WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal Homepage: www.ijrpr.com ISSN 2582-7421

Phytochemical Constituents and Therapeutic Applications of Silybum Marianum: Focus on Antioxidant and Anti-Inflammatory Activities

Vikas Singh*, Jitendra Kumar Malik, Yogesh Bhardwaj, Vivek Gupta, Gyan Singh

Research Scholar, Faculty of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.
- vikassingh979431@gmail.com
DOI : https://doi.org/10.55248/gengpi.07.0426.10836

ABSTRACT

Silybum marianum (Milk thistle) represents a compelling example of how traditional herbal medicine can inform modern evidence-based therapeutics. Historically valued for its hepatoprotective properties, the plant's seeds contain a bioactive flavonolignan complex known as silymarin, primarily composed of silibinin, silydianin, and silychristin. Growing scientific interest has extended its relevance beyond liver disorders, highlighting its potent antioxidant and anti-inflammatory potential across multiple chronic and degenerative conditions.

At the molecular level, silymarin functions as a multifunctional redox regulator. It directly scavenges reactive oxygen species, inhibits lipid peroxidation, and enhances endogenous antioxidant defenses by upregulating enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, largely through activation of the Nrf2 signaling pathway. Simultaneously, it exerts anti-inflammatory effects by suppressing NF-κB activation and downregulating pro-inflammatory mediators including TNF-α, IL-1β, IL-6, COX-2, and inducible nitric oxide synthase. This coordinated regulation of oxidative stress and inflammatory cascades positions *Silybum marianum* as a dual-action therapeutic agent with systems-level activity.

Emerging experimental and clinical studies further support its role in metabolic syndrome, neuroinflammation, cardiovascular diseases, and as an adjunct in cancer therapy. Advances in phytosome, liposomal, and nanoparticle-based delivery systems have significantly improved its bioavailability and therapeutic performance. However, challenges related to extract standardization, pharmacokinetic variability, regulatory harmonization, and large-scale randomized clinical validation remain. This review integrates current phytochemical, mechanistic, and translational evidence, emphasizing the innovative potential of *Silybum marianum* as a next-generation phytopharmaceutical for oxidative and inflammatory disorders.

Keywords: Silybum marianum; Silymarin; Silibinin; Antioxidant activity; Anti-inflammatory activity; Medicinal plant

1. Introduction

Oxidative stress and chronic inflammation are the key processes in the pathogenesis of many acute and chronic diseases, such as liver diseases, cardiovascular pathology, metabolic syndrome, neurodegenerative diseases, and cancer. Overproduction of reactive oxygen species (ROS) derails the redox homeostasis of the cell, which results in lipid peroxidation, DNA damage, protein oxidation, and mitochondrial dysfunction [1]. Ongoing oxidative stress also enhances the inflammatory signaling pathways, which is a self-sustaining loop in tissue damage and disease progression. Critical molecular mediators which include nuclear factor-kappa B (NF- -BG), cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines are important in maintaining this pathological condition [2].

Despite the popularity of synthetic antioxidants and nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical practice, their prolonged usage may be accompanied by such side effects as gastrointestinal irritation, cardiovascular risks, hepatotoxicity, and renal complications. In addition, most of the synthetic antioxidants have been found to have little efficacy in clinical studies, as a result of poor bioavailability or failure to regulate the complex intracellular pathways. These restrictions have been a catalyst to rising interests in safer and multitarget therapeutic substitutes of natural origin [3].

Phytochemicals in plants, especially polyphenols and flavonoids, have received a lot of interest due to their capacity to induce control over both oxidative and inflammatory processes at the same time. Of these, Silybum marianum (Milk thistle) holds the most prominent place in the traditional European and Mediterranean medicine, mainly in liver disease treatment. The silymarin bioactive flavonolignan complex has been widely researched as an antioxidant, anti-inflammatory, and cytoprotective agent [4].

The proposed review will critically analyze the phytochemical composition, molecular mechanisms of action, therapeutic advantages, approaches to formulation and perspectives of future research in Silybum marianum, especially on its antioxidant and anti-inflammatory effects [5].

2. Literature Search Methodology

An extensive and methodical search of the literature on Silybum marianum was made to provide the existing scientific data on the topic, focusing on the phytochemical structure, antioxidant effects, and anti-inflammatory activity of the substance. Peer-reviewed research articles, review papers, and clinical studies published within the latest year possible were actively found in electronic databases such as PubMed, Scopus, ScienceDirect, and Google Scholar [6].

The search strategy also used certain keywords and their combinations with the help of Boolean operators (AND, OR) in order to increase its relevance and accuracy of searching. Main search terms were Silybum marianum, silymarin, silibinin, anti-oxidant, anti-inflammatory, hepatoprotective and phytochemistry. Other keywords like oxidative stress,NF-B, cyto- cytokines and bioavailability were added to bring in mechanistic and translational research. Manual screening of reference lists of the selected articles was also done to locate more relevant publications [7].

Inclusion criteria included original experimental (in vitro and in vivo) and preclinical studies and clinical studies assessing antioxidant and anti-inflammatory activities and studies of phytochemical characterization and analytical profiling. Contextual relevance was also taken into account by the review articles that offered mechanistic information or summaries [8].

Any non-English publications, abstracts of conferences without complete data, duplicates of the same study, and those that did not provide enough methodological description and reproducibility were excluded. The extraction of data was centered on the study design, experimental models, drug dosage, key findings, major outcomes and molecular targets. The literature that was collected was systematically arranged into theme categories so that it could be clear, consistent, and critically synthesized all through the review [9].

3. Botanical Description and Ethnomedicinal Uses

3.1 Botanical Description

Silybum marianum is a plant in the family, Asteraceae and is also referred to as Milk thistle. It is a perennial or biannual plant, hard, straight, and the stem can be 1-2 meters tall. The plant has big and shiny green leaves that are characterized with unique white marbling on the veins. These are heavily lobed deep, reddish sharp spiny-margined leaves. The inflorescence is made up of single heads of purple flowers with rigid and spiny bracts in the form of a standard capitulum. The achene (seed) is a hard, brownish fruit, and, as it contains the flavonolignan complex silymarin, in large amounts, it is the major medicinal part. The plant is native to Mediterranean area and is currently being grown across the world in large amounts, both as a medicine and commercial crop [10].

3.2 Ethnomedicinal Uses

In the traditional European and Mediterranean herbal medicine, Silybum marianum was widely used especially in the treatment of liver and biliary diseases. It has been used in the treatment of jaundice, hepatitis, fatty liver and cirrhosis where it is said to facilitated liver regeneration and liver detoxification. Preparations of the seeds are usually in the form of extracts, tinctures or powdered formulations to stimulate the secretion of bile and enhance digestion thus acting as a digestive tonic [11].

In addition to hepatoprotection, the plant has also been applied as a natural anti-inflammatory agent in the treatment of inflammatory diseases such as mild gastrointestinal irritation and systemic inflammatory diseases. Traditionally, it has been seen as a general detoxifying herb that is assumed to guard the body against toxins, alcohol-induced injuries and environmental pollutants. These traditional ethnomedicinal uses have given the basis of current pharmacological research into its antioxidant and anti-inflammatory action [12].

Table 1: Taxonomical Classification and Traditional Uses of *Silybum marianum*[13]

S. No.	Parameter	Description
1	Kingdom	Plantae
2	Subkingdom	Tracheobionta (Vascular plants)
3	Superdivision	Spermatophyta (Seed plants)
4	Division	Magnoliophyta (Angiosperms)
5	Class	Magnoliopsida (Dicotyledons)
6	Subclass	Asteridae
7	Order	Asterales
8	Family	Asteraceae

S. No.	Parameter	Description
9	Genus	*Silybum*
10	Species	*Silybum marianum* (L.) Gaertn.
11	Common Names	Milk thistle, Blessed milk thistle, Marian thistle
12	Plant Parts Used	Seeds (primary), leaves (occasionally)
13	Major Traditional Use	Hepatoprotective (liver disorders)
14	Additional Traditional Uses	Digestive tonic, bile stimulant, detoxifying agent
15	Anti-Inflammatory Applications	Used in traditional medicine to manage inflammatory and biliary conditions

4. Phytochemical Profile

Silybum marianum is a biologically diverse plant whose main attribute is the chemical diversity of the phytoconstituents that enable the pharmacological versatility of the plant. The seeds are the main medicinal constituent and have a special combination of flavonolignans commonly known as silymarin, and other phenolic and lipid-soluble compounds that are part of its biological actions [14].

4.1 Major Bioactive Constituents

The silymarin complex is the most important phytochemical of the Silybum marianum seeds usually occupying about 7080 percent of the standardized seed extract. Silymarin is not a compound but a solution of closely related flavonolignans that are the result of the oxidative combination of a flavonoid (taxifolin) and phenylpropanoid unit. The major components are:

- **Silibinin (Silybin A and Silybin B):** The most abundant and biologically active constituent, responsible for the majority of hepatoprotective, antioxidant, and anti-inflammatory effects.
- **Silydianin:** Known for its hepatoregenerative and cytoprotective properties.
- **Silychristin:** Contributes to antioxidant and membrane-stabilizing activities [15].

In addition to silymarin, the seeds contain flavonoids such as taxifolin, which acts as a precursor molecule in flavonolignan biosynthesis. Other important constituents include phenolic acids, which enhance antioxidant capacity, tocopherols (vitamin E derivatives) contributing to lipid-phase antioxidant protection, and fatty acids such as linoleic and oleic acids, which form part of the seed oil fraction [16].

4.2 Chemical Characteristics

Silymarin belongs to the chemical class of flavonolignan complex, which is a unique type of hybrid molecules in terms of chemical structure, a flavonoid structure combined with a lignan structure. It is the structural specificity that preconditioned its wide range of biological action. The compounds form relatively lipophilic compounds, and this allows the compounds to interact with membranes but prevents aqueous solubility and oral bioavailability [17].

The aspect of stability is also significant because silymarin components can be destroyed in conditions of high heat, light or alkalinity. Weak water solubility and poor gastrointestinal absorption is a major issue and novel systems like phytosomes and nano-carriers have been developed to enhance systemic availability [18].

4.3 Analytical Techniques

Silymarin constituents cannot be correctly identified and quantified without using sophisticated forms of analysis. The most commonly used method of standardization and quantitative analysis of single flavonolignans is the High-Performance Liquid Chromatography (HPLC). Liquid Chromatography - Mass Spectrometry (LC-MS) offers in depth structural characterization and high sensitivity to minor constituents [19].

High-Performance Thin-Layer Chromatography (HPTLC) is commonly applicable in fingerprint profiling as well as quality control of herbal preparations. Moreover, spectrophotometric tests are also used in estimating the total phenolic and flavonoid content which aid in routine quality assessment and also the antioxidant evaluation. Combined, these methods of analysis guarantee the reproducibility, standardization, and quality control of phytopharmaceutical preparations of Silybum marianum [20].

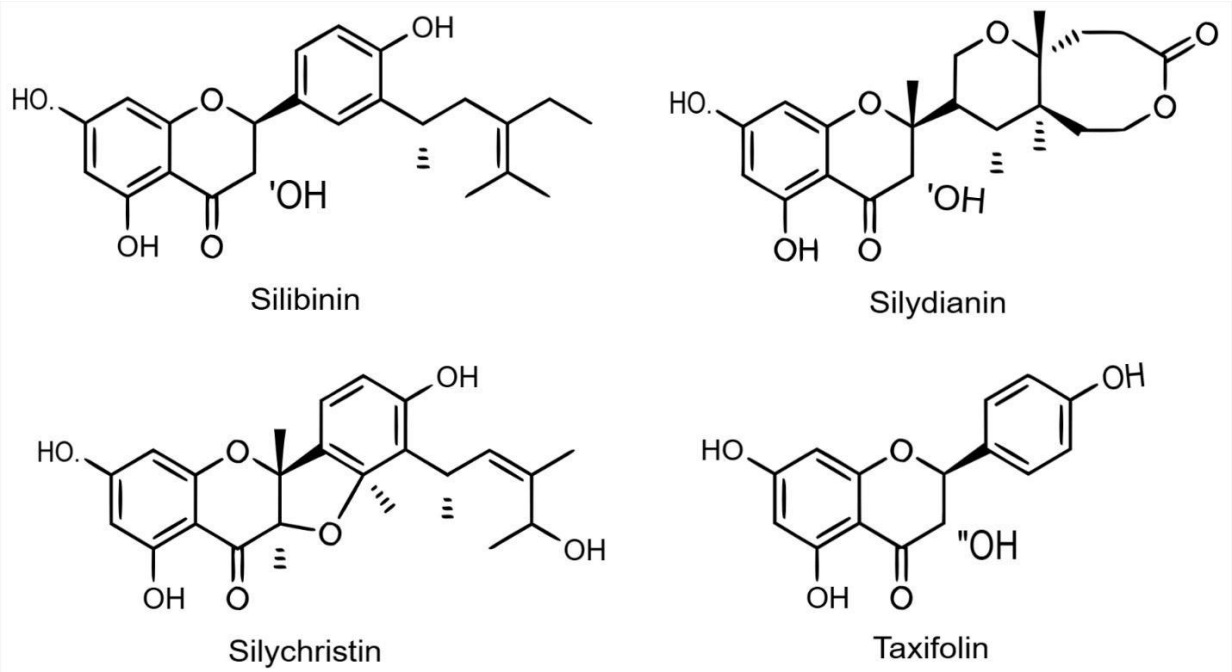

Figure 1: Chemical Structure of Major Flavonolignans of *Silybum marianum* [21]

Table 2: Major Phytochemical Constituents of *Silybum marianum* [22]

S. No.	Plant Part	Compound Class	Major Constituent	Chemical Nature	Reported Activity
1	Seeds	Flavonolignan	Silibinin (Silybin A)	Flavonolignan	Antioxidant, anti-inflammatory
2	Seeds	Flavonolignan	Silibinin (Silybin B)	Flavonolignan	Hepatoprotective
3	Seeds	Flavonolignan	Silydianin	Flavonolignan	Cytoprotective
4	Seeds	Flavonolignan	Silychristin	Flavonolignan	Membrane stabilizing
5	Seeds	Flavonoid	Taxifolin	Flavanonol	Antioxidant
6	Seeds	Flavonoid	Quercetin (trace)	Flavonol	Anti-inflammatory
7	Seeds	Phenolic acid	Caffeic acid	Hydroxycinnamic acid	Antioxidant
8	Seeds	Phenolic acid	Ferulic acid	Hydroxycinnamic acid	Free radical scavenger
9	Seeds	Tocopherol	α-Tocopherol	Vitamin E derivative	Lipid antioxidant
10	Seeds	Fatty acid	Linoleic acid	Polyunsaturated fatty acid	Anti-inflammatory support
11	Seeds	Fatty acid	Oleic acid	Monounsaturated fatty acid	Cardioprotective
12	Seeds	Sterol	β-Sitosterol	Phytosterol	Anti-inflammatory
13	Leaves	Polyphenols	Various phenolic compounds	Polyphenolic mixture	Antioxidant
14	Whole plant	Flavonoids	Apigenin (trace)	Flavone	Anti-inflammatory
15	Seed oil	Lipid fraction	Palmitic acid	Saturated fatty acid	Structural lipid component

5. Antioxidant Activity

Silybum marianum antioxidant activity has already been investigated and is regarded as one of the main pharmacological properties of this plant. Being the consequence of the excessive production of reactive oxygen species (ROS), oxidative stress is at the center of cellular damage and chronic illness development. Silibinin, silymarin is a flavonolignan complex, which plays a significant role in the redox-modulating effects of the plant by several complementary effects [23].

5.1 Mechanisms of Antioxidant Action

Silybum marianum exerts its antioxidant activity through both direct and indirect mechanisms.

- **Free radical scavenging:** Silymarin directly neutralizes reactive oxygen species such as superoxide anions, hydroxyl radicals, and peroxyl radicals by donating hydrogen atoms or electrons, thereby preventing oxidative damage to cellular components [24].
- **Inhibition of lipid peroxidation:** By stabilizing cell membranes and interrupting free radical chain reactions, silymarin reduces lipid peroxidation, a key process responsible for membrane damage and loss of cellular integrity [25].
- **Enhancement of endogenous antioxidant systems:** The plant extract has been shown to upregulate critical antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These enzymes play vital roles in detoxifying reactive intermediates and maintaining intracellular redox balance [26].
- **Activation of the Nrf2 signaling pathway:** Silymarin promotes nuclear translocation of Nrf2 (nuclear factor erythroid 2–related factor 2), leading to increased expression of antioxidant response element (ARE)-regulated genes involved in cellular defense mechanisms [27].

5.2 In Vitro Antioxidant Assays

The antioxidant capacity of *Silybum marianum* extracts and isolated compounds has been evaluated using various standardized in vitro assays:

- **DPPH radical scavenging assay:** Demonstrates dose-dependent radical scavenging activity.
- **ABTS assay:** Measures the ability to neutralize ABTS•+ radicals, confirming broad-spectrum antioxidant potential.
- **FRAP assay:** Assesses ferric reducing antioxidant power, reflecting electron-donating capacity.
- **ORAC assay:** Evaluates oxygen radical absorbance capacity, indicating protection against peroxyl radicals.
- **Total phenolic and flavonoid content estimation:** Correlates high phenolic content with strong antioxidant activity [28].

These assays collectively confirm the strong redox-modulating capacity of the plant's seed extracts.

5.3 In Vivo Evidence

Experimental animal studies further substantiate the antioxidant effects of *Silybum marianum*. Administration of silymarin has been associated with:

- **Reduction in malondialdehyde (MDA) levels,** a marker of lipid peroxidation.
- **Increased glutathione (GSH) levels,** enhancing intracellular antioxidant defense.
- **Protection against oxidative liver damage** induced by toxins such as carbon tetrachloride and alcohol.

Together, these findings highlight the significant antioxidant potential of *Silybum marianum*, supporting its therapeutic application in oxidative stress-related disorders [29].

Table 3: Summary of Antioxidant Studies of *Silybum marianum* [30]

S. No.	Extract/Compound	Experimental Model	Assay/Marker Used	Key Findings
1	Seed extract (ethanolic)	In vitro	DPPH assay	Strong dose-dependent radical scavenging activity
2	Seed extract (methanolic)	In vitro	ABTS assay	Significant ABTS•+ inhibition
3	Silymarin	In vitro	FRAP assay	High ferric reducing antioxidant power
4	Silibinin	In vitro	ORAC assay	Effective peroxyl radical scavenging
5	Seed extract	In vitro	Total phenolic content (TPC)	High phenolic concentration correlated with antioxidant activity
6	Seed extract	In vitro	Total flavonoid content (TFC)	Strong correlation with radical scavenging capacity
7	Silymarin	Rat model (CCl_4-induced toxicity)	MDA levels	Significant reduction in lipid peroxidation

S. No.	Extract/Compound	Experimental Model	Assay/Marker Used	Key Findings
8	Silibinin	Rat liver injury model	GSH levels	Increased glutathione concentration
9	Seed extract	Alcohol-induced oxidative stress (rats)	SOD activity	Elevated superoxide dismutase levels
10	Silymarin	Hepatotoxicity model	CAT activity	Enhanced catalase activity
11	Silibinin	Cell culture (hepatocytes)	GPx activity	Increased glutathione peroxidase activity
12	Seed extract	In vitro	Lipid peroxidation assay	Inhibited membrane lipid oxidation
13	Silymarin	Diabetic rat model	Oxidative stress biomarkers	Reduced systemic oxidative markers
14	Silibinin	Neuroprotective model	ROS measurement	Decreased intracellular ROS production
15	Standardized extract	Animal model	Nrf2 activation	Upregulated antioxidant gene expression

6. Anti-Inflammatory Activity

The anti-inflammatory effect of Silybum marianum has been closely associated with the effect of blocking important molecular pathways of the inflammatory signal. The flavonolignan complex silymarin targets a large number of transcription factors, cytokines, enzymes, and intracellular kinases involved in chronic inflammation [31].

6.1 Molecular Mechanisms

The silibinin and silymarin bear anti-inflammatory activity, and the mechanism by which they do this is by preventing the NF-κB signaling pathway, a key mediator of inflammatory gene expression. Silyminarin inhibits the transcription of pro-inflammatory mediators by inhibiting the nuclear translocation of NF- κB. This results in cytokines (tumor necrosis factor-alpha (TNF- 7), interleukin-1 beta (IL-1 7) and interleukin-6 (IL-6) down regulation which are vital in acute and chronic inflammatory reactions [32].

Also, silymarin inhibits the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) reducing the synthesis of prostaglandins and nitric oxide, which play a role in causing inflammation and tissue injury. Further to the regulatory effect it has on inflammatory cascades, it also regulates mitogen-activated protein kinase (MAPK) pathways, such as ERK, JNK, and p38 [33].

6.2 In Vitro Studies

In vitro studies that have been conducted on the models of lipopolysaccharide (LPS)-induced macrophages have revealed that silymarin has a significant inhibitory effect on the release of inflammatory cytokines. Cytokine assays show that there is a decrease in the secretion of TNF-alpham, IL-6, and IL-1 beta. Besides, silymarin treatment also reduces the production of nitric oxide, inhibiting the expression of iNOS, which indicates its ability to mitigate the effects of macrophage-mediated inflammatory reactions [34].

6.3 In Vivo Studies

These are further supported by animal research. Silymamarin has anti-inflammatory effects as the edema formation in the carrageenan induced paw edema model is reduced significantly with its administration [35]. The models of chronic inflammation have been associated with lower infiltration levels of the inflammatory cells and lower levels of serums of the inflammatory biomarkers. All these findings confirm that Silybum marianum has a strong anti-inflammatory effect on experimental systems [36].

7. Therapeutic Applications

The broad pharmacological profile of Silybum marianum extends beyond its traditional use in liver disorders. Owing to its potent antioxidant, anti-inflammatory, and cytoprotective properties, the plant has demonstrated therapeutic relevance in multiple systemic conditions [37].

7.1 Hepatoprotective Activity

The most widely reported application of Silybum marianum is its hepatoprotective effect. Silymarin safeguards the hepatocytes against liver toxicity due to carbon tetrachloride, alcohol, paracetamol, and other environmental toxin-induced injuries. Mechanistically, it stabilizes cellular membranes, prevents lipid peroxidation, increases protein synthesis and stimulates liver regeneration. Clinical research has shown good clinical effects in the diseases including viral hepatitis, alcoholic liver disease, non- alcoholic fatty liver disease (NAFLD), and cirrhosis. Its clinically relevant parameter lacks its capacity to lower serum transaminases and enhance liver function parameters [38].

7.2 Metabolic Disorders

There is emerging evidence that Silybum marianum has positive influences in the metabolic disorder. Its anti-diabetic effect is explained by the elevated insulin sensitivity, decreased oxidative stress, and adjustment of the inflammatory pathways. Moreover, silymarin also has lipid-lowering effects with a reduction in the total cholesterol and triglycerides, as well as low-density lipoprotein (LDL) and an increase in high-density lipoprotein (HDL), which contributes to maintaining metabolic homeostasis [39].

7.3 Neuroprotective Effects

The neuroprotective effects of silymarin are associated with the fact that the compound suppresses neuroinflammation and oxidative stress in the central nervous system. The experimental models point to reduced neuronal damage, lesser inflammatory cytokines expression, and preventive action against oxidative neuronal damage that may have some clinical value in neurodegenerative diseases [40].

7.4 Cardioprotective and Anticancer Potential

The anti-atherogenic effect of Silybum marianum is due to the decrease in the oxidative stress and the inflammatory mediators of vascular injury. Moreover, silymarin has been demonstrated to have cancer research potential, as it can regulate cell cycle advancement, cause apoptosis, and stop the proliferation of tumor cells, which is why silymarin may be used as a supplementary treatment [41].

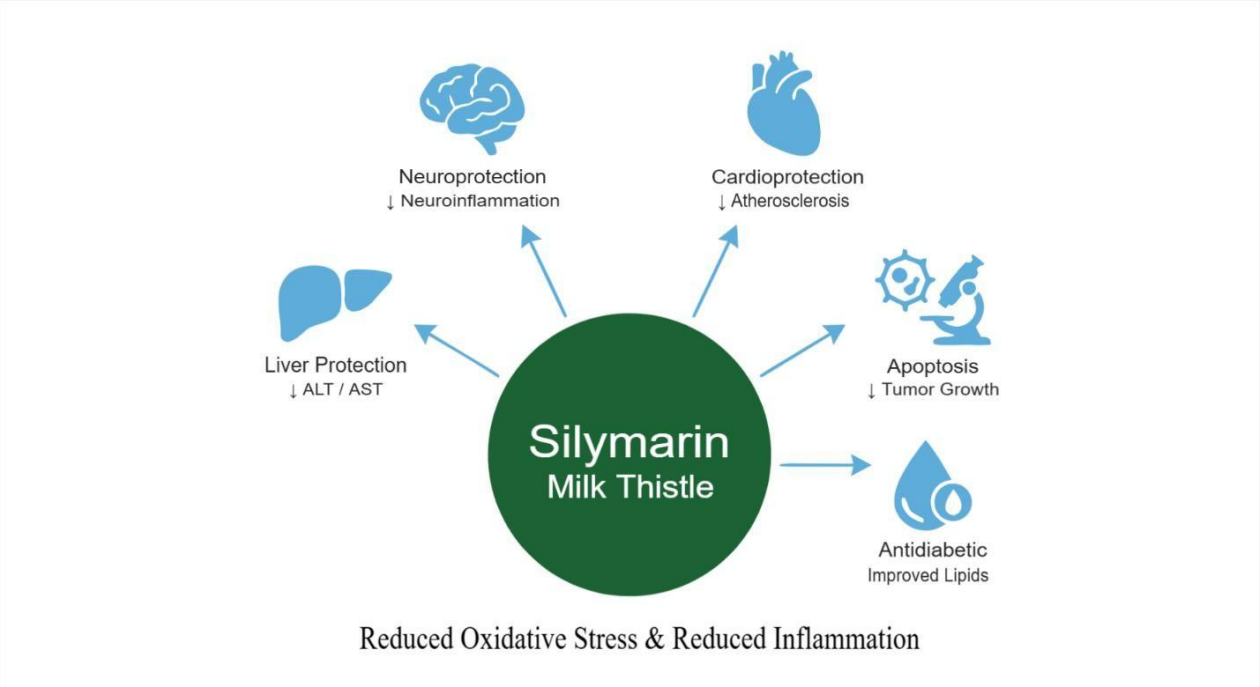

Figure 3: Therapeutic Applications of *Silybum marianum* in Oxidative and Inflammatory Disorders [42]

8. Formulation Approaches and Bioavailability Enhancement

Silybum marianum has drawbacks associated with low oral bioavailability and low water solubility of the major bioactive complex of silymarin in spite of its high therapeutic potential. The flavonolignans are lipophilic and have a poor gastrointestinal absorption with a high metabolism and first pass elimination leading to low systemic availability. In order to address these pharmacokinetic limitations, a number of sophisticated formulation methods have been formulated to improve solubility, stability and treatment efficacies [43].

Phytoseme technology can be seen as one of the most prosperous techniques. Under this system, silymarin is adsorbed on phospholipids (usually phosphatidylcholine), which results in a lipid-compatible molecular complex, thereby enhancing the permeability and absorption of cells in the membrane. Phytosomal formulations have proven to be far much more bio-available than the traditional extracts and are extensively utilized in the trade [44].

Silymarin is delivered by liposomal delivery systems that help to prevent its degradation and provide targeted delivery of silymarin to the body of the animal. Liposomes enhance the solubility and extend the circulation time increasing efficacy of therapeutic effect [45].

Formulations based on nanoparticles such as polymeric nanoparticles and solid lipid nanoparticles offer better surface area, controlled release and improved intestinal absorption. These systems also lead to improved distribution of tissues and prolonged pharmacological effect.

The other approach to enhance dissolution rate is solid dispersions where silymarin is dispersed in hydrophilic dispersants to enhance solubility and absorption. Together, these formulation developments have an enormous effect on the clinical applicability of Silybum marianum in that they help to overcome inherent bioavailability issues and optimize the therapeutic performance of this compound [46].

9. Safety, Toxicity and Clinical Evidence

Silybum marianum is considered to be safe (GRAS) when administered at therapeutic effective doses. There has been a broad safety margin and none of the experimentally tested models exhibit acute or chronic toxicity. The extract of the plant and its standardized silymarin extracts are well tolerated and can be used even in long-term therapy, which helps to propose their applicability to chronic diseases (liver disorders, metabolic diseases, etc.) [47].

The effects are rarely adverse and are mild in character. Side effects are mostly reported to include gastrointestinal disturbances including nausea, bloating, mild diarrhea, and dyspepsia which are short-lived. Cases of allergic reactions have also been reported, especially among the sensitive group of people to plants that belong to the Asteraceae family. The reactions are however uncommon and tend to be self-limiting [48].

The possible drug interactions should be taken into consideration, and it is possible that silymarin will affect the activities of cytochrome P450 enzymes and drug transporters, which can change the metabolism of some drugs. It has been proposed to interact with anticoagulants, antidiabetic agents and chemotherapeutic agents; however, clinically significant interactions are still in the relative rarity and need further exploration [49].

Silymarin has demonstrated improvement in liver enzyme levels and oxidative stress markers in clinical trials of silymamarin in liver diseases, such as hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease. Further researches point to positive effects in glycemic regulation and biomarkers of inflammation. Although the overall clinical evidence is very encouraging, dosage, formulation and study design variability highlights the importance of large well-designed randomized controlled trials to determine clear therapeutic efficacy and uniform treatment protocols [50].

10. Future Perspectives

Despite the proven significant antioxidant and anti-inflammatory properties of Silybum marianum, there are a number of issues that need to be considered to streamline its application in the clinic. Extract standardization is one of the main priorities. The difference in the cultivation conditions, harvesting procedures, extraction procedures, and the procedure of formulation can considerably change the concentration of bioactive flavonolignans. The standardized extraction procedures and determination of specific silibinin concentration in the markers, especially its content, is necessary to guarantee consistency of batches, reproducibility, and regulatory acceptability [51].

The other vital area is concerned with the large-scale randomized controlled clinical trial conduct. Although several preclinical trials and small clinical trials show therapeutic potential, large multicenter trials with normal dosages and clearly defined endpoints need to be conducted to establish efficacy on a wide variety of patient populations. These studies would enhance the evidence base and facilitate the stipulation of formal directives on the treatment [52].

There is also a need to further the study of the molecular pathways. Much more insight into silymarin-modulated signaling networks can be detected by advanced omics technologies, such as transcriptomics, proteomics, and metabolomics. Knowledge of its interactions with redox sensitive transcriptional regulators, inflammatory mediators and other metabolic regulators could provide further therapeutic opportunities [53].

Lastly, further progress in more advanced delivery systems, including nanocarriers, targeted liposomal systems, and sustained-release formulations will be essential in maximizing bioavailability and tissue specific delivery. The combination of these innovations can make Silybum marianum a scientifically proven and clinically dependable phytopharmaceutical to treat oxidative and inflammatory disorders [54].

11. Conclusion

Silybum marianum is a phytochemically rich medicinal plant characterized by a high concentration of flavonolignans collectively known as silymarin. These bioactive constituents, particularly silibinin, confer potent antioxidant and anti-inflammatory properties through multifaceted molecular mechanisms. By scavenging reactive oxygen species, enhancing endogenous antioxidant defenses, and modulating key inflammatory pathways such as NF-κB, MAPK, COX-2, and cytokine signaling cascades, *Silybum marianum* demonstrates significant cytoprotective and regulatory effects across various biological systems.

Substantial preclinical and emerging clinical evidence supports its therapeutic relevance, especially in liver disorders, metabolic diseases, neuroinflammation, and cardiovascular conditions. Its dual ability to regulate oxidative stress and inflammatory responses positions it as a multifunctional phytotherapeutic agent with systems-level activity rather than a single-target intervention. Advances in formulation strategies, including phytosomes and nanoparticle-based delivery systems, have further enhanced its pharmacokinetic profile and expanded its clinical applicability.

Despite promising findings, challenges remain regarding extract standardization, optimized dosing strategies, and the need for large-scale, well-designed clinical trials to confirm long-term safety and efficacy. Addressing these gaps will be essential for integrating *Silybum marianum* into evidence-based medical practice. Overall, the plant represents a promising candidate for pharmaceutical development and future translational research in oxidative and inflammatory disease management.

Acknowledgement: Nil

Conflict of Interest: Nil

References:

1. Leyane TS, Jere SW, Houreld NN. Oxidative stress in ageing and chronic degenerative pathologies: molecular mechanisms involved in counteracting oxidative stress and chronic inflammation. International journal of molecular sciences. 2022 Jun 30;23(13):7273.
2. Abdulkhaleq LA, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MN. The crucial roles of inflammatory mediators in inflammation: A review. Veterinary world. 2018 May 15;11(5):627.
3. Liu Y, Yang C, Zhang J, Ihsan A, Ares I, Martínez M, Lopez-Torres B, Martínez-Larrañaga MR, Wang X, Anadón A, Martínez MA. Recent progress in adverse events of carboxylic acid non-steroidal anti-inflammatory drugs (CBA-NSAIDs) and their association with the metabolism: the consequences on mitochondrial dysfunction and oxidative stress, and prevention with natural plant extracts. Expert Opinion on Drug Metabolism & Toxicology. 2024 Aug 2;20(8):765-85.
4. Ball KR, Kowdley KV. A review of Silybum marianum (milk thistle) as a treatment for alcoholic liver disease. Journal of Clinical Gastroenterology. 2005 Jul 1;39(6):520-8.
5. Ardelean ML, Cristina RT, Folescu M, Muselin F, Doma AO, Cocoș D, Dumitrescu E. Phytochemical profile and pharmacological applications of Silybum marianum (L.). Romanian Journal of Veterinary Sciences. 2025;58:4.
6. Wang X, Zhang Z, Wu SC. Health benefits of Silybum marianum: Phytochemistry, pharmacology, and applications. Journal of agricultural and food chemistry. 2020 Oct 13;68(42):11644-64.
7. Tiwari R, Latheef SK, Ahmed I, Iqbal HM, Bule MH, Dhama K, Samad HA, Karthik K, Alagawany M, El-Hack ME, Yatoo MI. Herbal immunomodulators-a remedial panacea for designing and developing effective drugs and medicines: current scenario and future prospects. Current drug metabolism. 2018 Mar 1;19(3):264-301.
8. Almasoudi HH, Saeed Jan M, Nahari MH, Alhazmi AY, Binshaya AS, Abdulaziz O, Mahnashi MH, Ibrar M, Zafar R, Sadiq A. Phenolic phytochemistry, in vitro, in silico, in vivo, and mechanistic anti-inflammatory and antioxidant evaluations of Habenaria digitata. Frontiers in pharmacology. 2024 Feb 29;15:1346526.
9. Nussbaumer-Streit B, Klerings I, Dobrescu AI, Persad E, Stevens A, Garritty C, Kamel C, Affengruber L, King VJ, Gartlehner G. Excluding non-English publications from evidence-syntheses did not change conclusions: a meta-epidemiological study. Journal of clinical epidemiology. 2020 Feb 1;118:42-54.
10. 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.
11. Flora K, Hahn M, Rosen H, Benner K. Milk thistle (Silybum marianum) for the therapy of liver disease. The American journal of gastroenterology. 1998 Feb 1;93(2):139-43.
12. Yatoo MI, Gopalakrishnan A, Saxena A, Parray OR, Tufani NA, Chakraborty S, Tiwari R, Dhama K, Iqbal HM. Anti-inflammatory drugs and herbs with special emphasis on herbal medicines for countering inflammatory diseases and disorders-a review. Recent patents on inflammation & allergy drug discovery. 2018 May 1;12(1):39-58.
13. Marceddu R, Dinolfo L, Carrubba A, Sarno M, Di Miceli G. Milk thistle (Silybum marianum L.) as a novel multipurpose crop for agriculture in marginal environments: A review. Agronomy. 2022 Mar;12(3):729.
14. Ncube B, Van Staden J. Tilting plant metabolism for improved metabolite biosynthesis and enhanced human benefit. Molecules. 2015 Jul 13;20(7):12698-731.
15. Lee JI, Hsu BH, Wu D, Barrett JS. Separation and characterization of silybin, isosilybin, silydianin and silychristin in milk thistle extract by liquid chromatography–electrospray tandem mass spectrometry. Journal of Chromatography A. 2006 May 26;1116(1-2):57-68.

16. Surai PF. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. Antioxidants. 2015 Mar 20;4(1):204-47.

17. Romanucci V, Di Fabio G, Zarrelli A. A new class of synthetic flavonolignan-like dimers: Still few molecules, but with attractive properties. Molecules. 2018 Dec 29;24(1):108.

18. Ahmad U, Faiyazuddin M, Hussain MT, Ahmad S, M Alshammari T, Shakeel F. Silymarin: an insight to its formulation and analytical prospects. Acta physiologiae plantarum. 2015 Nov;37(11):253.

19. Lombard KA, Geoffriau E, Peffley E. Flavonoid quantification in onion by spectrophotometric and high performance liquid chromatography analysis. HortScience. 2002 Jul 1;37(4):682-5.

20. Stratil P, Klejdus B, Kubáň V. Determination of total content of phenolic compounds and their antioxidant activity in vegetables evaluation of spectrophotometric methods. Journal of agricultural and food chemistry. 2006 Feb 8;54(3):607-16.

21. AbouZid S, Ahmed OM. Silymarin flavonolignans: Structure–activity relationship and biosynthesis. Studies in natural products chemistry. 2013 Jan 1;40:469-84.

22. Javeed A, Ahmed M, Sajid AR, Sikandar A, Aslam M, Hassan TU, Dogar S, Nazir Z, Ji M, Li C. Comparative assessment of phytoconstituents, antioxidant activity and chemical analysis of different parts of milk thistle silybum marianum L. Molecules. 2022 Apr 20;27(9):2641.

23. Abdullaev AA, Inamjanov DR, Abduazimova DS, Omonturdiyev SZ, Gayibov UG, Gayibova SN. Sílybum Mariánum's impact on physiological alterations and oxidative stress in diabetic rats. Biomedical and Pharmacology Journal. 2024 Jun 25;17(2):1291-300.

24. Anthony KP, Saleh MA. Free radical scavenging and antioxidant activities of silymarin components. Antioxidants. 2013 Dec 10;2(4):398-407.

25. Abd El HA. Lipid peroxidation end-products as a key of oxidative stress: effect of antioxidant on their production and transfer of free radicals. InLipid peroxidation 2012 Aug 29. IntechOpen.

26. Fujita M, Hasanuzzaman M. Approaches to enhancing antioxidant defense in plants. Antioxidants. 2022 May 8;11(5):925.

27. Keshk WA, Zahran SM, Katary MA, Ali DA. Modulatory effect of silymarin on nuclear factor-erythroid-2-related factor 2 regulated redox status, nuclear factor-κB mediated inflammation and apoptosis in experimental gastric ulcer. Chemico-biological interactions. 2017 Aug 1;273:266-72.

28. Thaipong K, Boonprakob U, Crosby K, Cisneros-Zevallos L, Byrne DH. Comparison of ABTS, DPPH, FRAP, and ORAC assays for estimating antioxidant activity from guava fruit extracts. Journal of food composition and analysis. 2006 Sep 1;19(6-7):669-75.

29. Bouaïcha N, Maatouk I. Microcystin-LR and nodularin induce intracellular glutathione alteration, reactive oxygen species production and lipid peroxidation in primary cultured rat hepatocytes. Toxicology letters. 2004 Mar 14;148(1-2):53-63.

30. Ahmad N, Abbasi BH, Fazal H. Evaluation of antioxidant activity and its association with plant development in Silybum marianum L. Industrial Crops and Products. 2013 Aug 1;49:164-8.

31. Akhtar MT, Saadia M, Irfan MI. Silybum marianum extract as a next-generation multifunctional therapeutic: potent antioxidant, antidiabetic, antimicrobial, anti-inflammatory, and anti-biofilm activities validated by phytochemical profiling and molecular docking. 3 Biotech. 2026 Jan;16(1):26.

32. Zhao Y, Zhou Y, Gong T, Liu Z, Yang W, Xiong Y, Xiao D, Cifuentes A, Ibáñez E, Lu W. The clinical anti-inflammatory effects and underlying mechanisms of silymarin. IScience. 2024 Nov 15;27(11).

33. Zhao J, Sharma Y, Agarwal R. Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradecanoylphorbol 13-acetate–caused modulation of antioxidant and inflammatory enzymes, and cyclooxygenase 2 and interleukin-1α expression in SENCAR mouse epidermis: Implications in the prevention of stage I tumor promotion. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center. 1999 Dec;26(4):321-33.

34. Kim EJ, Lee MY, Jeon YJ. Silymarin inhibits morphological changes in LPS-stimulated macrophages by blocking NF-κB pathway. The Korean journal of physiology & pharmacology: official journal of the Korean Physiological Society and the Korean Society of Pharmacology. 2015 May;19(3):211-8.

35. De La Puerta R, Martinez E, Bravo L, Ahumada MC. Effect of silymarin on different acute inflammation models and on leukocyte migration. Journal of Pharmacy and Pharmacology. 1996 Sep;48(9):968-70.

36. Bellik Y, Boukraâ L, Alzahrani HA, Bakhotmah BA, Abdellah F, Hammoudi SM, Iguer-Ouada M. Molecular mechanism underlying anti-inflammatory and anti-allergic activities of phytochemicals: an update. Molecules. 2012 Dec 27;18(1):322-53.

37. Abenavoli L, Izzo AA, Milić N, Cicala C, Santini A, Capasso R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytotherapy research. 2018 Nov;32(11):2202-13.

38. Shivaprasad HN, Gharabude V, Thimmannagari S, Krishnamani M, Soni G. Silymarin: A Historical and Scientific Exploration of its Medicinal Properties. Pharmacognosy Reviews. 2025 Jan 1;19(37).

39. Hüttl M, Markova I, Miklankova D, Zapletalova I, Poruba M, Racova Z, Vecera R, Malinska H. The beneficial additive effect of silymarin in metformin therapy of liver steatosis in a pre-diabetic model. Pharmaceutics. 2021 Dec 27;14(1):45.

40. Yardım A, Kucukler S, Özdemir S, Çomaklı S, Caglayan C, Kandemir FM, Çelik H. Silymarin alleviates docetaxel-induced central and peripheral neurotoxicity by reducing oxidative stress, inflammation and apoptosis in rats. Gene. 2021 Feb 15;769:145239.

41. Markova I, Malinska H, Hüttl M, Miklankova D, Oliyarnyk O, Poruba M, Racova Z, Kazdova L, Večeřa R. The combination of atorvastatin with silymarin enhances hypolipidemic, antioxidant and anti-inflammatory effects in a rat model of metabolic syndrome. Physiological Research. 2021 Jan 14;70(1):33.

42. Eita AA. Milk thistle (Silybum marianum (L.) Gaertn.): An overview about its pharmacology and medicinal uses with an emphasis on oral diseases. Journal of oral biosciences. 2022 Mar 1;64(1):71-6.

43. Mihailović V, Srećković N, Popović-Djordjević JB. Silybin and Silymarin: Phytochemistry, bioactivity, and pharmacology. InHandbook of dietary flavonoids 2023 Sep 1 (pp. 1-45). Cham: Springer International Publishing.

44. Ramadan MF. Chemistry, Functionality, and Techno-Applications of Pheno-phospholipids. InPheno-phospholipids and Lipo-phenolics: Novel Structured Antioxidants 2021 Feb 16 (pp. 9-33). Cham: Springer International Publishing.

45. Dixit N, Baboota S, Kohli K, Ahmad S, Ali J. Silymarin: A review of pharmacological aspects and bioavailability enhancement approaches. Indian journal of pharmacology. 2007 Jul 1;39(4):172-9.

46. Di Costanzo A, Angelico R. Formulation strategies for enhancing the bioavailability of silymarin: the state of the art. Molecules. 2019 Jun 7;24(11):2155.

47. Fanoudi S, Alavi MS, Karimi G, Hosseinzadeh H. Milk thistle (Silybum Marianum) as an antidote or a protective agent against natural or chemical toxicities: a review. Drug and chemical toxicology. 2020 May 3;43(3):240-54.

48. Jani RK. Gastrointestinal tract and digestion challenges in chronic diseases and applications of functional foods and nutraceuticals. InMolecular Mechanisms of Action of Functional Foods and Nutraceuticals for Chronic Diseases 2023 Apr 19 (pp. 307-364). CRC Press.

49. Doehmer J, Tewes B, Klein KU, Gritzko K, Muschick H, Mengs U. Assessment of drug–drug interaction for silymarin. Toxicology in vitro. 2008 Apr 1;22(3):610-7.

50. Mirzaei E, Sabetian G, Masjedi M, Heidari R, Mirjalili M, Dehghanian A, Vazin A. The effect of silymarin on liver enzymes and antioxidant status in trauma patients in the intensive care unit: a randomized double blinded placebo-controlled clinical trial. Clinical and Experimental Hepatology. 2021 Jun 22;7(2):149-55.

51. Ramesh MM, Shankar NS, Venkatappa AH. Driving/Critical Factors Considered During Extraction to Obtain Bioactive Enriched Extracts. Pharmacognosy Reviews. 2024 Jan 1;18(35).

52. James S, Rao SV, Granger CB. Registry-based randomized clinical trials—a new clinical trial paradigm. Nature Reviews Cardiology. 2015 May;12(5):312-6.

53. Lei Y, Wang K, Deng L, Chen Y, Nice EC, Huang C. Redox regulation of inflammation: old elements, a new story. Medicinal research reviews. 2015 Mar;35(2):306-40.

54. Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike UG. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023 Jun 1;9(6).