Pharmacognosy Reviews, 2025; 19(37):102-108.
www.phcogrev.com

Review Article

Silymarin: A Historical and Scientific Exploration of its Medicinal Properties

Hebbani Nagarajappa Shivaprasad, Vinaya Gharabude, Sravani Thimmannagari*, Madhu Krishnamani, Gaurav Soni

Research and Development Centre, Botanic Healthcare Pvt. Ltd., TSIIC Industrial Development Area, Nacharam, Uppal, Hyderabad, Telangana, INDIA.

ABSTRACT

Silybum marianum, or milk thistle, has been used medicinally for over 2,000 years, mainly to treat liver conditions. Silymarin, a complex mixture of flavonolignans, is present in the plant, which contributes to its pharmacological properties. Silymarin, especially its active compound silybin used particularly for liver health. This review compiles information from databases such as Google Scholar, PubMed, ScienceDirect, and ResearchGate. It is used in traditional medicine to treat liver conditions like cirrhosis and hepatitis, promoting regeneration, reducing oxidative stress, and enhancing detoxification. It also boosts glutathione levels, lowers liver fibrosis, and has been shown to protect the liver from a number of toxins, including alcohol and environmental pollutants. Various research studies confirm its safety with no serious side effects and it has been proven fairly low in toxicity. Further validating its role as a promising therapeutic agent for liver diseases.

Keywords: Milk thisle, Hepatoprotective, Silymarin, Pharmacology, Herbal medicine.

Correspondence:
Sravani Thimmannagari
Manager-Technical Business Development, Research and Development Centre, Botanic Healthcare Pvt. Ltd., TSIIC Industrial Development Area, Nacharam, Uppal, Hyderabad-500076, Telangana, INDIA.
Email: research1@botanichealthcare.net

Received: 17-11-2024;
Revised: 05-01-2025;
Accepted: 29-04-2025.

INTRODUCTION

Herbal plants have been used as medicines for many years in traditional and folk medicine, which is based on the usage of plants and plant extracts. For thousands of years, traditional and folk medicine all around the world have used herbal remedies made from plant extracts to treat a variety of human ailments.[1] Ancient Greeks and Romans (Theophrastus, 4th century B.C.) believed that herbal medicines were the most effective means of treating and preventing illnesses.[2] *Silybum marianum* (L.) is an annual or biennial herb of the genus Silybum in the family Asteraceae.[3] The word "milk thistle" arises from the plant's characteristic spiked leaves with white veins, which were thought to hold the milk of the Virgin Mary.[4] Geographically, the plant can be found in Southern Europe, Asia Minor, Northern Africa, and Southern Russia.[5] The plant has been used medicinally for more than 2000 years, mostly to treat conditions relating to the liver.[6] Milk thistle is recognized by various regional names across the world, including blessed milk thistle, holy thistle, St. Mary's thistle, and Marian thistle in English. In other languages, it is called Mariendistel in German, Cardo mariano in Spanish, Chardon-Marie in French, and Shui Fei Ji in Chinese. The plant is also referred to by names like Mary thiqal in Persian and Akub in Arabic. These diverse names reflect its widespread use and recognition in traditional medicine globally.[7,8]

History

The milk thistle's therapeutic qualities were initially noted by the Greek physician and botanist Dioscorides (40-90 AD). Milk thistle was later identified by John Gerard in 1597 as the most effective treatment for depressing illnesses.[9] Theophrastus (371-287 BC) was the first to mention milk thistle as *Pternix*, indicating its long history of medicinal use. Both Pliny the Elder and Dioscorides also described its uses in their works. Milk thistle was an effective remedy for hepatobiliary disorders by the 16th century. Its efficacy in treating spleen and liver blockages was noted by Nicholas Culpeper in his book The English Physitian in 1652. Early European colonists brought milk thistle to the Americas, and by the turn of the 20th century, herbalists were using it to treat conditions affecting the kidneys, liver, spleen, and menstruation. Interest in its therapeutic qualities persisted until the 1960s, when German research rekindled interest in its capacity to treat liver disorders and shield the liver from harmful toxins.[8,10] Dioscorides was the first to mention milk thistle as a treatment for serpent bites. Pliny the Elder also documented its use for promoting bile flow. In the Middle Ages, it has been identified as an antidote for liver toxins, and later British herbalist Nicholas Culpepper has utilized it as a treatment for the obstruction in the liver. As early as 1898, Eclectic physicians recognized its utility

DOI: 10.5530/phrev.20250002

in the treatment of congestion in the liver, spleen, and kidneys. Nowadays, milk thistle is widely used in traditional medicine as a supplement to liver support. The German Commission E even recommends using it to treat hepatic cirrhosis, dyspepsia, toxin-induced liver damage, and supportive therapy for chronic liver inflammation.[11]

Traditional Uses

Milk thistle is a common remedy for jaundice and other biliary disorders in Europe. It is also a useful treatment for fungal food poisoning. The roots, when boiled, are consumed as a vegetable, while the herb is traditionally used to treat intermittent fevers, dropsy, and uterine problems. An extract from the plant is used externally for cancer therapy, while the leaves are known for their ability to induce sweating and promote digestion. The seeds are recognized for their ability to relieve spasms, soothe irritation, and their spicy characteristics, frequently utilized for addressing liver and gallbladder problems and managing bleeding. Alcoholic extracts of the seed enhance intestinal peristalsis and act as a soothing mild purge, while the flowers, leaves, and seeds are consumed in European diets, with its seeds sometimes used as a coffee substitute and to counteract Amanita mushroom toxins.[8,12]

Botanical Description

Milk thistle is an upright, stout, annual or biennial plant that grows to a height of 5-10 feets. It has large, prickly, dark green leaves with milk-white veins, which create a flat rosette shape in its initial growth stages, giving it a speckled look. The leaves are elongated and have wavy lobes or are arranged pinnately, characterized by their spiny margins. During its flowering season, from June to September, the plant produces large purple flower heads, each containing a single, fragrant flower surrounded by sharp spines (Figure 1). The plant produces dark, transversely wrinkled achenes that are 6-7 mm long, with a long white pappus and a yellow ring at the apex. The leaves and stems release a milky sap when they break. Originally indigenous to the Mediterranean region, milk thistle has now expanded throughout Europe, the Americas, and Australia. Because of its fast and strong growth, it is considered as a weed in some places.[13,14]

Chemical Constituents

The primary and most well-known active ingredient in milk thistle extract is silymarin, a complex blend found in the seeds, leaves, and fruits of the plant.[15] Flavonolignans, the collective name for silymarin compounds, consist of a hybrid structure with non-conventional lignans. These compounds naturally exist as stereoisomers due to their symmetrical molecular structure.[16] Silymarin is a complex of several flavonolignans, which includes silybin A, silybin B, isosilybin A, isosilybin B, silydianin, and silychristin, with silybin being the most prevalent.[17] The first biologically active ingredient to be extracted from *Silybum marianum* seeds was discovered in 1968 by Wagner *et al*. That same year, Pelter *et al*., isolated silybin, which was later identified as silicristin by Wagner *et al*. Silydianin was discovered, and its regional isomer, isosilydianin, was reported. Later, isosilicristin was identified, and various isomers of silybins were isolated. Besides flavonolignans, *S. marianum* also contains compounds like naringenin, and kaempferol, along with other substances such as saccharin and dihydropyran-4-one[3]. Milk thistle also contains bioactive polyphenolic substances and taxifolin, fatty acids (linoleic, oleic), sterols (cholesterol, stigmasterol), and sugars. Silybin, the most biologically active flavonolignan, constitutes 50-70% of the silymarin extract.[18] The European Pharmacopeia specifies a two-step silymarin extraction that involves removing lipids with n-hexane and then extracting silymarin with methanol. Alternative methods like Soxhlet extraction and microwave-assisted extraction offer improved efficiency and avoid the defatting step.[19] The chemical structures of the above mentioned flavonolignans and flavonoids are illustrated in Figure 2.

Pharmacological Properties

Pharmacological findings on Milk Thistle (MT) components, particularly silymarin and silybin, have shown their hepato-protective, antioxidant, anti-inflammatory, and anti-fibrotic properties.[20] These compounds also promote protein biosynthesis, liver regeneration, enhance lactation, and possess immunomodulatory effects. Due to these benefits, MT is considered a promising treatment for liver diseases. Figure 3 summarizes the diverse biological actions associated with silymarin.[21,22]

Silymarin: A Promising Hepatoprotective Agent Against Various Liver Toxicities and Damage

The hepatoprotective properties of silymarin, an extract from the plant *Silybum marianum*, have been widely investigated in relation to many types of liver damage, such as fungal and xenobiotic infections. It was observed that it neutralizes the hepatotoxicity caused by carbon tetrachloride, phalloidine, and alpha-amanitin by significantly reducing the prolongation of hexobarbital sleeping duration and improving serum levels of transaminases

Figure 1: Aerial part of Milk thistle.

Source: licence version

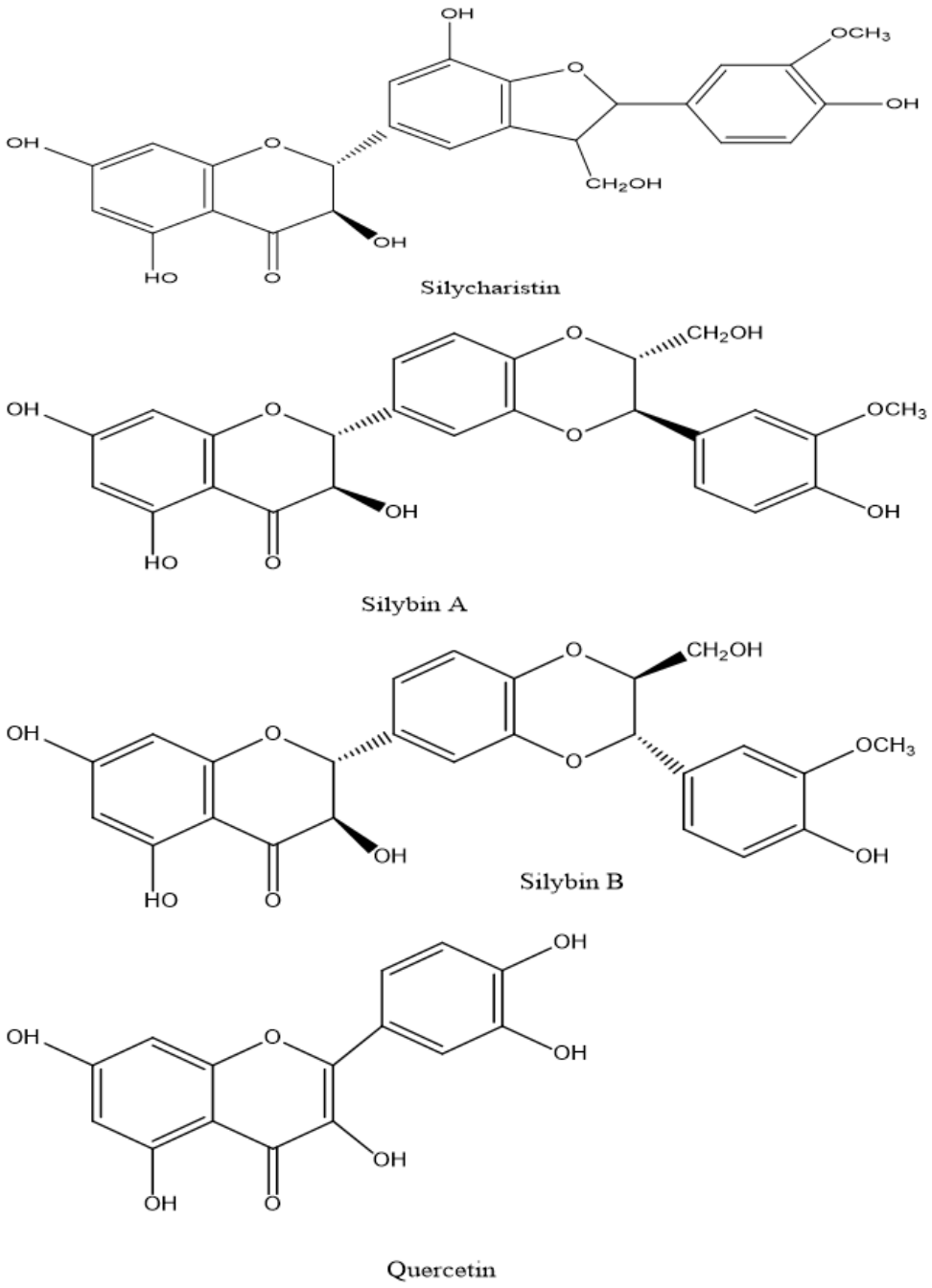

Figure 2: Structures of some of the compounds present in Milk thistle.

and sorbitol dehydrogenase. Silymarin has been proven in rats to protect the liver from paracetamol, galactosamine, and praseodymium, while also increasing serum enzyme levels and regenerating liver tissue. It reduced lipid peroxidation, preserved hepatocyte membrane integrity, and restored liver enzyme activity in diverse hepatic damage models. It has also been shown that silymarin protects against ethanol-induced liver damage, acetaminophen-induced centrilobular necrosis, and oxidative stress due to iron-induced hepatotoxicity. In addition, studies have shown that silymarin can protect against *Amanita phalloides* poisoning in a variety of animal models, preventing severe liver damage when supplied either before or after exposure. Furthermore, silymarin has been shown to increase liver regeneration, as seen in partial hepatectomy models, and improve liver function in chronic liver damage, including cirrhosis induced by carbon tetrachloride. It has shown to protect liver function against Fumonisin B1-induced free radical liver damage by increasing cellular regeneration. Silymarin has hepatoprotective activity as the above-mentioned effects cause oxidative stress to act upon inhibition of lipid peroxidation and

inflammation. It is one of the promising therapeutic agents in preventing and treating liver diseases.[23]

Preclinical and Clinical Evidence

The study evaluated the effect of silymarin on body weight, biochemical parameters, and antioxidant status in ethanol-exposed rats, comparing it with ascorbic acid. For four weeks, ethanol (1.6 g/kg body weight/day) was given to male Wistar rats weighing 200-220 g and 16-18 weeks of age. Ethanol exposure increased TBARS levels, and SOD and GST activities, while reducing GSH content and catalase, GR, and GPx activities. Silymarin and ascorbic acid treatments reversed these changes. Silymarin showed hepatoprotective effects, though less potent than ascorbic acid. The study also suggested that ethanol abstinence promotes hepatic regeneration, with preventive treatment being more effective than curative.[24]

The study aim is to develop and evaluate silymarin phytosomes and compare them to milk thistle extract for their hepatoprotective effects in rats with CCl_4-induced liver damage. With a 485% loading efficiency, soybean and egg yolk lecithin were used to create phytosomes. Rats were given phytosomes as part of the *in vivo* experiment, and liver function was evaluated. Compared to milk thistle extract, phytosome formulas P2 and P4 showed faster release. The findings demonstrated that phytosomes had superior hepatoprotective effects by significantly lowering superoxide dismutase and glutamic pyruvic transaminase activities. According to the study, phytosomes are more effective and have higher bioavailability than the extract.[25]

Effects of silymarin on mice's liver damage caused by acute Ethanol (EtOH) administration together with EtOH, 200 mg/kg body weight of silymarin was administered to the mice. Acute EtOH exposure caused liver damage, increased serum ALT, reduced hepatic GSH, and elevated TNF production. Silymarin supplementation significantly reduced these effects, attenuating liver damage and oxidative stress. The results suggest that because of its anti-inflammatory and antioxidant qualities, silymarin may be a promising treatment for alcohol-induced liver disease.[26]

The potential of silymarin and milk thistle seed methanolic extract to protect male rats' kidneys from cisplatin-induced damage was examined. The rats were administered a single dose of cisplatin (3 mg/kg, i.p.), followed by silymarin (50 mg/kg) or an extract (0.6 g/kg) either 2 hr before or after the cisplatin injection. When silymarin or the extract was given as a pre-treatment, it notably reduced kidney damage and decreased Blood Urea Nitrogen (BUN) and Serum creatinine (Scr) levels. In contrast, post-treatment with silymarin or the extract lowered BUN and Scr levels, though it did not completely prevent renal injury. These results suggest that milk thistle may help protect against cisplatin-induced kidney toxicity and could be considered as a complementary therapy to reduce renal damage.[27]

In this study, rats were given oral doses of silymarin extract (20 or 100 mg/kg body weight) followed by a single dose of Carbon Tetrachloride (CCl_4, 2 mL/kg body weight) in order to investigate the hepatoprotective effects of silymarin. The results after 24 hr revealed a dose-dependent reduction in liver damage, as evidenced by improvements in liver-to-body weight ratio, serum transaminase levels, and histological analysis.

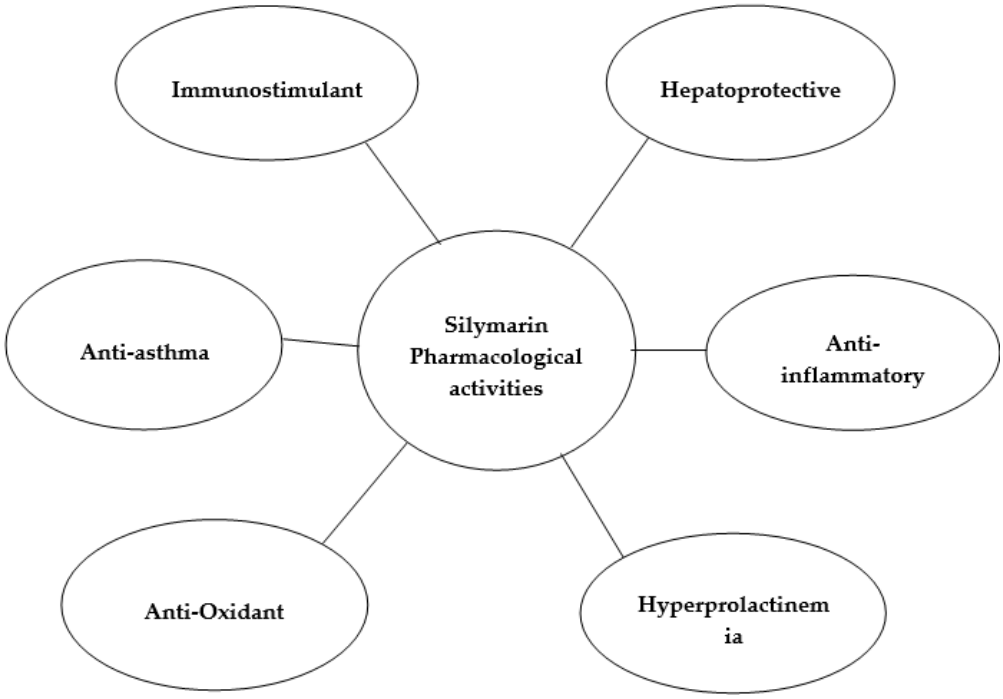

Figure 3: Pharmacological properties of Milk thistle.

Furthermore, silymarin extract decreased the expression of the pro-inflammatory chemokine MCP-1, the pro-fibrogenic cytokine TGF-beta, and collagen I in isolated human Hepatic Stellate Cells (HSCs). According to these results, silymarin may have anti-fibrogenic properties in chronic liver disease since it has hepatoprotective effects that include both lowering liver damage and directly modifying HSCs.[28]

Evaluation of silymarin's effect on severe preeclampsia was the aim of the study. For the study, 60 patients with severe preeclampsia were randomized to either the silymarin study group or the placebo control group. The study group received 70 mg of silymarin, administered three and 24 hr after pregnancy termination. Liver enzymes (AST and ALT) were measured at 12, 36, and 60 hr post-treatment. Silymarin was found to help improve liver function in severe preeclampsia, though further studies are needed for optimal dosing.[29]

The study aimed to assess the impact of silymarin on markers of oxidative stress and high-sensitivity C-Reactive Protein (hs-CRP) levels in individuals with type 2 diabetes. For 45 days, 40 patients with stable medications, ages 25 to 50, were randomized to receive either 140 mg of silymarin three times a day or a placebo. Silymarin significantly increased antioxidant activity (SOD, GPX, TAC) and reduced hs-CRP and malondialdehyde levels compared to the placebo group. All patients completed the study without adverse effects. The study concluded that silymarin improves antioxidant status and reduces inflammation in type 2 diabetes patients.[30]

The study was conducted to determine silymarin's efficacy in reducing radiotherapy-induced mucositis in head and neck cancer patients. For six weeks, beginning with the first day of radiation therapy, twenty-seven patients were randomly assigned to receive either a placebo or 420 mg of oral silymarin in three different doses. Silymarin significantly reduced the severity and delayed the onset of oral mucositis, yielding lower mucositis scores than the placebo group.

During therapy, both groups' mucositis scores increased, although the silymarin group progressed more slowly. The study revealed that silymarin can significantly lower the severity and prevent the onset of mucositis in these patients.[31]

The study aimed to determine the effectiveness of silymarin in slowing the progression of diabetic nephropathy in people with type 2 diabetes. Sixty patients with macroalbuminuria, despite maximum renin-angiotensin system inhibitor treatment, were randomly assigned to receive either 420 mg of silymarin or a placebo daily for three months. Silymarin significantly reduced Urinary Albumin-Creatinine Ratio (UACR), TNF-α, and MDA levels compared to the placebo group. The silymarin group experienced a larger drop in UACR than the other group. The study concluded that silymarin may be a promising addition to treating diabetic nephropathy.[32]

The aim of the test is to evaluate silymarin's effect on cirrhosis patients' survival. The study included 170 patients, with 87 receiving silymarin (140 mg three times daily) and 83 receiving a placebo. The average treatment duration was 41 months. The silymarin group had a significantly higher 4-year survival rate (58% vs. 39% in the placebo group) (p=0.036). The treatment was especially beneficial for patients with alcoholic cirrhosis and those classified as Child A. No side effects were reported, suggesting that silymarin may reduce mortality in cirrhosis patients, particularly those with alcohol-related liver damage.[33]

This research examined the anti-inflammatory effects of silymarin, piroxicam, and meloxicam in patients with Osteoarthritis (OA) of the knee, piroxicam (20 mg/day), meloxicam (15 mg/day), silymarin (300 mg/day), or combinations of piroxicam and meloxicam were administered to 220 patients. After eight weeks, silymarin dramatically lowered IL-1 alpha, IL-8, C3, and C4 levels in the blood. While meloxicam raised IL-1 alpha levels, piroxicam decreased IL-8 but had no effect on IL-1 alpha as well. The combination of silymarin with piroxicam showed better anti-inflammatory effects compared to meloxicam.[34]

The study assesses the effectiveness of Milk Thistle (MT) in reducing chemotherapy-associated hepatotoxicity in children with Acute Lymphoblastic Leukaemia (ALL). A total of 50 children with hepatic toxicity were enrolled and randomly assigned to receive either MT or a placebo orally for 28 days. Liver function was evaluated throughout the study, with results showing no significant changes at day 28; however, at day 56, the MT group demonstrated a significant reduction in AST levels. MT showed no antagonistic interactions with chemotherapy agents and exhibited a modest synergistic effect with vincristine *in vitro*.[35]

A study was carried out to determine whether silymarin helps patients with acute clinical hepatitis with their symptoms and lab results. A total of 105 patients with elevated ALT levels were randomly assigned to receive either 140 mg of silymarin or a placebo three times daily for four weeks, with an additional four-week follow-up. Silymarin significantly accelerated the resolution of symptoms like dark urine, jaundice, and scleral icterus, but did not significantly affect liver function tests like ALT, AST, or direct bilirubin. There were no reported side effects, and silymarin and the placebo were both well tolerated. According to the study's findings, silymarin is safe to use and reduces some acute hepatitis symptoms while having little effect on liver enzymes.[36]

Safety and Toxicity

Two-year toxicity studies on milk thistle and *goldenseal* in rats and mice revealed that goldenseal root powder increased liver tumours, likely due to topoisomerase inhibition by berberine. Milk thistle extract, rich in antioxidant flavonolignans like silibinin, was found to reduce spontaneous tumours, such as

liver tumours in male mice and mammary gland tumours in female rats. While these results suggest that milk thistle may have protective effects.[37]

Higher oral dosages of silymarin were tested for safety, dose-exposure relationships, and acute effects in noncirrhotic HCV patients who had not responded to interferon-based treatment. Four groups of eight patients each received 140, 280, 560, or 700 mg of silymarin every 8 hr for seven days. The findings demonstrated silybin A and B's steady-state exposures increased significantly, suggesting nonlinear pharmacokinetics. Serum transaminases and HCV RNA levels did not significantly decrease, and no adverse events linked to the medication were documented. Higher doses of silymarin may be able to overcome the low bioavailability seen with standard doses, as doses as high as 2.1 g/day were well tolerated and safe.[38]

Milk thistle extract, administered at doses of 175 mg, 350 mg, and 525 mg, was well tolerated by healthy volunteers, with no significant adverse effects reported. After 28 consecutive days of administration at a dose of one capsule three times daily, no serious safety concerns were observed.[39]

Silymarin extract is generally well tolerated, with no serious adverse drug reactions reported. Mild flushing during intravenous treatment is occasionally observed, but it is typically of low intensity. Based on an estimated 9,000 patients treated, silymarin extract infusion therapy can be considered safe.[40]

Silymarin extract has no reported serious adverse events in the study, indicating it is safe for use in chronic HCV cirrhotic patients at both high dose (1,050 mg/day) and regular dose (420 mg/day). Both doses were well tolerated, with the high dose showing more significant improvements in liver biochemical markers and quality of life.[41]

Silymarin, administered at a dose of 140 mg twice daily, was well tolerated with minimal adverse effects in patients undergoing cisplatin treatment. The study demonstrated its safety and potential as a prophylactic option to reduce cisplatin nephrotoxicity.[42]

Mechanism of Action of Silymarin on Liver Health

Silymarin, a hepatoprotective substance obtained from *Silybum marianum*, protects the liver via multiple mechanisms. Silymarin increases liver enzyme levels in glucuronidation, which is responsible for the elimination of toxins. It maintains glutathione levels, supports regeneration activity in the liver with the help of stimulating hepatocyte growth, and inhibits activation of hepatic stellate cells, thus avoiding fibrosis.[43] In addition, silymarin stabilizes mast cells, inhibits neutrophil migration, lowers pro-inflammatory cytokines like TNF-α and IL-6, and has anti-inflammatory properties. Silymarin also acts to inhibit the bioactivation of poisonous toxins such as those from *Amanita mushrooms* by blocking cytochrome P450 enzymes. Silymarin fixes the free liver tissue by promoting the synthesis of proteins and ribosomes and inhibiting lipoxygenase, which lowers the production of leukotrienes. Further aiding detoxification, it also inhibits beta-glucuronidase, which stops toxins from being reabsorbed in the gut. Silymarin is a useful treatment for liver diseases like NAFLD, NASH, and chronic hepatitis because of its anti-inflammatory, anti-fibrotic, antioxidant, and detoxifying properties.[44,45]

CONCLUSION

In conclusion, milk thistle, or *Silybum marianum*, has a long history of medicinal use, especially for liver-related disorders. Extensive pre-clinical and clinical studies support its efficacy in treating liver diseases, including cirrhosis, hepatitis, and drug-induced liver damage. Silymarin's mechanisms of action, such as antioxidant activity, liver regeneration, and inflammation reduction, make it a promising therapeutic agent. Furthermore, its safety profile, with minimal side effects, highlights its potential in clinical applications. Further research and clinical studies are required to fully assess its therapeutic range, optimal dosage, and bioavailability. Milk thistle remains a useful herbal remedy with significant therapeutic potential, particularly in liver health management.

ACKNOWLEDGEMENT

The authors sincerely thank Botanic Healthcare Pvt. Ltd. for providing resources and support for this review work. The support and contributions of the staff are sincerely appreciated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MT: Milk thistle; **SOD:** Superoxide dismutase; **GST:** Glutathione-S transferases; **GSH:** Glutathione; **EtOH:** Ethyl alcohol; **BUN:** Blood urea nitrogen; **Scr:** Serum creatinine; **HSCs:** Hepatic stellate cells; **hs-CRP:** High-sensitivity C-reactive protein; **UACR:** Urinary albumin creatinine ratio; **ALL:** Acute lymphoblastic leukaemia.

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Cite this article: Shivaprasad HN, Gharabude V, Sravani T, Krishnamani M, Soni G. Silymarin: A Historical and Scientific Exploration of its Medicinal Properties. Pharmacog Rev. 2025;19(37):102-8.