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Review Article

Characteristics of Milk Thistle (*Silybum marianum*) and the Association with Liver Diseases: A Review of *In Vitro* and *In Vivo* Studies

Running Title: Milk Thistle and Liver Diseases

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Abstract

Milk thistle (*Silybum marianum*) belongs to the Asteraceae family. This family is noted for its composite flower heads and its broad distribution. This plant boasts glossy green leaves featuring marbled white veins and vibrant purple blooms and has been used in traditional medicine for over 2,000 years, particularly to treat liver disorders. This study aims to determine the characteristics of milk thistle and its association with liver diseases. The biochemical properties of milk thistle are attributed mainly to its complex mixture of bioactive compounds, particularly flavonolignans, collectively known as silymarin. Silymarin complex includes silybin, isosilybin, silychristin, and silydianin. Another active compound in milk thistle is a flavonoid. Flavonoids comprise taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodyctiol, and chrysoeriol. Furthermore, milk thistle contains macronutrients and micronutrients, making it highly nutritious. Milk thistle and its active components help reduce the incidence of liver disease through their anti-inflammatory, antioxidant, and anti-fibrotic effects. These actions are achieved by regulating the levels and activity of the nuclear factor erythroid 2-related factor 2 (NRF2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), superoxide dismutase (SOD), glutathione peroxidase (GPx), interleukin one beta (IL-1β), tumor necrosis factor-alpha (TNF-α), malondialdehyde (MDA), catalase (CAT), aspartate aminotransferase (AST), bilirubin, cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C).

Main Points: The biochemical properties of milk thistle are largely attributed to bioactive compounds, particularly flavonolignans, collectively known as silymarin. Milk thistle and its active components play a role in decrease the incidence of liver diseases through their anti-inflammatory, antioxidant, and anti-fibrotic effects.

Keywords: Milk thistle, Silydianin, Liver, Flavonoid, NRF2, NF-κB.

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Introduction

Milk thistle (*Silybum marianum*) belongs to the Asteraceae (or Compositae) family, which comprises other familiar plants such as sunflowers, daisies, and chrysanthemums. This family is noted for its composite flower heads and its broad distribution (1). This plant is characterized by its spiny leaves and sharp thorns on its stems and flowers, which are characteristics of the milk thistle. The prickly nature of Milk Thistle gives it a distinctive appearance, which can sometimes make it an invasive weed in certain areas. Milk thistle typically grows in the wild and remains in the vegetative stage during its initial growing season after seed germination, which is why it is generally considered a biennial. The growth periods of this plant differ depending on the time of planting (2, 3). Furthermore, this plant boasts glossy green leaves featuring marbled white veins and vibrant purple blooms. It has been used in traditional medicine for over 2,000 years, particularly for the treatment of liver and gallbladder disorders (4). Liver diseases such as hepatitis, cirrhosis, nonalcoholic fatty liver disease (NAFLD), and drug-induced liver damage continue to pose substantial global health problems (5). There are often limitations in conventional treatments, which have led to enhanced attention being paid to natural liver-protective agents, such as milk thistle. This study aims to determine the biochemical characteristics of milk thistle and its association with liver diseases.

Methods

A thorough review was conducted using the PubMed, Google, Scopus, and Google Scholar databases to identify relevant studies for the evaluation. Most of the analyzed studies were published between 2015 and 2025. The keywords included milk thistle, liver, silymarin, silybin, isosilybin, silychristin, silydianin, flavonoid, taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodyctiol, chrysoeriol, NRF2, NF-κB, iNOS, COX-2, SOD, GPx, IL-1β, TNF-α, MDA, CAT, AST, bilirubin, cholesterol, triglycerides, and LDL-C. The research was written using original articles and reviews.

Biochemical Properties of Milk Thistle

The biochemical properties of milk thistle are attributed mainly to its complex mixture of bioactive compounds, particularly flavonolignans, collectively known as silymarin (6).

Results and Discussions

Primary Bioactive Components

Silymarin Complex

The main pharmacological component of milk thistle is silymarin, a mixture of flavonolignans extracted from the plant's fruits (achenes) (7). Silymarin typically constitutes 1.5-3% of the fruit's dry weight and contains several isomeric compounds:

Silybin: Known as silibinin, it is a bioactive flavonolignan and the main active ingredient in silymarin, a standardized extract derived from the seeds of the Milk thistle plant. Silybin comprises 50-70% of silymarin. It is widely known for its hepatoprotective, antioxidant, anti-inflammatory, and potential anticancer properties. Silybin is comprised of two diastereomers, silybin A and silybin B, which occur in roughly equivalent concentrations (8). Silibinin plays a significant role in downregulating

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inflammatory chemokines, thrombosis, and contractility markers in inflammatory conditions (9).

Isosilybin: It is also referred to as isosilibinin, which exists as two diastereoisomers, isosilybin A and isosilybin B, which exhibit distinct biological activities. It accounts for about 5% of silymarin's content. Isosilybin has multiple anticancer activities (10).

Silychristin: It is also known as silicristin. It exists as two stereoisomers: silychristin A and silychristin B. It has antioxidant, anti-inflammatory, hepatoprotective, and anticancer effects. Silicristin accounts for about 20% of silymarin content (11).

Silydianin: It is a bioactive flavonolignan compound found in the seeds of Milk thistle. Silydianin is traditionally used for liver protection and other medicinal purposes. It comprises approximately 10% of the silymarin content (12).

These flavonolignans are formed through the oxidative coupling of the flavonoid taxifolin with coniferyl alcohol. The chemical structure of silybin, the primary active constituent, consists of two central units: a taxifolin-derived moiety and a coniferyl alcohol-derived phenyllpropanoid unit, linked by an oxeran ring (13).

Flavonoids

In addition to silymarin, Milk thistle comprises a variety of other bioactive compounds. One of the most important of them is flavonoid.

Flavonoids: The compounds present in them include taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodyctiol, and chrysoeriol.

Taxifolin or dihydroquercetin is a flavonol, a subclass of bioactive flavonoids presents in plants such as milk thistle, onions, Douglas fir bark, and Siberian larch. It is one of the key components of silymarin (14). Taxifolin enhances the therapeutic effects of milk thistle through its antioxidant, hepatoprotective, anti-inflammatory, and anticancer effects (15).

Quercetin, a flavonoid found in milk thistle, is associated with its therapeutic properties alongside silymarin. This ingredient enhances silymarin's antioxidant effects by increasing glutathione production, a vital antioxidant for detoxification. Furthermore, quercetin inhibits inflammatory enzymes, improves liver function markers and cardiovascular health, and reduces the incidence of cancer and neurodegenerative diseases (16).

Dihydrokaempferol, also known as aromadendrin, is a dihydroflavonol that belongs to the same subclass of flavonoids as kaempferol. These substances have been identified in milk thistle seeds and other organs (e.g., leaves, stems). Their roles in body health are similar to those of taxifolin and quercetin (17).

Apigenin is a secondary but valuable component of milk thistle that enhances its antioxidant and anti-inflammatory effects. Although it has not been as extensively studied as silymarin, it highlights the complex phytochemistry of milk thistle and its potential multifaceted health benefits (18).

Naringin is a flavanone glycoside that is not a primary or significant component of milk thistle. This substance is mainly found in citrus fruits (e.g., grapefruit) and has been studied for its antioxidant, anti-inflammatory, and liver-protective properties (19).

Eriodictyol is not a primary component of milk thistle; it is significant in the plant's phytochemistry because of its structural resemblance to taxifolin. However, unlike taxifolin, eriodictyol is not directly involved in the formation of milk thistle's signature flavonolignans (20).

Chrysoeriol is a flavone found in various plants (e.g., Capsicum species, Olea europaea, and Medicago sativa). Like eriodictyol and naringin, it is not a significant component of milk thistle. The advantages it offers for the body are similar to those of silymarin (21).

Macronutrients

Protein: Based on dry matter (DM) of Milk thistle seeds, its protein content is 20-30%, making it comparable to other plant-based protein sources like lentils and chickpeas. The protein is distributed throughout the seed. The endosperm is rich in protein. After oil extraction, the residue contains 25-30% protein. One notable indicator of milk thistle protein is its high content of sulfur-containing amino acids, such as methionine, which are typically found in lower amounts in plant proteins. Milk thistle protein contains small amounts of leucine, histidine, arginine, and proline. However, according to the standards, there is a balance of aromatic amino acids and tryptophan (22).

Fat: Milk thistle contains various saturated and unsaturated fatty acids. Linoleic acid (ω-6) is a predominant fatty acid that constitutes about 50% of the total lipids and is essential for human health but prone to oxidation. Oleic Acid (ω-9) is the second most abundant (about 30% of the total lipids), known for its stability and cardiovascular benefits (23). Furthermore, trace amounts of linolenic acid (ω-3) and gadoleic acid are also present in Milk thistle (24). Saturated fatty acids include palmitic acid and stearic acid, along with minor amounts of arachidic and behenic acids present in this plant (24).

Fiber: Milk thistle seeds are a relatively good source of dietary fiber, which supports digestive health and metabolism. Their fiber content differs depending on how they are prepared, with whole or ground seeds providing more benefits than processed teas or supplements. For optimal absorption, the seeds should be combined with foods rich in fat. Fibers, like glucose, help with digestion and regulate bowel movements (26).

Carbohydrate: Milk thistle contains varying amounts of carbohydrates depending on the form in which it is consumed (as seeds, supplements, or tea). Whole milk thistle seeds contain up to 38 grams of carbohydrates per 100 grams of seeds (27). Most milk thistle supplements are carbohydrate-free (28). When consumed as a tea, milk thistle typically contains no carbohydrates because the brewed liquid contains minimal soluble nutrients (29).

Micronutrients

Milk thistle contains various minerals that contribute to its nutritional value. Calcium plays a crucial role in maintaining bone health and supporting muscle function. Milk thistle seeds have small amounts of calcium, but the specific content depends on factors such as growing conditions and processing techniques (30). Magnesium supports nerve function, muscle relaxation, and energy production. Also, it is present in small quantities in Milk thistle seeds (31). Potassium is found in Milk thistle seeds, especially in the byproducts of oil extraction. It is crucial for the functioning of the heart and kidneys (2). Furthermore, analysis of milk thistle seeds revealed negligible levels of iron, zinc, phosphorus, and sodium (32).

Mechanisms of Action of Milk Thistle in Liver Diseases

Antioxidant and Anti-inflammatory Effects

The nuclear factor erythroid 2-related factor 2 (NRF2) and peroxisome proliferator-activated receptor alpha (PPARα) are essential transcription

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factors that are pivotal in protecting cells from oxidative stress and inflammation (33). The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a protein complex that is essential for regulating immune responses and promoting inflammation (34, 35). Cho et al. showed that silibinin induction in human gastric cancer MKN-1 cells infected with *H. pylori* and silibinin administration (20 mg/kg or 200 mg/kg) for 4 or 8 weeks in *H. pylori*-infected C57BL/6 mice downregulated NF-κB and the inflammatory factors inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (36). Ou et al. stated that silibinin (105 mg/kg/day) intake for 8 weeks in C57BL/6 mice with nonalcoholic steatohepatitis (NASH) resulted in upregulation of PPARα and NRF2 target genes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). Additionally, silibinin reduced NF-κB nuclear translocation and the expression of NF-κB target genes, including interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). Consequently, treatment with silibinin notably reduced hepatic steatosis and fibrosis in NASH mice (37). In a randomized controlled trial (RCT) published by Hashemi Jabali, the active ingredients in milk thistle led to a decrease in serum levels of the oxidative agent malondialdehyde (MDA) in laying hens (38). Boukazoula et al. reported that a notable rise in the serum content of SOD, catalase (CAT), and reduced glutathione (GSH), along with a decrease in MDA levels, was observed in athletes who were administered an aqueous extract of the seeds and leaves of milk thistle (39). C-reactive protein (CRP) is a factor expressed by NF-κB. In an RCT published by Gargari et al., silymarin complex (140 mg, thrice per day) was given for 45 days to patients with type 2 diabetes mellitus (T2DM). This treatment reduced CRP concentrations by approximately 30% (40). Furthermore, Speciale et al. demonstrated the pretreatment of human umbilical vein endothelial cells (HUVECs) with silibinin mitigated the TNF-α-induced expression of a chemotactic agent monocyte chemoattractant protein-1 (MCP-1), along with plasminogen activator inhibitor 1 (PAI-1), an essential component in coagulopathy and thrombosis, and endothelin-1 (ET-1), a peptide that plays a role in hemostatic vasoconstriction (9).

Protein kinase C (PKC) aggravates oxidative stress through activation of NADPH oxidase (41). In a study published by Ni et al., silymarin downregulated NADPH oxidase components in diet-induced obesity (DIO) mice (42).

Hepatoprotective and Detoxification Properties of Milk Thistle

Part of the hepatoprotective and detoxification properties of milk thistle is due to its anti-inflammatory and antioxidant effects. The inherent hepatoprotective and detoxification activity of silymarin results from its control of free radicals that are produced by the hepatic metabolism of toxic substances such as ethanol, acetaminophen, or carbon tetrachloride. Free radicals damage cell membranes. Milk Thistle protects against drug-induced liver damage by maintaining glutathione levels and restraining damage to cell membranes. Silymarin, due to its antioxidant properties, combats the byproducts of alcohol metabolism that produce free

radicals. Silymarin has been shown to increase the survival of patients with alcoholic cirrhosis. Therefore, silymarin stabilizes hepatocyte membranes by reducing oxidative stress, thereby preventing toxins from entering these cells. The hepatoprotective effect is also caused by the inhibition of the cyclooxygenase cycle, leukotrienes, and free radical production in Kupffer cells. Other effects include protection against genomic damage, enhanced protein synthesis, mitigated activity of hepatic oncogenes, and iron chelation. Furthermore, due to the phenolic nature of silymarin, it is able to transfer electrons to stabilize free radicals and reactive oxygen species (ROS) (43-45). ROS plays a crucial role in the initiation and maintenance of liver fibrosis. Silymarin prevents oxidative damage to liver cells by scavenging free radicals and mitigates the activation of hepatic stellate cells (HSCs), which are the main collagen-producing cells in liver fibrosis. Activated HSCs are the major effectors of extracellular matrix deposition in liver fibrosis. El-Lakkany et al. showed that silymarin (750 mg/kg/day) administration for 6 weeks in *Schistosoma mansoni*-infected mice downregulated hepatic transforming growth factor-β1 (TGF-β1) and matrix metalloproteinase-2 (MMP-2). They are vital profibrogenic cytokines (46). Alpha-smooth muscle actin (α-SMA) is a marker of HSC activation. Gharbia et al. stated that the intake of silymarin (50 mg/kg) for 2 weeks in mice with liver fibrosis downregulated α-SMA and attenuated the production of collagen type I (the major collagen in fibrotic liver) (47). Furthermore, Milk thistle enhances liver regeneration by stimulating the synthesis of ribosomal RNA and proteins (48). Silymarin blocks HCV activity in liver inflammation, hindering infection by blocking virus entry, RNA and protein expression, and production (49). Braun et al. reported that HCV-RNA levels decreased after patients were treated with silibinin 20 mg/kg/day for 2 weeks (50). Silymarin restrains the activity of HCV RNA-dependent RNA polymerase (NS5B). Polyak et al. demonstrated that silymarin pure extract hindered NS5B and infectious virion production in Huh7 human hepatoma cells (51).

It was shown that milk thistle improves liver enzyme content. In a clinical trial published by Ahmed et al., adjunctive treatment with silymarin in patients with hepatitis C resulted in attenuation of alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and bilirubin levels (52).

One of the complications of T2DM is the development of liver diseases. In T2DM, insulin sensitivity decreases, and subsequently, lipid indices such as cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) increase. Elevated levels of these indices lead to the development of fatty liver and other liver disorders (53-55). Ni et al. showed that plasma cholesterol, LDL-C levels, and hepatic triglyceride content were lowered in DIO mice that consumed silymarin (30 mg/kg) for one month. As a result, silymarin mitigated hepatic steatosis (42).

Conclusion

The biochemical properties of milk thistle are largely attributed to its complex mixture of bioactive compounds, particularly flavonolignans, collectively known as silymarin. Silymarin complex, along with

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other active components of this plant, plays a role in reducing the incidence of liver diseases through its anti-inflammatory, antioxidant, and anti-fibrotic effects. These actions are achieved by regulating the levels and activity of NRF2, NF-κB, iNOS, COX-2, SOD, GPx, IL-1β, TNF-α, MDA, CAT, AST, bilirubin, cholesterol, triglycerides, and LDL-C. Therefore, it is expected that Milk thistle has the potential to prevent liver disease based on the results obtained. However, more studies are needed to examine the effects of this herb at different doses on more factors related to liver health.

Table 1. *In vivo* studies on the effects of milk thistle and its active compounds on factors involved in liver disease

Study	Dosage	Duration of treatment	Affected agents	Model	Reference
Cho et al	20 mg/kg or 200 mg/kg	4- or 8-week	NF-κB, iNOS, COX-2	*H. pylori*-infected C57BL/6 mice	36
Ou et al	105 mg/kg	8 weeks	IL-1β, TNF-α SOD, GPx	C57BL/6 mice with NASH	37
Hashemi Jabali et al	100 mg/kg	---	MDA, SOD, CAT, GSH	Half-marathon athletes	38
Gargari et al	420 mg/kg	45 days	CRP	T2DM patients/RCT	40
El-Lakkany et al	750 mg/kg	6 weeks	TGF-β1, MMP-2	*Schistosoma mansoni*-infected mice	46
Gharbia et al	50 mg/kg	2weeks	α-SMA, collagen type I	Mice with liver fibrosis	47
Braun et al	20 mg/kg	2 weeks	HCV-RNA	HIV/Hepatitis C coinfected patients	50
Ahmed et al	400 mg/kg	8 weeks	ALT, AST, ALP, bilirubin	Hepatitis C patients	52
Ni et al	30 mg/kg	4 weeks	Cholesterol, triglyceride, LDL-C	DIO mice	42

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, iNOS: inducible nitric oxide synthase, COX-2: cyclooxygenase-2, α-SMA: alpha-smooth muscle actin, DIO: Diet-induced obesity

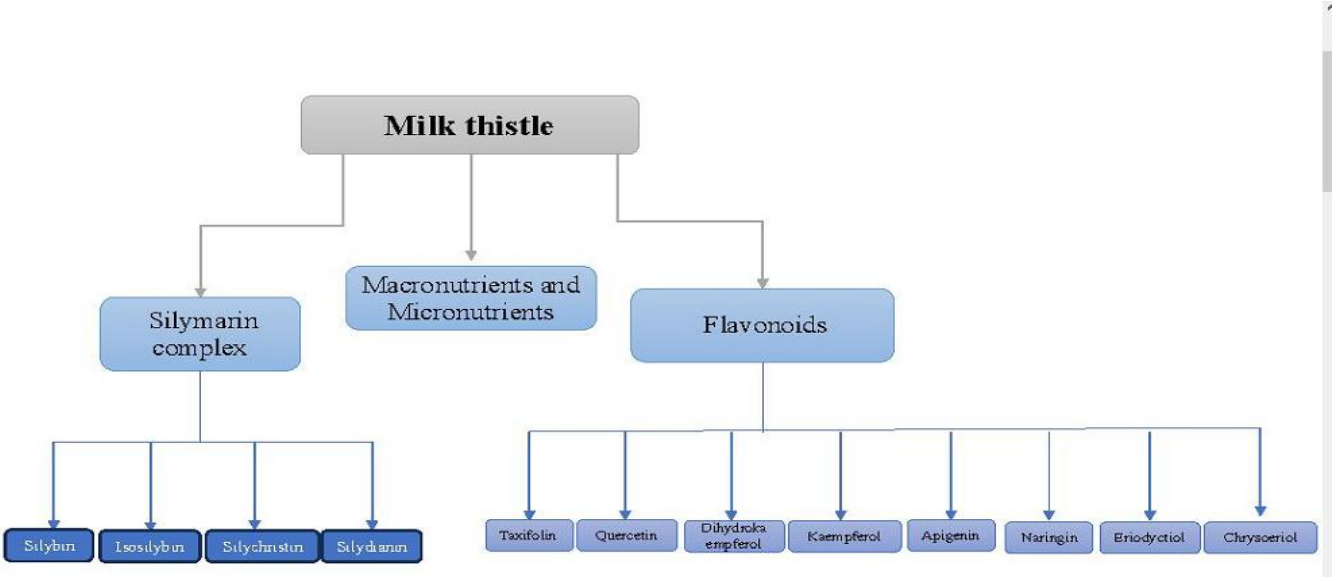

Figure.1. Active ingredients in milk thistle. They include silymarin complex, flavonoids, Macronutrients, and micronutrients. Silybin, isosilybin, silychristin, and silydianin are components of the silymarin complex. Flavonoids comprise taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodyctiol, and chrysoeriol.

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