

MILK THISTLE'S: A BOON FOR MULTIPLE THERAPY

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► ABSTRACT

► This article reviews on published reports pertaining to milk thistle's (*Silybum marianum*) benefits in the treatment of various diseases. This plant used from ancient times as a hepatoprotective drug. Along the hepatoprotective action of Silymarin, a flavonolignan from 'milk thistle' was also effective in gastrointestinal disorders and its antitumoral activities, antioxidant, antiinflammatory agent, nephroprotector, radiation and skin protector. silymarin owns also other actions as an, anti-lipid peroxidative, antifibrotic,, immunomodulatory, liver regenerating, etc. It was also studied its neuro-psihiatric and cardiac action. A systematic review of this evidence to clarify what is known and identify gaps in knowledge would be important to guide design of future studies of the mechanisms of milk thistle and clinical trials.

► **KEYWORDS:** Silymarin, disease, pharmacokinetics, regeneration, herbal medicine

Medicinal species: *Silybum marianum* L. Gaertn., *Cardus marianus* L.

Common names: Holy thistle, marian thistle, Mary thistle, milk thistle, Our Lady's thistle, St. Mary thistle, wild artichoke, Mariendistel (Ger), Chardon-Marie.

Milk thistle should not be confused with blessed thistle, *Cnicus benedictus*. Milk thistle is sold as Legalon® in Germany.

Botanical family: Compositae/Asteraceae

Plant description: Milk thistle is a tall, biennial herb, five to ten feet high, with hard, green, shiny leaves that have spiny edges and are streaked with white along the veins. The solitary flower heads are reddish-purple with bracts ending in sharp spines. The small hard fruits in the flowers, known technically as achenes, resemble seeds and are the part of the plant used medicinally.

Where it's grown: Southern and western Europe, South America and North America in the eastern United States and California.

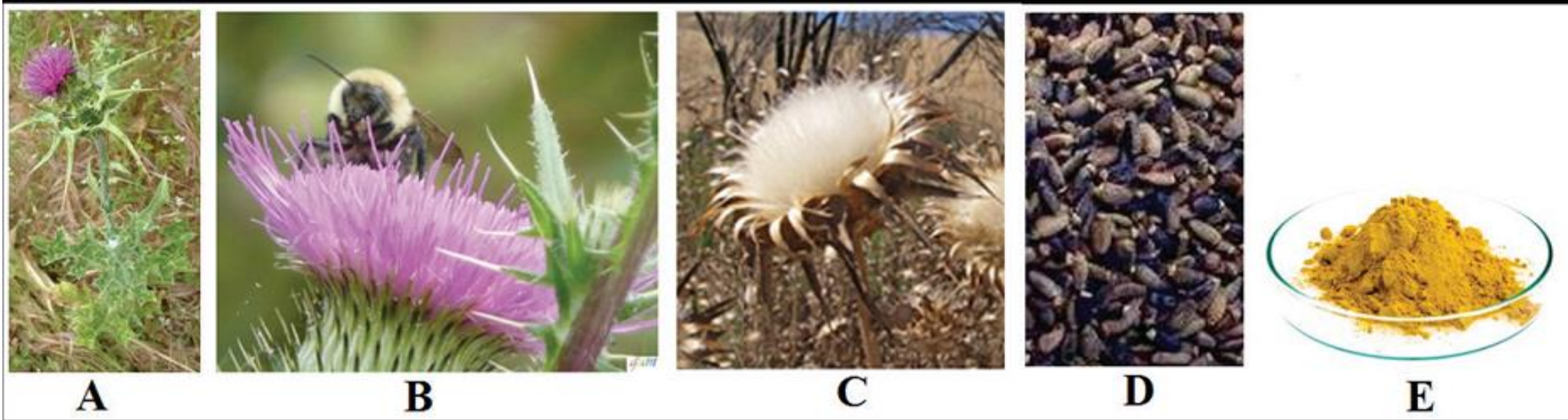


Figure 1: *A. Milk-thistle plant (Silybum marianum), B. Its flower, C. Its dried flower. D. Its seeds, E. Its seeds extract (silymarin flavonolignans). In this figure pictures A, C. and D are public-domain-pictures. B is from the photograph collection of GA Mansoori and E is from healthynewage.com.*

Milk Thistle

Potentially Active Chemical Constituents

➤ **Flavonoids/flavonolignans:**

Silymarin (which includes silybin [silibinin], silidianin, silychristin [silichristin] and isosilybin), apigenin, dehydrosilybin, deoxysilychristin, deoxysildianin, siliandrin, silybinome, silyhermin, neosilyhermin

➤ **Other:**

Silybonol; myristic, oleic, palmitic and stearic acids; betaine hydrochloride

Pharmacokinetics

- ▶ Silymarin is insoluble in water and typically administered as a sugar coated tablet or as an encapsulated standardized extract.
- ▶ The absorption by oral route is as low as 2-3 per cent of the silybin recovered from rat bile in 24 h. About 20-40 per cent of the administered dose of silymarin is excreted in bile as sulphates and glucuronide conjugates in human beings. The peak plasma levels after an oral dose are achieved in 4-6 h in experimental animals and in human beings and elimination half-life is approximately 6 h.
- ▶ The pharmacokinetic variables (mean \pm SD), after an oral dose of 240 mg silybin in 6 healthy volunteers has been reported to be as follows: Absorption half life 0.17 ± 0.09 h, elimination half life 6.32 ± 3.94 h, maximum plasma concentration 0.34 ± 0.16 mg/ml and time to maximum plasma concentration 1.32 ± 0.45 h.

- ▶ Pharmacokinetic studies with silybin phosphatidylcholine complex have shown an increase in the oral bioavailability of silybin in healthy human subjects, probably by a facilitatory role of drug complex on the passage of the drug across the gastrointestinal tract. Silybin dihemisuccinate is given in emergency cases with the poisoning of *Amanita phalloides*

- ▶ Mechanism of action
- ▶ The preclinical studies using different hepatotoxic substances showed that silymarin has multiple actions as a hepatoprotective agent. The **antioxidant property** and **cell-regenerating functions** as a result of **increased protein synthesis** are considered as most important.
- (i) Antioxidant properties: which are capable of counteracting the damaging effects of oxidation due to Free radicals, including the superoxide radical, hydroxyl radical (OH), hydrogen peroxide (H₂O₂), and lipid peroxide radicals have been implicated in liver diseases. And increased exposure to xenobiotics . The cytoprotective effects of silymarin are mainly attributable to its antioxidant and free radical scavenging properties. It can also interact directly with cell membrane components to prevent any abnormalities in the content of lipid fraction responsible for maintaining normal fluidity.
- (ii) Stimulation of protein synthesis: Silymarin can enter inside the nucleus and act on RNA polymerase enzymes resulting in increased ribosomal formation. This in turn hastens protein and DNA synthesis. This action has important therapeutic implications in the repair of damaged hepatocytes and restoration of normal functions of liver.

(iii) Anti-inflammatory actions:

The inhibitory effect on 5-lipoxygenase pathway resulting in inhibition of leukotriene synthesis is a pivotal pharmacological property of silymarin. Leukotriene (B4) synthesis was reduced while prostaglandin (E2) synthesis was not affected at higher concentrations of use of silibinin.

(iv) Antifibrotic action: Liver fibrosis can result in remodeling of liver architecture leading to hepatic insufficiency, portal hypertension and hepatic encephalopathy. These processes involve complex interplay of cells and mediators. In the initial phase there will be proliferation of hepatic parenchymal cells. The conversion of hepatic stellate cells (HSC) into myofibroblast is considered as the central event in fibrogenesis. Silymarin inhibits NF- κ B and also retards HSC activation. It also inhibits protein kinases and other kinases involved in signal transduction and may interact with intracellular signaling pathways.

► **Experimental Studies**

► **Potential Clinical Benefits of Milk Thistle**

- **1. Cardiovascular:** Silymarin prevents cytostatic induced cardiotoxicity in rats. In this respect, silymarin pretreatment inhibited Adriamycin-induced cardiotoxicity due to inhibition of lipid peroxidation and protection against GSH depletion (El-Shitany et al., 2008). Treatment with silymarin prevents increase in AST and CK serum activity and myocardial excitability of rats caused by doxorubicin. It also significantly reduces doxorubicin prooxidative activity and decreases histological changes in liver and heart tissue of animals treated with doxorubicin (Raskovic et al., 2011).
- **2. Pulmonary: none**
- **3. Renal and electrolyte balance:** (Renal protectant) silymarin diet inhibits ferric nitrilotriacetate (Fe-NTA) induced renal carcinogenesis and nephro-inflammation through decreased of protein expression of iNOS and COX-2, secretion of proinflammatory cytokines, ODC activity, [3H]-thymidine incorporation into DNA (Kaur et al, 2010). Renal cancer Caki-1 cell proliferation and induced apoptosis through inhibiting the activation of EGFR and ERK was inhibited. Also, was decreased the expression of surviving, up-regulating the expression of p53 and triggering the cascades of caspase pathway (Li et all 2008)

- ▶ **4. Gastrointestinal/hepatic: Hepatoprotectant; treatment of hepatitis, antilipidemic**
- ▶ **5. Neuro-psychiatric: In a cell study, milk thistle silymarin significantly inhibited the LPS-induced activation of microglia and the production of inflammatory mediators, such as tumour necrosis factor-alpha and nitric oxide (NO), and reduced the damage to dopaminergic neurons and Milk thistle extract protected cultured rat hippocampal neurons against oxidative stress-induced cell death.**
- ▶ **6. Endocrine: Antidiabetic and pancreatic protectant**
- ▶ **7. Hematologic: none**
- ▶ **8. Rheumatologic: none**

- ▶ **9. Reproductive: none**
- ▶ **10. Immune modulation: Anti-inflammatory**
- ▶ **11. Antimicrobial: none**
- ▶ **12. Antineoplastic: Chemoprevention**
- ▶ **13. Antioxidant: Antioxidant**
- ▶ **14. Skin and mucus membranes: Psoriasis: Traditional use Silymarin/silibinin is found in some high-end moisturizers to prevent cutaneous oxidative damage and photoaging (Singh et al, 2009). Silymarin suppressed skin lesions in mice and reduced plasma level of IL-4 (Kang et al, 2008). In other study was observed that silymarin causes inhibition of chemically induced messenger RNA expression of TNF- α and IL-1 α in mouse skin (Singh et al, 2002). Silymarin inhibit YPA-caused lipid peroxidation in mouse skin epidermis, which supports its strong antioxidant activity (LahiriChatterjee, 1999).**
- ▶ **15. Other/miscellaneous: Green synthesis of nanoparticles**

▶ Adverse events

- ▶ Silymarin is reported to have a very good safety profile. Both animal and human studies showed that silymarin is non toxic even when given at high doses (>1500 mg/day). However, a laxative effect is noted at these doses may be due to increased bile secretion and bile flow.
- ▶ Most commonly noted adverse effects were related to gastrointestinal tract like bloating, dyspepsia, nausea, irregular stool and diarrhoea. It was observed in 2 to 10 per cent of patients in clinical trials, which were similar to placebo. It also produced pruritus, headache, exanthema, malaise, asthenia, and vertigo.
- ▶ Some serious adverse events were reported in three patients. A 57 yr old lady developed serious symptoms of gastroenteritis associated with collapse while the other two reported cases were allergic in nature after ingestion of herbal tea containing silymarin.

Future prospects

- ▶ Milk thistle appears to be safe and have multiple health benefits on various liver conditions viz; liver cirrhosis, alcoholic hepatitis, alcoholic fatty liver, liver poisoning, and viral hepatitis. There is no current evidence to indicate that milk thistle directly affects the Hepatitis C Virus (HCV).
- ▶ (i) Antiviral properties: It is viewed that herbal drugs which have antiviral, immunomodulatory and anti-inflammatory effects on hepatocyte may prove to be useful in chronic hepatitis. Though, silymarin does not have antiviral properties, phyllanthin (from *Phyllanthus amarus*) and glycyrrhizin (from *Glycyrrhiza glabra*) have been shown to possess antiviral properties against hepatitis virus B and C respectively. It may be possible in future to combine the hepatoprotective herbal drugs (like silymarin + glycyrrhizin or phyllanthin) to achieve the desired antiviral, immunomodulatory and anti-inflammatory activities.

- ▶ (ii) Hepatocellular carcinoma (HCC): One of the most concerning areas of hepatitis C virus (HCV) is the risk for HCC. Interestingly the incidence of HCC was lower in the silymarin treated population.
- ▶ (iii) Co-infection with HIV: HIV and HCV co-infections appear to progress more rapidly and lead to the increased risk for liver disease especially more rapid progression to hepatic cirrhosis. Silymarin alone or in the combination may be useful to arrest the disease progression.
- ▶ (iv) Tissue phase of malaria: Silymarin, in experimental studies, has shown significant hepatoprotective activity in Plasmodium berghei induced hepatic changes in Mastomys natalensis. In future, hepatoprotective herbal drugs may be useful in tissue phase of malaria.
- ▶ (v) While silymarin appears to have few side effects, it is not known whether it exerts any drug interaction with interferon, ribavirin, lamivudine, or other conventional treatment for hepatitis B or C.
- ▶ (vi) Chemoprotective and anticancer agents: Silymarin as a chemoprotective and anticancer agent is becoming increasingly apparent. It inhibits carcinogenic action of many chemicals. Silybin has significantly decreased the incidence of urinary bladder neoplasm by nitrosamine and skin carcinogenesis by benzyl peroxide or 12- O-tetradecanoylphorbol-13-acetate. Various mitogenic, signaling and cell cycle regulators were modulated by silybin and probably act at the receptor level itself.

vii) Adjuvant therapy of cancer: Silymarin has protected liver in a case of promyelocytic leukemia receiving 6-mercaptopurine and methotrexate. The liver toxicity was successfully treated by 800 mg of silymarin and conjunction therapy was without any adverse effects . The drug may be of help in cisplatin induced nephrotoxicity, doxorubicin induced apoptotic death and better compliance with HIV medication.

(viii) Neuroprotective and neurotropic activity: Silymarin may be useful in the treatment and prevention of some neurodegenerative and neurotoxic process partly due to antioxidant activity and may be due to some unknown mechanism. Silymarin inhibits TNF- α and reduced production of inducible nitric oxide synthase which cause microglia activation. Further silymarin may be of use in protecting primary hippocampal neurone against oxidative stress induced apoptosis and neuromodulatory action against persistent viral infections leading to encephalitis.

- ▶ (ix) Miscellaneous activities: Silymarin may be useful in end stage diabetic nephropathy. However more studies are required for its beneficial properties in human diabetic mellitus. It may have protective effect against toxic drugs like amiodarone, doxorubicin and other anthracycline cardiotoxic drugs. It may protect against UV irradiation as a preventive against photocarcinogens and may inhibit P-glycoprotein (P-gp) function and increase the susceptibility to the treatment of cancer and bacterial infections by acting on membrane efflux proteins like P-gp. It may have anti-atherosclerotic activity by antioxidative protection of cholesterol transporting lipoproteins. New derivatives of silybin are expected to meet the various challenges.
- ▶ Conclusion:
- ▶ Silymarin is a favoured drug for different liver diseases because of its oral effectiveness, good safety profile, availability in India and most importantly at an affordable price. It has established efficacy in the restoration of liver function and regeneration of liver cells. It may prove superior to polyherbal formulations for its better standardization, quality control and free from contamination from heavy metals and microbial toxins. Silymarin may make a breakthrough as a new approach to protect other organs in addition to liver.

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