics treated with silymarin, patients experienced decreases in blood glucose and insulin requirements. It exhibits anti-ulcer activity in rats. [5,13] In one study of post parturient cattle given milk thistle seed meal, milk production was increased and ketonuria reduced, as compared to controls. [19]

The value of silymarin in the treatment of psoriasis may be due to its ability to improve endotoxin removal by the liver, inhibition of cyclic adenosine monophosphate phosphodiesterase, and leukotriene synthesis. Abnormally high levels of cyclic adenosine monophosphate and leukotrienes are observed in patients with psoriasis and normalization of these levels may improve the condition. [12,20]

#### **Adverse effects**

Human studies performed with milk thistle seeds indicated little need for concern with adverse effects. Human studies demonstrate that milk thistle seed extract (silymarin) is safe and well tolerated. It is generally nontoxic and causes no side effects when administered to adults in a dose range of 200-900 mg/day in two or three divided doses. Higher dose (> 1500 mg/day) could produce minor gastrointestinal disturbances involving mild laxative effect which may be due to increased bile secretion and flow. Mild allergic reactions (pruritus, urticaria, arthralgia) are observed, but rarely enough to discontinue. Commonly noted adverse effects such as bloating, dyspepsia, epigastric pain, flatulence, nausea, irregular stool and laxation are observed in 2-10 % of patients in clinical trial. Headaches and dermatological symptoms are also noted. [3,21]

Silymarin was found nontoxic in rats and mice after oral doses of 2500 or 5000 mg/kg body weight without producing any unwanted symptoms. Similar reports were also obtained for rabbits and dogs. No evidence of ante- or postnatal toxicity in animals was reported. These data reveal that the acute toxicity of silymarin is very low. [3,7]

It was found that silymarin at higher concentrations have an inhibitory effect on both phase I and phase II hepatic drug metabolizing (biotransformation) cytochrome enzyme systems. But the plasma concentrations at therapeutic doses are very less as compared to that needed for the inhibition. So it exhibits no beneficial or harmful drug interactions at normal doses. [3]

Safety of milk thistle seed in pregnancy and lactation was not studied in humans. Traditionally has been considered safe in lactation, however, no clinical studies have been performed. Safety in children also has not been studied yet. No known contraindications have yet been reported. [3,4]

**SUMMARY AND CONCLUSION:**

Milk thistle (*Silybum marianum*) seeds have been used for over 2000 years as natural remedy for the treatment of several diseases especially for liver and still widely used for the same. The active constituents of milk thistle seed are three isomeric flavonolignans viz. silibinin or silybin, silychristin, and silidianin collectively known as silymarin extracted from the milk thistle seeds, available commercially as standardized extract. Milk thistle seed extract (silymarin) and its constituents (mainly silibinin) act as antioxidant and hepatoprotective and effective in treating toxin poisoning, hepatitis, cirrhosis, and fibrosis of liver; stimulate liver regeneration. Although the human studies regarding management of alcoholic cirrhosis and hepatitis are equivocal. Milk thistle seed demonstrates anti-inflammatory, immunomodulatory, lipid and biliary effects. It also has antiviral, antitumor and other therapeutic properties. Milk thistle seed preparations are safe, well tolerated and cause no serious side effects in humans except mild gastrointestinal and allergic reactions.

Milk thistle seed shows great promise to be a superior herbal drug. Its good safety profile, better standardization and quality control, easy availability and low cost are added advantages. More definitive research is warranted to corroborate its wide range of phytotherapeutic effects. Further research on milk thistle seed may make a breakthrough as a new approach in disease prevention in addition to liver complications.

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