IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Carduus Marianus (Milk Thistle) In The Treatment Of Jaundice: A Comprehensive Review Of Pharmacological And Clinical Evidence

Dr. Meenakshi[1], Dr. Shailendra Singh[2]

[1] B.H.M.S., M.D. (Hom.), Department of Materia Medica, State National Homoeopathic Medical College, Lucknow, Uttar Pradesh, India

[2] M.B.B.S., Ex-Resident, Department of Neuropsychiatry, L.L.R.M. Medical College, Meerut, Uttar Pradesh, India

Abstract

Silybum marianum is a medicinal herb historically used as a hepatoprotective agent. It has been used for the treatment of several hepatic diseases marked by functional impairment or progressive necrosis. Its hepatoprotective function is distinctive and operates via several mechanisms, including antioxidant and "anti-inflammatory effects, regulation of cell permeability, membrane stabilisation, encouragement of liver regeneration, and suppression of collagen fibre deposition, which may contribute to cirrhosis. The majority of documented data regarding *Silybum marianum* pertains to hepatic disorders; however, recent findings indicate its advantageous properties across a diverse array of conditions, including renal protection, hypolipidemic and anti-atherosclerotic effects, cardiovascular protection, prevention of insulin resistance—particularly in cirrhotic patients—cancer, and Alzheimer's disease prevention. It is furthermore used as a dietary treatment. This review article intends to elucidate several facets of Silybum marianum, particularly the findings from recent publications about its impact on various disorders, in addition to discussing its hepatoprotective properties.

Keywords: Alzheimer's disease, Antioxidant activity, Hepatoprotective, Liver regeneration, Renal protection, *Silybum marianum.*

1. Introduction

Silybum marianum (L.) Gaertn., formerly classified as *Carduus marianus*, is a member of the Asteraceae family. It is a herbaceous plant with special therapeutic characteristics and may also serve as a host for some infections. The plant is readily identifiable by the white veins on its leaves [1,2]. The purple blossoms are located near the branch's apex. The seeds exhibit a colouration ranging from black to dark brown and possess a white silky pappus. Silybum marianum has been used to address several health issues, including illnesses of the stomach, liver, and gallbladder. For the last 2000 years, diverse elements of plants have been used in the formulation of traditional medicines. The primary use of this medicinal plant is its hepatoprotective effect, which may be traced to early Greek texts. In the 18th century, it was used for the treatment of plague and congestive liver and spleen conditions. Since the 20th century, it has been used for the treatment of

ailments such as liver cirrhosis, jaundice, hepatitis, and liver toxicity. Furthermore, it has been used to enhance lactation in nursing moms and to treat individuals afflicted with depression [3,4].

Silybum has significant therapeutic properties, including demulcent, anticancer, antidepressant, antioxidant, digestive tonic, hepatoprotective, hepatoregenerative, cardioprotective, immunostimulatory, and neuroprotective actions. Silybum marianum is a well recognised medicinal herb, and Silymarin is the newly investigated active compound [5,6]. A variety of individual and composite items derived from this species are now available on the market. Recent developments in molecular biology have accelerated the extraction and identification of active principles. Research is ongoing to identify curative ingredients for the production of more effective, cost-efficient, and readily accessible medications [7].

Figure 1. ***Silybum marianum***

2. Botany and Morphology

Milk thistle, Blessed milk thistle, *Cardus marianus*, Mary thistle, Saint Mary's thistle, Blessed milk thistle, Mediterranean milk thistle, Silybum marianum, and Scotch thistle are just a few of the numerous names given to this member of the Asteraceae family. Mary thiqhal is the Arabic name for Silybum marianum, a plant with glossy, light-green leaves [8]. A glabrous, light-green, spiky shrub with upright stems, Silybum marianum blooms every two years. Large, variegated leaves with white spots along their veins characterise this plant. It is composed of several pinnate segments that resemble triangular-ovate shapes [9]. The green mass decorated with longitudinal ridges is the culmination of the simple or slightly branched, often vigorous branches of Silybum marianum [10]. It has a conical shape and a cottony stem; it may reach a height of 200 cm. Oblong to lanceolate leaves and an often hollow stem characterise this plant.

Depending on its shape, *Silybum marianum* may be either lobate or pinnate; it has glossy green leaves with milk-white veining and spiky borders. The reddish-purple inflorescences of this plant may reach a length and breadth of 12 cm (Figure 1)

Table 1- Morphological characteristics of milk thistle [11]

Row	Morphological Characteristics	Description, Color and Texture	Dimensions
1	Plant habit	High, erect	–
2	Stem	Glabrous, Stout, rigid, or slightly downy and not spiny, branched or unbranched	3 m, 40–200 cm, 200–250 cm
3	Leaf	Alternate, glossy, dark green with milk-white veins running throughout Stem leaves: clasp the stem, alternate and smaller, not quite as lobed Basal leaves: alternate, large, deeply lobed and glabrous with spiny margins	Length: 75 cmWidth: Up to 30 cm
4	Spines	Woody	Spines of leaves: 3–4.5 cmSpines of bracts: 1.9–5 cm
5	Root	One long taproot	–
6	Receptacles	Including rows of broad, leathery bracts tipped with very stiff spines (1.9–5 cm) long and fringed with smaller spines	1.5–1.9 cm
7	Inflorescence	Capitula, large and spherical, borne singly at the stem's or branch's tip, encircled with bristly bracts	Diameter of flower head: about 5 cm
8	Florets	Tubular, hermaphrodite	13–25 mm
9	Number of achenes	–	150 per capitulum, 6000 per plant
10	Seed	The fruit has a flat, heavy pappus and an achene that may be any shade of black, brown, white, or glossy brown; it also has an oily taste and a scent similar to chocolate.	Broad: 3 mmThickness: 1.5 mmLength: 6–8 mm,Pappus scales: 15–20 mm

➢ Growth Regions

This plant proliferates throughout European, Asian, and American nations. In Iran, it is extensively disseminated in Poshtkooh, Noode, Kelardasht, Gonbad-e Kavus, Hezar Valley, Moghan, Gorgan, and Mollathani in Ahvaz, as well as in Hamidiyeh, Ramhormoz, Izeh, Shoush, and Kazeroun in various other places [12].

➢ Growing period

Milk thistle may be either an annual or a biennial plant, depending on the weather. The seasons of autumn and spring are ideal for seed germination. According to studies, light and temperature have a role in milk thistle seed germination. Germination rates for fresh milk thistle seeds are greater at lower temperatures, and they seem to need an after-ripening period. For at least nine years, the seeds will still be viable. It takes a long time for seeds that are incubated at high temperatures to mature, according to Young (1978). According to Mel'nikova (1983), the ideal germination temperature range for S. marianum is 20 to 25°C, while the lowest and maximum constant germination temperatures are 10°C and 35°C, respectively

[13,14]. According to Ghavami and Ramin (2007), germination was more successful at 15°C compared to 25°C and 35°C. in the quantity of basal leaves grows after seedling establishment, milk thistle begins to overwinter in a rosette [15]. As soon as it gets chilly, milk thistle begins to bloom, which happens in the late winter or early spring. From April until May, flowers begin to open their petals. July marks the maturity of the achenes. The whole life cycle of a milk thistle plant is around 125–140 days long. This time is divided into many stages, such as the seedling phase (15–20 days), the vegetative phase (45–60 days), the flowering, fruit-bearing, and withering phases. Anthesis typically lasted five days in a capitulum. The ripe fruits were plucked around seventeen days later. On average, each plant may produce 55 capitula. One seed head could produce anything from one hundred to ninety-nine seeds. Seed flavonolignan accumulation is stage-dependent, reaching a maximum in the late stages of flowering [16].

Table 3 - Some ecological factors of milk thistle growth

Factor	Descriptions and Reports
Climate	Capable of thriving in a wide range of mild subtropical climates; for example, when temperatures are lower and precipitation is heavier, the plant's vegetative phase lasts longer, meaning there are less blossoms when the time comes to collect the seeds.
Altitude	The number of secondary flower heads was larger in hilly areas compared to flat areas: 700-1100 m in India, 1800-2400 m in Pakistan, and 0-420 m in Iran.
Soil	Performs well in a variety of soil types, Soil with a deeper clay content and an abundance of nutrients From very light sand to very heavy clay soil Soils with a pH between 5.5 and 6.06 are ideal for growth.

- **Chemical Compounds**

This plant's seeds contain a number of compounds, some of which are described here: silybin, silidianin, silibinin A and B, silicristin, apigenin, dehydrosilybin, deoxysilybin cristin, and deoxysilybin dianin. There is as much as 4% silymarin in the dried seed extract of this plant. In the family of flavonoids known as silymarin, you'll find silicristin, silibinin A and B, silidianin, and dihydroxysilibin. Included in this plant's extract are stearic acids, palmitic and myristic, as well as other flavonolignans including sylandrin, silybinom, and silyhermin, all of which may have hepatoprotective properties. Beyond that, there is up to 20% oil in the plant's dried seeds, and it has no medicinal use. Peak blood concentrations of silymarin are achieved in 2–4 hours after effective absorption from the gastrointestinal tract. Eight hours is the duration of excretion's half-life [17,18]. The biliary system helps remove 80% of this drug. Bioavailability of this drug depends on the formulation. Among the silymarin components, silylibin is the most powerful antioxidant and hepatoprotective agent; its concentration in bile is sixty times higher than that of the other molecules.

.

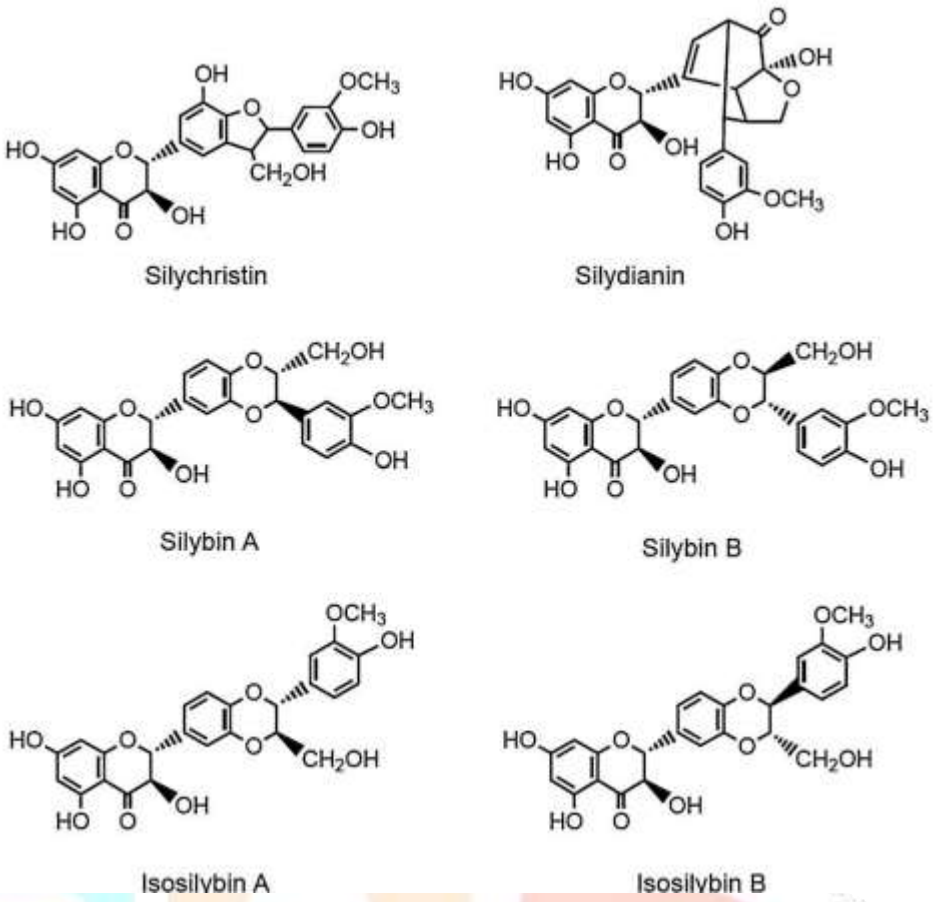

Figure 2- Chemical compositions of milk thistle

3. Ethnomedicinal, Traditional and Present Use

3.1 Traditional use

In Europe, milk thistle is used for jaundice and other biliary disorders. It is said to be a dependable galactagogue whether used as a dietary supplement or in infusion form. Silymarin is often used as an effective remedy for food poisoning caused by fungi.

- **Root:** Eating the root as a potherb is a common culinary practice.
- **Herb:** For uterine problems, dropsy, and intermittent fevers, use herb. They say that a decoction of it may help with cancer by applying it topically.
- **Leaves:** The aroma and taste of the leaves are soothing and refreshing. Diabetics are the source of inspiration for flourishing skulls and young leaves that are served as salad.
- **Seeds:** Seeds have a strong odour, calm the nerves, and prevent spasms. They are helpful in reducing bleeding, treating jaundice, and removing calculi from the liver and gallbladder.

Galenical preparations of both seeds and oil operate as mild purgatives, while alcoholic extracts of the plant and, to a lesser extent, the seeds themselves, promote peristalsis in the small intestine. Instead of coffee, you may use seeds [19]. The achene is a coffee replacement, while the flowers, leaves, and roots have all been used as vegetables in European cooking. Some people use it instead of spinach. There is a medical application for the flower head. It counteracts the toxic effects of Amanita mushrooms.

3.2 Present use

The drug in its raw form contains 15-30% lipids, mostly triglycerides (linoleic acid at 60%, oleic acid at 30%, and palmitic acid at 9%), about 30% proteins and sugars (arabinose, rhamnose, xylose, glucose), tocopherol at 0.038 percent, sterols at 0.063 percent (including cholesterol, compesterol, and stigmasterol), and flavonoids like quercetin, taxifolin, eriodictyol, and chrysoeriol. Flavanolignans, also known as flavanone derivatives, are the active components. These were first discovered as a mixture of addition products produced from coniferyl alcohol, phenylpropanol, and the 2,3-dihydroflavonol taxifolin [20].

Among the many components of this compound, which makes up 1.5-3% of the medicine's dry weight, are the following (Figure 2): silybin (or silybinin or silibinin) (approximately 50 to 60%), isosilibyn (approximately 5%), silychristin (approximately 20%), silydianin (approximately 10%), silimonin, isosilychristin, isosilibinin, and others. Spectrophotometry, High Performance Liquid Chromatography (HPLC), and Thin Layer Chromatography (TLC) are some of the microscopical techniques that may be used to characterise the medicine [21].

4. Pharmacological Properties Related to Liver Protection

4.1 Antioxidant Activity

Milk thistle's antioxidant capabilities were evaluated by testing its interaction potential with relevant biological reactive oxygen species (ROS) or oxidants, such as hydroxyl radical (OH-), superoxide anion radical (O2), hydrogen peroxide (H2O2), and hypochlorous acid (HOCl). Researchers Kiruthiga et al. found that when antioxidant enzymes like catalase, glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione transferase (GST) are activated after silymarin administration, erythrocytes exposed to hydrogen peroxide (H2O2) have lower levels of malondialdehyde (MDA), a measurement for lipid peroxidation [22-25].

4.2 Hepatoprotective Mechanisms

Silymarin, extracted from *Silybum marianum*, is the most often prescribed remedy for those with hepatic diseases. It was shown to be quite beneficial for persons with liver cirrhosis due to excessive alcohol use. Silymarin has a positive safety profile; nevertheless, certain studies suggest it may cause gastrointestinal issues and dermatological responses. Milk thistle may act as a protective agent against liver diseases. The exact mechanism of action is unknown. It is proposed that it competes with toxins for binding and infiltration in hepatocytes [26]. Initial clinical studies indicate that milk thistle is beneficial for individuals with alcoholic cirrhosis. Nevertheless, thorough experimental research are essential to draw any conclusive results. Individuals with chronic liver conditions used milk thistle as a dietary supplement. This treatment was deemed safe and appropriate. Nonetheless, the experimental studies conducted on people with chronic liver diseases using this plant species did not reduce mortality, increase liver histology, or improve biochemical markers of liver function. Abascal and Yarnel assert that several studies have shown the powerful and beneficial characteristics of Silymarin. In light of safety, clinicians advocate for its use despite the lack of clinical studies. This plant species may be used as food, brewed as tea, and included into different formulations for the treatment of nonspecific diseases. The seeds and fruit extract of Silybum marianum have been used in herbal medicine for the treatment of hepatic diseases [27,28].

Silybum marianum and its derivatives offer protection against toxins and hepatic cirrhosis. The results are encouraging; however, the current data and experiments are insufficient (due to inadequate sample size, dose standardisation, limited patient information, and inconsistency within the treated population) to support the use of this plant for treating patients with alcoholic liver disease [29]. Different formulations of Silymarin are produced by encapsulating them inside lipid microspheres. The effectiveness of Silymarin was seen to be improved in lipid microspheres. This suggests that they may function as conduits for efficient administration. This method of administering Silymarin improves the effectiveness of hepatoprotective pharmaceutical agents. The flavonoid constituents of Silybum marianum have shown significant hepatoprotective properties [30]. The effects of polyphenolic extracts from Silybum marianum and Cichorium intybus were assessed in rats with induced hepatotoxicity. Their research illustrates the hepatoprotective attributes of these extracts against liver cellular damage induced by Thioacetamide.

4.3 Anti-viral and Anti-inflammatory Effects

One of the most powerful anti-inflammatory substances is *silybum marianum*. The anti-inflammatory activity in biological tissues is due to the secondary metabolites of silymarin. While these results are based on preclinical studies, the whole examination has the potential to reveal some surprising things about

Silymarin's impacts. Silymarin slows thrombocyte activity in mice at lower doses, but it may trigger inflammation at higher doses. Flavonolignans such as silybin, silydianin, and silychristin make up silymarin, which is extracted from the fruit of the Silybum marianum plant. Analysed were its effects on inflammation caused by papaya latex and arthritis caused by mycobacterial adjuvant in rats, specifically looking at its anti-arthritic and anti-inflammatory capabilities [31]. The results show that blocking 5-lipoxygenase has significant anti-inflammatory and antiarthritic properties.

The oedema in rats' paws caused by carrageenan and the inflammation in mice's ears caused by toxic agents can be reduced with oral administration of Silymarin in the form of tablets or capsules. Thus, indomethacin and Silybum marianum are chemically indistinguishable. The results of these studies proved that milk thistle reduced inflammation. A number of species, including turmeric (Curcuma longa), have been around for a while and are known to reduce inflammation [32]. Some people find that this herb works best when used regularly to ease discomfort in the joints, particularly the wrists. To determine whether Silybum marianum had anti-inflammatory effects, researchers studied albino rats. The greatest reduction in rat paw oedema was seen in the methanolic extracts of the leaves and the leaf callus. This happened because, compared to regular leaves, the leaf callus extracts contained far higher concentrations of secondary metabolites. There is evidence that both extracts may reduce inflammation [33].

Activity	References
Antioxidant activity	Admah et al. 2013 [34]
Inflammatory effects	Qin et al. 2017b [35]
Antiviral activities	Das et al. 2008 [36]
Antidiabetic activities	Maghrani et al. 2004 [37]
Anti-amnesia effects	Nazir et al. 2018 [38]
Cardio-protection	Vilahur et al. 2018 [39]
Hepatic protection	Shaker et al. 2010 [40]
Wilson's disease	Jedlinszki et al. 2016 [41]
Obsessive–Compulsive Disorder	Sayyah et al. 2010 [42]
Sepsis and Burn prevention	Toluk et al. 2007 [43]
Application in veterinary	Cullere et al. 2016 [44]
Hypocholesterolaemic activity	Skottova and Krecman 1998 [45]
Anti-hypertensive activity	Jadhav et al. 2011 [46]
Neuroprotective activity	Kittur et al. 2002 [47]
Anti-cancer activity	Bhatia et al. 1999 [48]
Anti-aflatoxin activities	Alhidary et al. 2017 [49]
Antidote activity	Fanoudi et al. 2018 [50]

4.4 Treating certain women problems

Silymarin is regarded as a remarkable pharmaceutical for women. Numerous research have been undertaken to investigate the impact of Silymarin" in addressing female health issues. The fruits of Silybum marianum have been used by nursing women to enhance milk production. However, its mechanism of action remains unclear [51]. These data indicate that Silymarin may be an effective choice to address lactation insufficiency. Following therapy for a designated period, blood prolactin levels significantly rose. It aids in the treatment of menstruation problems and alleviates menstrual discomfort. Consequently, it has garnered popularity, with women preferring oral use in capsule form. It also functions as an anti-aging component in lotions and creams [52].

4.5 Veterinary medicines

The milk In order to boost the chicks' body weight and fatten them, thistle seed cakes were added to their diet. In hens and turkeys, silymarin enhanced hatchability and boosted body weight. As a

hepatoprotective agent, silymarin lowers lipid levels while raising glycogen contents. The impact of fruit extract on the quality and performance of grill chickens was investigated by Schiavone et al. Changes in growth performance were not significantly impacted by the therapy [53]. Silymarin may enhance the quality of the meat, however. Although it hasn't shown any hepatoprotective effects, it did increase muscles' resilience to oxidative stress. Studies were conducted on white carneaux pigeons (Columba livia) that were exposed to B1 aflatoxin to determine the hepatoprotective effects of silymarin extract. No hepatoprotective effects of silymarin extract have been shown in studies using hepatobiliary scintigraphy and histology. However, biliary-duct hyperplasia, necrosis, lymphocyte infiltration, and hepatic inflammation were the outcomes of aflatoxin consumption [54]. Hepatotoxicity occurs when ruminants graze in the fields and sometimes consume sawfly larvae (Arge pullata). The hepatotoxicosis that sawfly larvae induce in ruminants may be effectively treated using a substance that was isolated from *Silybum marianum*. In dogs with Giardia parasitosis, when the administration of the antibiotic metronidazol results in hepatic problems, silymarin was also utilised. Serum markers of liver inflammation were much higher in the positive control group than in the dogs treated with silymarin, demonstrating the efficacy of silymarin in treating liver diseases [55] .

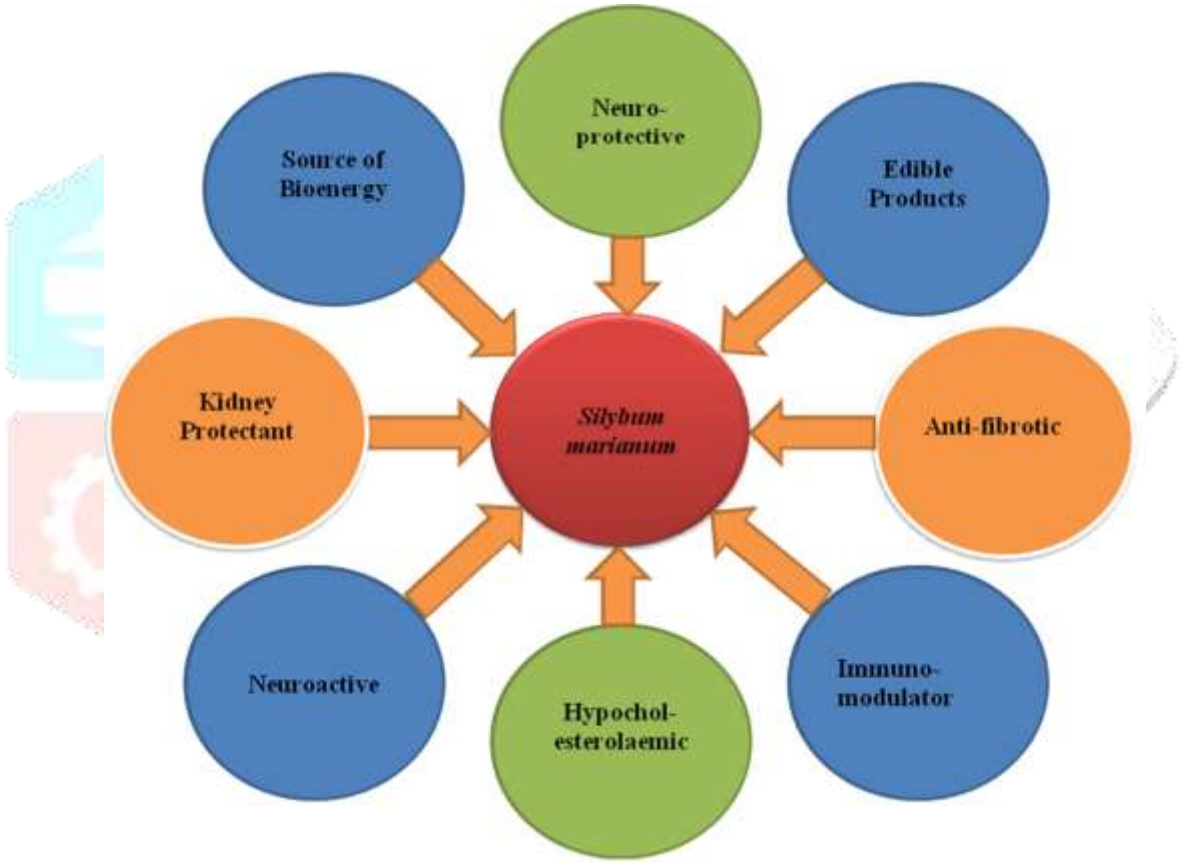

Figure 3. *Silybum marianum* multifunctional role

5. Clinical Studies and Human Trials

The majority of clinical trials evaluating the efficacy of silymarin are challenging to interpret due to limitations such as small sample sizes, variability in disease aetiology and severity, inconsistencies in patient alcohol consumption, heterogeneous dosing regimens, lack of standardised control groups, and poorly defined endpoints. Evidence of statistically significant biochemical or histological enhancement in liver damage has been rare. Moreover, the inherent capacity of liver damage to ameliorate with the elimination of hepatotoxins, such as the cessation of alcohol use or the resolution of acute hepatitis, has often been overlooked in these investigations [56].

5.1 Acute viral hepatitis

Medications containing silymarin have been shown in double-blind studies to decrease complications, speed up recovery, and decrease hospitalisation times for patients with acute viral hepatitis. The subjects of the double-blind study by Magliulo et al. were either given a placebo or silymarin 140 mg three times a day for at least three weeks (28 patients, with a mean treatment duration of 26.6 days) for the treatment of acute hepatitis A or B. There was a failure to enquire about any preexisting liver conditions or alcohol use. The treated group showed significantly lower mean levels of AST, ALT, and total bilirubin after five days compared to the placebo group [57].

Bilirubin normalisation occurred in 40% of patients compared to 11% and AST normalisation occurred in 82% of patients compared to 52% after three weeks. The percentage of patients who developed immunity remained unchanged. The length of hospital treatment was significantly shorter in individuals given silymarin compared to those getting just supportive care, according to a second controlled investigation (23.3 vs 30.4 days). Further, the silymarin group showed a shorter time to immunity onset among the hepatitis B patients (30.4 vs. 41.2 days, respectively) [58]. Patients who had elevations in AST or ALT levels after the commencement of medication were excluded from the study, perhaps mistakenly, since such a reaction is favourable in individuals receiving interferon treatment.

5.2 Alcoholic liver disease

A six-month, double-blind experiment including individuals with persistent alcohol misuse and histological evidence of chronic alcoholic hepatitis was documented in a series of publications. In 17 individuals administered silymarin 140 mg b.i.d. for 6 months, total bilirubin, AST, and ALT levels normalised, but GGT and procollagen III levels dramatically reduced, in contrast to the values seen in 19 placebo patients. The positive effects of silymarin on histology, lymphocyte proliferation, and lipid peroxidation were also documented. Ninety-seven individuals exhibiting persisting liver function test abnormalities after more than one month of alcohol abstinence were randomised to receive either silymarin or a placebo for four months. There was a 30% reduction in average blood AST levels at the end of therapy compared to a 5% increase in the placebo group. Silymarin resulted in a 41% reduction in ALT levels, whereas placebo caused a 3% increase. There was no discernible change in bilirubin levels. Many patients were able to restore normal bromophthalein retention after treatment, and the histological damage was significantly reduced. Participation in the study was contingent upon participants' voluntary and unsupervised abstinence from alcohol. [59] Of 66 patients who met biochemical and histological criteria for acute alcoholic hepatitis, 31 were given silymarin (dose unknown), and 35 were given a placebo. The investigation was double-blind, randomised, and placebo-controlled. In the treatment group, mean AST, ALT, and GGT levels normalised far more often than in the placebo group, and the process was much faster (13 days vs. 24 days). A greater proportion of silymarin patients achieved normalisation of all three indicators compared to the placebo group. Marked disparities across the groups were seen by day 7 [60].

5.3 Toxin and drug-induced hepatitis

Silymarin treatment has been investigated for exposure to both natural and industrial toxins. Its involvement in acute poisoning from the Amanita phalloides mushroom has been thoroughly assessed. In preliminary investigations, isolated livers from canines, rabbits, rodents, murines, and swine were subjected to elevated concentrations of phalloidin. Silymarin provided before to sacrifice effectively reduced histologic damage. Lyophilised Amanita phalloides was offered to 23 beagles, leading to vomiting and diarrhoea after an average of 16 hours. Twelve canines got just supportive care, while four succumbed after entering a coma within 35 to 54 hours. Of the eleven dogs administered silybin at a dosage of 50 milligram per kilogram five hours and twenty-four hours post-poisoning, none succumbed [61]. Liver function tests reached lower peak values, prothrombin time prolongation was reduced, and histological evidence of hemorrhagic necrosis was significantly decreased. Silymarin has been shown as beneficial in treating Amanita toxicity in people. In an uncontrolled trial, 60 consecutive patients received silybin at a dosage of

20 milligram per kilogram per day, commencing 24 to 36 hours post-Amanita intake. The survival rate was unequivocally 100%.

A subsequent European study with 220 patients yielded a death rate of 12.8%, compared to a 22.4% rate among patients who did not undergo silymarin treatment (38, 39). Fourteen individuals chronically exposed to organophosphates (malathion) and administered silymarin for one month had no improvement in liver function tests compared to ten matched controls. Serum levels of "pseudocholinesterase" increased markedly, perhaps indicating the inhibition of the toxin's "anticholinesterase activity" by silymarin (40). Silymarin treatment for exposure to various solvents, paints, and adhesives causing subacute or chronic liver disease has not resulted in notable enhancement of AST and ALT levels. In contrast, Szilard administered treatment to 30 patients exposed to toluene and/or xylene for more than 5 years, seeing improvements in AST, ALT, and platelet counts. The published studies of silymarin for drug-induced hepatitis were limited in size and hence not dependable, however the reported outcomes are favourable. Sixty patients undergoing therapy with psychotropic drugs (phenothiazines or butyrophenones) were allocated into two groups, with one group having their medication terminated and the other maintaining the same dosage. Both groups were then subdivided, with half of each getting silymarin at a dosage of 800 mg per day, while the other half received a placebo for a duration of 90 days. Silymarin treatment led to enhanced liver function tests, irrespective of the discontinuation of psychiatric medications [62]. Saba observed an enhancement in biochemical indicators in 19 individuals administered psychiatric medicines after 6 months of silymarin therapy. Martines et al. observed that silymarin safeguarded against histological alterations in the livers of women who were either pregnant or using oral contraceptives. Silymarin seems to mitigate the hepatotoxic damage induced by halothane.

5.4 Chronic hepatitis/cirrhosis (undifferent!ated)

Ferenci instructed 170 patients with biopsy-confirmed cirrhosis (92 alcoholic, 78 nonalcoholic) to refrain from alcohol use, thereafter administering silymarin 140 mg t.i.d. to 87 patients and a placebo to 83 patients for a duration of 2-6 years (mean follow-up of 41 months). One hundred five patients completed the follow-up period. Biochemical parameters showed no significant alterations. Nonetheless, survival rates improved in the treated cohort (77% overall compared to 67%, and 82% against 68% at 2 years). Survival rates were elevated in individuals with a history of alcohol addiction ($p = 0.01$). Only Child's A patients among nonalcoholics saw benefits. No difference in survival was seen in Child's classes B and C. An 8-week course of high-dose silymarin (560 mg/day) was administered to 2,637 patients suffering from chronic liver disease. In 63% of instances, the symptoms were reported to have resolved subjectively [63]. There was a 36% drop in average AST, a 34% drop in average ALT, and a 46% drop in average GGT. Additionally, the number of cases where the inspecting clinicians noted palpable hepatomegaly dropped.

A 12-month research was carried out by JSiesewetter to assess the histological effects of silymarin on patients with chronic persistent or "aggressive" hepatitis, whether or not they had cirrhosis. The analysis included two double-blind experiments. Exclusion criteria included no individuals using more than 80 g/day of medicine, a history of silymarin or steroids, or any other drugs. There were no significant variations in the improvement of liver function tests between the two groups over the 3- to 12-month monitoring period. Improved portal inflammation, parenchymal alterations, and piecemeal necrosis were seen. Only 36 out of 60 patients who were recruited had their findings reported due to a lack of follow-up. The usage of silymarin for the treatment of hepatic diseases dates back hundreds of years. It has the potential to improve the clinical results of hepatitis, whether it's caused by alcohol, drugs, toxins, or viruses. Due to factors such as inconsistent presence or absence of alcohol, small patient enrolment, variable diagnoses within the same study, lack of standardisation in silymarin preparations, dosage, and outcome measures, and cautious interpretation, the reported trials of the compound should be approached with caution. There have been no reported negative side effects of silymarin [64,65]. The need for well-designed, randomised, placebo-controlled studies for targeted diagnosis has never been greater than with herbal remedies for a wide range of medical issues.

6. Safety, Toxicity, and Side Effects

- **Toxicity and Contraindications:** Individuals with sensitivities to natural goods may have several types of allergic responses. Silybum marianum has also been shown to cause an allergic reaction. One Englishwoman reportedly had an adverse reaction to Silybum marianum after swallowing a pill with many plant extracts. But which plant in the capsule really caused the reaction is unclear. A patient with a history of kiwi fruit allergies has had anaphylaxis.
- **Chronic Toxicity.** The prolonged usage of this plant is safe, with no occurrences of abnormalities. No reports indicate negative herb responses throughout illness progression or in individuals with organ-specific disorders.
- **Acute Toxicity.** Silymarin was shown to have no notable adverse effects in animals, even at elevated dosages. Some medical professionals have speculated that a little laxative effect might appear in the first few days of taking the plant as a result of its stimulatory effects on the gallbladder and liver. The herb's side effects were less severe than those of a placebo in a randomised controlled trial. A research including several thousand participants revealed minimal instances of side effects, mostly confined to minor gastrointestinal issues.
- **Drug Interactions With Other Herbal or Chemical Medicines.** A study found that silybum marianum helped diabetics with alcohol-induced liver cirrhosis need less insulin. Nevertheless, the effects of the plant on changes in glucose metabolism in healthy persons have not been studied. In a double-blind study including six women who had used psychoactive drugs regularly, researchers found that two liver enzymes, alanine transaminase and aspartate transaminase, were significantly higher. There was a decrease in lipoperoxidase levels and liver damage compared to the control group after 90 days of taking 400 mg of silymarin bi-daily. Pharmacological drugs like paclitaxel, cisplatin, methotrexate, and fluorouracil can have their side effects reduced by sixty-six Silymarin [66]. Other drugs that can be reduced include lipid-lowering drugs, psychoactive substances, metronidazole, nitrous oxide, acetaminophen, and cyclosporine.

7. Future Prospects

The potential for Carduus marianus (milk thistle) in the future is to bring together the promising clinical and pharmacological data with large-scale, methodologically sound trials that can confirm its hepatoprotective effect and safety in various patient groups. Although the current literature emphasizes silymarin, the main flavonolignan complex of milk thistle, as a strong antioxidant, membrane stabilizer, and regulator of liver regeneration, its translation into uniform clinical regimens is lacking because of disparity in formulations, dosing, and bioavailability [67]. Future studies need to focus on the formulation of very bioavailable formulations—like phytosome-based, nanoencapsulated, or liposomal silymarin—that can bypass poor solubility and augment systemic absorption so that therapeutic levels are reached in hepatic tissue. Moreover, multi-omics platforms such as transcriptomics, proteomics, and metabolomics should be used to delineate the specific molecular networks targeted by silymarin in jaundiced livers, especially its regulation of inflammatory cytokines, bile acid homeostasis, and cholestatic mechanisms. Since jaundice frequently arises secondary to disorders like drug-induced hepatotoxicity, viral hepatitis, alcoholic liver disease, and biliary obstruction, subsequent trials would advantageously stratify etiologically to ascertain efficacy according to condition and to tailor treatments.

In addition, the combination of silymarin with standard antivirals, anti-inflammatories, or bile acid modulators promises synergistic therapy and earlier clearance of bilirubin and enhancement of markers of liver function than monotherapy. Preclinical research also needs to investigate silymarin's ability to modulate the course of fibrosis and counteract early cirrhotic alterations in chronic jaundice. Translationally, pharmacokinetic–pharmacodynamic studies are critical to determine the best doses, treatment duration, and safety profiles, especially in special populations like neonates with hyperbilirubinemia, pregnant women, and comorbid or polypharmacy patients. Regulatory harmonization of herbal supplements is also essential, with consistency in active compound content, quality control, and labeling to promote physician confidence in the use of standardized milk thistle preparations. Concurrently, artificial intelligence and machine learning

can be used to assess large data sets from clinical trials and actual patient outcomes, allowing for predictive modeling of therapeutic response and biomarkers for patient selection [68].

Public health policy must also take into account the incorporation of milk thistle into preventive care programs for high-risk populations, with an emphasis on lifestyle adjustment, monitoring of liver health, and education regarding evidence-based herbal therapy. With increased global interest in natural hepatoprotectants, interprofessional dialogue among ethnobotanists, pharmacologists, clinicians, and policy-makers will become necessary to maximize the full therapeutic potential of Carduus marianus in jaundice treatment. Through coming together of advanced pharmacological research with aggressive clinical verification, creative delivery technologies, and integrative healthcare models, milk thistle may transform from a historical herbal treatment into a scientifically validated, worldwide available pillar in the treatment and prevention of jaundice.

11. Conclusion

S. marianum is among the most significant medicinal plants cultivated globally. The traditional knowledge, pharmacology, therapeutic applications, and phytochemistry of the S. marianum plant are explored in this article. The plant has a long history of usage as a medicinal and magical remedy. The outstanding benefits of S. marianum have caused it to attract a lot of attention. Flavonolignans have been the subject of in vitro pharmacological studies, which have led to in vivo development in animal models and human trials. While several pharmacological processes linked to biological activity have been identified, there is still a need for more clarity on the whole pharmacological mechanisms of S. marianum. Phytochemical and pharmacological studies identified silymarins, which exhibit beneficial anti-diabetic, antiamnesic, and hepatic-protective properties, as chemical indicators for assessing the quality of *S. marianum* and its derivatives. However, pharmacokinetic studies on the primary constituents, especially the bioactive components, are largely lacking, necessitating robust validation to substantiate scientific claims regarding the therapeutic potential of *S. marianum* and its pharmaceutical products, including cardioprotective activity.

References

1. Baquar SR. The Role of Traditional Medicine in Rural Environment, In: Traditional Medicine in Africa, Issaq, S. (Editor), East Africa Educational Publishers Ltd., Nairobi 1995, pp. 141-142.
2. Khan FA, Zahoor M, Ullah N, Khan S, Khurram M, Khan S, Ali J. A general introduction to medicinal plants and silybum marianum. Life Science Journal 2014; 11(9s): 471-481.
3. World Health Organization. Containing Antimicrobial Resistance: Review of the Literature and Report of a WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance. WHO/ CDS/CSR/DRS/99.2; 1999.
4. Ncube NS, Afolayan AJ, Okoh AI, Assessment techniques of antimicrobial properties of natural compounds of plant origin: current methods and future trends, African Journal of Biotechnology 2008; 7: 1797-1806.
5. Aiyelaagbe O, Antibacterial activity of Jatropa multifida roots. Fitoterapia 2001; 72: 544-546.
6. Prince L, Prabakaran P. Antifungal activity of medicinal plants against plant pathogenic fungus Colletotrichum falcatum. Asian Journal of Plant Science Research 2011; 1: 84-87.
7. WHO, Quality control methods for herbal materials, Updated edition of Quality control methods for medicinal plant materials, 1998.
8. Rai VM, Pai VR, Kedilaya PH, Hegde S. Preliminary phytochemical screening of members of Lamiaceae family: Leucas linifolia, Coleus aromaticus and Pogestemon patchouli. International Journal of Pharmaceutical Science Review and Research 2013; 21(1): 131-137.

9. Lamaeswari G, Ananti T. Preliminary phytochemical screening and physicochemical characterization of Canna indica L.International Journal of Pharmaceutical Science Review and Research 2012; 14: 76-79.
10. Karthikeyan A, Shanthi V, Nagasathaya A, Preliminary phytochemical and antibacterial screening of crude extract of the leaf of Adhatoda vasica L. International Journal of Green Pharmaceae 2009; 3: 78-80.
11. Kingston DG. Modern natural products drug discovery and its relevance to biodiversity conservation. J Nat Prod 2011; 74:496-511.
12. Azim Khan M, Blackshaw RE, Marwat KB. Biology of milk thistle (Silybum marianum) and the management options for growers in North-Western Pakistan. Weed Biology and Management 2009; 9: 99-105.
13. Mel'nktov T M. Morphological-biological characteristics of Silybum marianum seeds as sowing material. Khimiko –
14. Ghavami N, Ramin AA. Salinity and temperature effects on seed germination of milk thistle. Commun Soil Sci Plant Anal 2007; 38: 2681-91.
15. Narayana DBA, Katayar CK, Brindavanam NB. Original system: search, research or research. IDMA Bull 1998; 29:413-6.
16. Hogan F, Krishnegowda N, Mikhailova M, Kahlenberg M. Flavonoid, silibinin inhibits proliferation and promotes cellcycle arrest of human colon cancer. J Surg Res2007; 143:58- 65.
17. Schuppan D, Jia J, Brinkhaus B, Hahn EG. Herbal products for liver diseases: A therapeutic challenge for the new millennium. Hepatology 1999; 30:1099-1104.
18. Bisset N. Herbal Drugs and Pharmaceuticals. CRC Press Boca Ratan, London, 1994, 121-123.
19. Lee DY, Liu Y.Molecular structure and stereochemistry of silybin A, silybin B, isosilybin A and isosilybin B, isolated from Silybum marianum (milk thistle). J Nat Prod 2003; 66: 1171- 1174.
20. Ladas EJ, Cheng B, Hughes D. Milk thistle (Silybum marianum) is associated with reductions in liver function tests (LFTs) in children undergoing therapy for acute lymphoblastic leukemia (ALL). Society of Integrative Oncology, Boston, Mass 2006.
21. Bhatia N, Zhao J, Wolf DM. Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin. Cancer Lett 1999; 147: 77-84.
22. Duthie SJ, Johnson W, Dobson VL. The effect of dietary flavonoids on DNA damage (strand breaks and oxidised pyrimdines) and growth in human cells. Mutat Res 1997; 390: 141-151.
23. Allain H, Schück S, Lebreton S. Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease. Dementia Geriatr Cogn Disord 1999; 10: 181-185.
24. Hernandez R, Nazar E. Effect of silymarin in intrahepatic cholestasis of pregnancy. Ethiopia 1982; 47: 22-29.
25. Greenlee H, Abascal K, Yarnell E, Ladas E. Clinical applications of Silybum marianum in oncology. Integr Cancer Ther 2007; 6: 158-165.
26. Eliss RH, Covell S, Roberts EH, Sumerfield RG. The influence of temperature on seed germination rate in grain legumes. II. Interspecific variation in chickpea (Cicer arietinum L.) at temperature. J Exp Bot 1986;37: 1503-1515.
27. http://www.zipcodezoo.com/Plants/S/Sylibum_marianum.
28. Patel CJ, Tyagi S, Kumar U, Patel S, Patel Ph, Bharat C. Clinical benefits of milk thistle (silybum marianum): a recent review. Journal of Drug Discovery and Therapeutics 2013; 1 (1): 08-11
29. Kirtikar KR, Basu BD. Indian Medicinal Plants, Vol. 2, International Book Distributors, Dehradun, 2006, 1417-1418.
30. Morazzoni P, Bombardelli E. Silybum marianum (Carduus marianus). Fitoterapia. 1995; LXVI: 3-42. 28. Luper S. A review of plants used in the treatment of liver disease: part 1. Altern Med Rev 1998; 3:410-421.

31. Schuppan D, Jia JD, Brinkhaus B, et al. Herbal products for liver diseases: a therapeutic challenge for the new millennium. Hepatology 1999; 30: 1099-1104.
32. Culpeper N. The English Physitian: Or an Astrologo-Physical Discourse of the Vulgar Herbs of This Nation. London: Peter Cole, 1652.
33. Giese LA. Complementary healthcare practices. Gastroenterol Nurs 2001; 24:38-40. 32. Libster M. Delmar′s integrative herb guide for nurses. Thamson Learning. 2002, pp: 669 -77.
34. Ahmad N, Abbasi BH, Fazal H. Evaluation of antioxidant activity and its association with plant development in Silybum marianum L. Industrial Crops and Products. 2013a; 49:164- 168.
35. Qin NB, Jia CC, Xu J, Li DH, Xu FX, Bai J et al. New amides from seeds of Silybum marianum with potential antioxidant and antidiabetic activities. Fitoterapia. 2017a; 119:83-89.
36. Das SK, Mukherjee S, Vasudevan DM. Medicinal properties of milk thistle with special reference to silymarin: An overview. Nat Prod Rad 2008; 7:182-192. 66. Cardile AP, Mbuy GK. Anti-herpes virus activity of silibinin, the primary active component of Silybum marianum. Journal of Herbal Medicine. 2013; 3(4):132-136.
37. Maghrani M, Zeggwagh NA, Lemhadri A, Amraoui ME, Michel JB, Eddouks M. Study of the hypoglycacemic activity of Fraximus excelsior and Silybum marianum in an animal model of type 1 diabetes mellitus. Journal of Ethnopharmacology. 2004: 91:309-316.
38. Nazir N, Karim N, Abdel-Halim H, Khan I, Wadood SF, Nisar M. Phytochemical analysis, molecular docking and antiamnesic effects of methanolic extract of Silybum marianum (L.) Gaertn seeds in scopolamine induced memory impairment in mice. Journal of ethnopharmacology 2018; 210:198-208
39. Vilahur G, Casaní L, Peña E, Crespo J, Juan-Babot O, Ben-Aicha S et al. Silybum marianum provides cardioprotection and limits adverse remodeling post-myocardial infarction by mitigating oxidative stress and reactive fibrosis. International Journal of Cardiology, 2018.
40. Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and Silybum marianum extracts prevent liver damage. Food and Chemical Toxicology. 2010; 48(3):803-806.
41. Jedlinszki N, Kálomista I, Galbács G, Csupor D. Silybum marianum (Milk thistle) products in Wilson's disease: a treatment or a threat?. Journal of Herbal Medicine. 2016; 6(3):157-159.
42. Sayyah M, Boostani H, Pakseresht S, Malayeri A. Comparison of Silybum marianum (L.) Gaertn. With fluoxetine in the treatment of Obsessive-Compulsive Disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2010; 34(2):362-365.
43. Toklu HZ, Akbay TT, Erkanli G, Yuksel M, Ercan F, Sener G. Silymarin, the antioxidant component of Silybum marianum, protects against burn-induced oxidative skin injury. Burns 2007; 33:908-916
44. Cullere M, Zotte AD, Celia C, Monterrubi ALR, Gerencser Z, Szendro Z et al. Effect of Silybum marianum herb on the productive performance, carcass traits and meat quality of growing rabbits. Livestock Science 2016; 194:31-36.
45. Skottova N, Krecman V. Silymarin as a potential hypocholesterolaemic drug. Physiol Res 1998; 47:1-7.
46. Jadhav GB, Upasani CD. Antihypertensive effect of Silymarin on DOCA salt induced hypertension in unilateral nephrectomized rats. Orient Pharm Exp Med 2011; 11:101- 106.
47. Kittur S, Wilasrusmee S, Pedersen WA, et al. Neurotrophic and neuroprotective effects of milk thistle (Silybum marianum) onneurons in culture. J Mol Neurosci 2002; 18(3):265-269.
48. Bhatia N, Zhao J, Wolf DM, Agarwal R. Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin. Cancer Letters 1999; 147:77-84.
49. Alhidary IA, Rehman Z, Khan RU, Tahir M. Anti-aflatoxin activities of milk thistle (Silybum marianum) in broiler. World's Poultry Science Journal 2017; 73: 2-7
50. Fanoudi S, Alavi MS, Karimi G, Hosseinzadeh H. Milk thistle (SilybumMarianum) as an antidote or a protective agent against natural or chemical toxicities: a review, Drug and Chemical Toxicology 2018, DOI: 10.1080/01480545.2018.1485687

51. Derosa G, D'Angelo A, Maffioli P. The role of a fixed Berberis aristata/ Silybum marianum combination in the treatment of type 1 diabetes mellitus. Clinical Nutrition. 2016; 35(5):1091- 1095.
52. Ebrahimpour-Koujan SE, Gargari BP, Mobasseri M, Valizadeh H, Jafarabadi MA. Effects of Silybum marianum (L.) Gaertn. (Silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: A randomized, triple-blind, placebo-controlled clinical trial. Phytomedicine. 2015; 22:290-296.
53. Ebrahimpour- Koujan SE, Gargari BP, Mobasseri M, Valizadeh H, Jafarabadi MA. Lower glycemic indices and lipid profile among type 2 diabetes mellitus patients who received novel dose of Silybum marianum (L.) Gaertn. (silymarin) extract supplement: A Triple-blinded randomized controlled clinical trial. Phytomedicine. 2018; 44:39-44.
54. Ulas T, Tursun I, Demir ME, Dal MS, Buyukhatipoglu H. Comment on: Infusion of lin−/sca-1+ and endothelial progenitor cells improves proinflammatory and oxidative stress markers in atherosclerotic mice. International journal of cardiology. 2013; 164(1):128. 74. Erel O. A new automated colorimetric method for measuring total oxidant status. Clinical biochemistry. 2005; 38(12):1103- 1111.
55. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clinical biochemistry. 2004; 37(2):112-119.
56. Aghazadeh S, Amini R, Yazdanparast R, Ghaffari SH. Antiapoptotic and anti-inflammatory effects of Silybum marianum in treatment of experimental steatohepatitis. Experimental and toxicologic pathology. 2011; 63(6):569-574.
57. Zhu SY, Jiang N, Yang J, Tu J, Zhou Y, Xiao X et al. Silybum marianum oil attenuates hepatic steatosis and oxidative stress in high fat diet-fed mice. Biomedicine and Pharmacotherapy 2018; 100:191-197.
58. Albassam AA, Frye RF, Markowitz JS. The effect of milk thistle (Silybum marianum) and its main flavonolignans on CYP2C8 enzyme activity in human liver microsomes. Chemicobiological interactions 2017; 271:24-29.
59. Kosina P, Dokoupilova A, Janda K, Sladkova K, Silberova P, Pivodova V et al. Effect of Silybum marianum fruit constituents on the health status of rabbits in repeated 42-day fattening experiment. Animal Feed Science and Technology 2017; 223:128-140.
60. Mehdiyeva NP, Alizade VM, Bussmann RW, Paniagua-Zambrana NY, Khutsishvili M, Kikvidze Z, Khojimatov OK, Batsatsashvili K, Sikharulidze S, Tchelidze D, Maisaia I. Silybum marianum (L.) Gaertn. Asteraceae. InEthnobotany of the Caucasus 2024 (pp. 1-9). Springer, Cham.
61. Tewari D, Mocan A, Parvanov ED, Sah AN, Nabavi SM, Huminiecki L, Ma ZF, Lee YY, Horbańczuk JO, Atanasov AG. Ethnopharmacological approaches for therapy of jaundice: Part II. Highly used plant species from Acanthaceae, Euphorbiaceae, Asteraceae, Combretaceae, and Fabaceae families. Frontiers in pharmacology. 2017 Aug 10;8:519.
62. Panwar N, Sood G, Sood A, Sood BM. HimPharm's Guide to Milk Thistle Extract Silybum marianum Extract or Silymarin Carduus marianus extract Silybum or Holy Thistle Extract.
63. Murphy JM, Caban M, Kemper KJ. Milk thistle (Silybum marianum). Longwood Herbal Task Force. 2000.
64. Devi KP. Milk thistle (Silybum marianum). InNonvitamin and nonmineral nutritional supplements 2019 Jan 1 (pp. 321-325). Academic Press.
65. Bahmani M, Shirzad H, Rafieian S, Rafieian-Kopaei M. Silybum marianum: beyond hepatoprotection. Journal of evidence-based complementary & alternative medicine. 2015 Oct;20(4):292-301.
66. Sidhu MC, Saini P, Sidhu C, Saini P. Silybum marianum: a plant of high medicinal importance—a review. World J Pharm Res. 2012 Mar 10;1(2):72-86.
67. Suchy JrP, Strakova E, Kummer V, Herzig I, Pisarikova V, Blechova R, Maskova J. Hepatoprotective Effects of Milk Thistle (Silybum marianum) Seed Cakes during the Chicken Broiler Fattening. Acta Veterinaria Brno, 2008; 77: 31-8

68. Porwal O, Ameen MM, Anwer ET, Uthirapathy S, Ahamad J, Tahsin A. Silybum marianum (Milk Thistle): Review on Its chemistry, morphology, ethno medical uses, phytochemistry and pharmacological activities. Journal of Drug Delivery and Therapeutics. 2019 Sep 1;9(5):199-206.