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Review Paper

Milk Thistle (*Silybum Mariyam*) As an Antidote & Protective Agent Against Natural or Chemical Toxicity

Sapna Shinde*, Priyanka Nemane

Rajesh Bhaiyya Tope College of Pharmacy Nipani-bhalgoan Chhatrapati sambhaji nagar –431006.

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ABSTRACT

Background: *Silybum marianum* (L.) Gaertn., commonly designated milk thistle, is an annual or biennial herb of the family Asteraceae that has accumulated over two millennia of ethnopharmacological use as a hepatoprotective agent. Its principal bioactive complex, silymarin—a polyphenolic mixture of flavonolignans including silybin A, silybin B, isosilybin A, isosilybin B, silychristin, and silydianin—exhibits a broad pharmacological spectrum that extends well beyond classical hepatology. **Objectives:** This review consolidates current knowledge regarding the botanical classification, phytochemical composition, pharmacokinetics, molecular mechanisms of action, clinical evidence, and safety profile of *S. marianum*, with emphasis on its roles as a hepatoprotectant, antioxidant, anti-inflammatory, anticancer, antidiabetic, and cardioprotective agent. **Methods:** A systematic literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar using the keywords silymarin, *Silybum marianum*, silybin, hepatoprotection, antioxidant, and milk thistle, covering publications from 1980 to 2025. **Results:** Silymarin modulates hepatic injury through multiple interdependent pathways: direct scavenging of reactive oxygen species, suppression of NF- κ B-mediated inflammatory signalling, inhibition of transforming growth factor- β 1-driven hepatic stellate cell activation, induction of hepatocyte regeneration, and modulation of bile salt transport. Beyond the liver, emerging preclinical and clinical data support its utility in colorectal, prostate, and breast cancers; type 2 diabetes mellitus; hyperlipidaemia; and neurodegenerative conditions. Bioavailability of standard oral preparations remains a pharmacokinetic limitation, prompting development of phytosome complexes, nanosuspensions, and self-emulsifying drug delivery systems that significantly enhance systemic exposure. The safety profile is favourable, with adverse events generally confined to mild, transient gastrointestinal disturbance at therapeutic doses. **Conclusion:** *S. marianum* and its constituent flavonolignans represent

*Corresponding Author: Sapna Shinde

Address: Rajesh Bhaiyya Tope College of Pharmacy Nipani-bhalgoan Chhatrapati sambhaji nagar –431006

Email ✉: shindesapna867@gmail.com

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a clinically relevant, mechanistically diverse therapeutic platform. Rigorous randomised controlled trials utilising standardised silymarin preparations, validated biomarkers, and adequate sample sizes are urgently required to translate extensive preclinical promise into definitive clinical guidance.

INTRODUCTION

Silybum marianum (L.) Gaertn., a robust annual or biennial member of the tribe Cardueae within the family Asteraceae, occupies a singular position in the history of phytomedicine. Written references to its medicinal application can be traced to the first century CE when Dioscorides and Pliny the Elder independently described preparations of the plant for the management of hepatic complaints.^[1,2] Over subsequent centuries, its use propagated throughout Mediterranean, Central Asian, and South Asian healing traditions, culminating in its contemporary designation as one of the best-selling botanical supplements worldwide.

The therapeutic identity of *S. marianum* is inextricably linked to silymarin, a standardised mixture of structurally related flavonolignans and one chalcone predominantly concentrated in the pericarp of the achene (commonly, though imprecisely, termed the 'seed').^[3,4] Among the constituents of silymarin, silybin (comprising diastereomers silybin A and silybin B) is quantitatively dominant, contributing approximately 50–70% of total flavonolignan content, and is also pharmacologically the most potent.^[5]

The global burden of liver disease is substantial: chronic hepatitis B and C, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD)/metabolic-associated fatty liver disease (MAFLD) collectively affect hundreds of millions of individuals worldwide, placing enormous strain on healthcare systems.^[6] In this context, silymarin has attracted sustained scientific interest as an

adjunctive hepatoprotective therapy, supported by an increasingly detailed mechanistic rationale that encompasses antioxidant, anti-inflammatory, antifibrotic, and pro-regenerative activities.^[7]

Beyond hepatology, compelling preclinical evidence now supports the relevance of silymarin in oncology, metabolic diseases, dermatology, and neuroprotection. However, translation from bench to bedside has been hampered by the inherently poor aqueous solubility and low oral bioavailability of the constituent flavonolignans, the heterogeneity of commercial preparations, and a paucity of high-quality randomised controlled trials (RCTs).^[8,9]

The present review aims to provide an integrated, evidence-based synthesis of the botanical, phytochemical, pharmacokinetic, mechanistic, and clinical dimensions of *S. marianum*, drawing on original research articles, systematic reviews, and meta-analyses published through 2025. We also examine advances in novel delivery technologies designed to overcome bioavailability limitations and outline priority areas for future clinical investigation.^[10]

2. Botanical Description and Taxonomy

2.1 Systematic Classification

Silybum marianum occupies the following taxonomic hierarchy: Kingdom Plantae; Phylum Tracheophyta; Class Magnoliopsida; Order Asterales; Family Asteraceae; Tribe Cardueae; Genus *Silybum* Adans.; Species *S. marianum* (L.) Gaertn. The binomial was established by the German botanist Joseph Gaertner in 1791 on the basis of Carolus Linnaeus's original description.



Table 1. Taxonomic classification of *Silybum marianum*.

Taxonomic Rank	Classification
Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Asterales
Family	Asteraceae
Genus	<i>Silybum</i> Adans.
Species	<i>S. marianum</i> (L.) Gaertn.

2.2 Morphological Features

S. marianum is a stout, erect herb attaining heights of 1.0–2.5 m. In its first growing season it produces an extensive basal rosette of deeply lobed, glossy green leaves displaying conspicuous white to silver venation—a visual characteristic that, according to Christian legend, originated from the Virgin Mary's milk spilling onto the plant's foliage, hence the vernacular name 'milk thistle' and the species epithet *marianum*.^[11] Mature leaves are coriaceous with undulate, spine-tipped margins. Stems are hollow, ribbed, and lactiferous. Inflorescences are solitary capitula, 4–8 cm in diameter, bearing tubular florets of purple to reddish-violet coloration enclosed by coriaceous, spiny phyllaries. Fruits are achenes, brown to black, obliquely obovoid (6–7 × 3 mm), topped by a prominent pappus of fused, feathery bristles that facilitates anemochorous dispersal.

2.3 Geographic Distribution and Ecology

The natural range of *S. marianum* encompasses the Mediterranean basin, the Canary Islands, the Near and Middle East, Central Asia, and the western Himalayan foothills, where it grows between 250 m and 2,400 m altitude on disturbed, rocky, or calcareous soils.^[12] As a ruderal competitive, drought-tolerant ruderal, it has naturalised across temperate and subtropical zones globally—North

and South America, Southern Africa, and Southern Australia—often appearing in disturbed habitats, roadsides, and agricultural margins. Commercial cultivation for silymarin extraction is concentrated in Hungary, Poland, Germany, Iran, China, and India, with the sub-Himalayan regions of Jammu, Kashmir, and Punjab representing important South Asian production centres.^[13]

2.4 Traditional Uses and Ethnopharmacological Significance

Ethnobotanical records document uses of virtually all plant parts. Young leaves and stems have been consumed as vegetables and salads in Mediterranean cultures. Roots, flowers, and leaves were prepared as decoctions for jaundice, gallbladder inflammation, hepatic congestion, and splenomegaly.^[14] In South Asian traditions, the plant has been used for managing menstrual irregularities, galactagogue purposes, and skin disorders. Contemporary ethnobotanical surveys in the Kashmir Valley and Punjab corroborate the plant's sustained relevance in local herbal practice, particularly for hepatic and biliary complaints.^[15]

3. Phytochemical Composition

3.1 Silymarin: Definition and Composition



The term 'silymarin' refers to a standardised lipophilic extract of *S. marianum* pericarp enriched in polyphenolic flavonolignans that arise biosynthetically through oxidative coupling between the flavonoid taxifolin and the lignan coniferyl alcohol.^[16] Seven major flavonolignans have been characterised: silybin A (SbA), silybin B (SbB), isosilybin A (ISbA), isosilybin B (ISbB), silychristin (SC), isosilychristin (ISC), and silydianin (SD). A flavonoid aglycone, 2,3-dehydrosilybin, and a chalcone, 5-methoxy-hydnocarpin D, are minor components. The relative abundance of individual flavonolignans varies substantially with geographic origin, growing conditions, harvest stage, and processing methodology.^[17]

Silybin, the predominant constituent (50–70% of silymarin), exists as an approximately equimolar mixture of the SbA and SbB diastereomers that differ in the configuration at C-7 and C-8 of the dihydrobenzofuran ring. SbA exhibits greater antioxidant activity than SbB in most in vitro assays, whereas SbB demonstrates higher aqueous solubility.^[18] Commercial silymarin preparations are typically standardised to contain 70–80% total flavonolignans by UV spectrophotometry (PhEur or USP method), though isotope ratio mass spectrometry (IRMS) and validated HPLC methods provide superior specificity.^[19]

3.2 Other Phytochemicals

Beyond silymarin, *S. marianum* contains fixed oils (20–30% of seed dry weight) rich in linoleic acid (60%), oleic acid (30%), and palmitic acid; sterols including β -sitosterol and stigmasterol; tocopherols; biogenic amines (tyramine, histamine); quercetin and kaempferol glycosides; tannins; alkaloids (leonurine); and protein (25–30% of seed weight with favourable amino acid profile).^[20] Mucilaginous polysaccharides with immunomodulatory properties have also been isolated from the seeds.^[21]

3.3 Analytical Methods for Quality Control

Quality control of milk thistle-derived products is critical given documented variability in commercial preparations. Standard analytical platforms include thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), HPLC with UV or mass spectrometric detection, and ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS). The latter provides unequivocal structural characterisation and quantification of individual diastereomers—a capability lacking in less discriminating UV methods that measure the aggregate silymarin complex.

Molecular authentication employing DNA barcoding (ITS2 and trnH-psbA markers) and metabarcoding approaches can identify adulteration and species substitution in multi-ingredient products. Nuclear magnetic resonance (NMR) fingerprinting offers a comprehensive, non-destructive metabolomic profiling tool that complements chromatographic data.^[22]

4. Pharmacokinetics and Bioavailability

4.1 Absorption

The pharmacokinetics of silymarin flavonolignans have been extensively characterised in both healthy volunteers and hepatic disease patients. Following oral administration of the standardised extract Legalon® (140 mg silymarin per capsule), peak plasma concentrations (C_{max}) of unconjugated (free) flavonolignans are reached within 1–4 h, with SbA displaying the highest absolute bioavailability among individual constituents. However, the absolute oral bioavailability of silymarin is remarkably low—estimated at $0.45 \pm 0.28\%$ in healthy subjects—primarily attributable to poor aqueous solubility, limited intestinal permeability, and extensive pre-systemic glucuronidation and sulphation.^[23]



4.2 Distribution, Metabolism, and Excretion

After absorption, flavonolignans undergo rapid phase II conjugation (glucuronidation and sulphation) in the intestinal wall and hepatic first pass, generating circulating conjugated metabolites that predominate in plasma. Distribution follows a two-compartment model; the liver—the primary therapeutic target—achieves concentrations substantially higher than plasma through active uptake mediated by organic anion transporting polypeptides (OATPs).^[24] Stereoselective metabolism is evident: apparent clearance of SbB and isosilybin A exceeds that of SbA and isosilybin B, reflecting distinct affinity for glucuronosyltransferase isoforms. Biliary excretion of conjugates constitutes the primary elimination pathway, with renal clearance accounting for a minor fraction; mean elimination half-life ranges from 6 to 8 hours.^[25]

4.3 Novel Delivery Systems to Overcome Bioavailability Limitations

Multiple pharmaceutical strategies have been pursued to enhance silymarin bioavailability. The silybin-phosphatidylcholine complex (Siliphos®), marketed as the phytosome, enhances oral absorption 4- to 10-fold relative to standard silymarin by augmenting intestinal membrane permeability.^[26] Nanosuspensions, solid lipid nanoparticles, self-emulsifying drug delivery systems (SEDDS), and nanostructured lipid carriers (NLCs) have demonstrated promising results in preclinical settings. Co-crystallisation and salt formation techniques to alter the solid-state properties of silybin represent additional solid-dosage-form strategies. These formulation advances are anticipated to underpin future clinical trials employing more bioavailable silymarin preparations.^[27]

5. Mechanisms of Hepatoprotective Action

5.1 Antioxidant Activity

Oxidative stress is a central mediator of hepatocellular injury across virtually all aetiologies of liver disease. Silymarin counteracts oxidative damage through multiple complementary mechanisms. Directly, it functions as a chain-breaking antioxidant, quenching hydroxyl ($\bullet\text{OH}$), superoxide anion ($\text{O}_2^{\bullet-}$), and peroxy ($\text{ROO}\bullet$) radicals via hydrogen atom transfer; silybin and 2,3-dehydrosilybin demonstrate the highest radical-scavenging potency within the silymarin complex.^[28] Indirectly, silymarin upregulates the nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1) pathway, promoting transcription of cytoprotective enzymes including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), glutamate-cysteine ligase (GCL), and superoxide dismutase (SOD), thereby bolstering endogenous antioxidant capacity.^[29]

5.2 Anti-inflammatory Mechanisms

Hepatic inflammation orchestrated by activated Kupffer cells and recruited immune effectors critically drives fibrogenesis and hepatocellular loss. Silymarin suppresses this inflammatory cascade principally through inhibition of nuclear factor- κB (NF- κB) nuclear translocation, reducing transcription of pro-inflammatory mediators including TNF- α , IL-1 β , IL-6, and IL-12.^[30] Additionally, silymarin inhibits the 5-lipoxygenase pathway, attenuating leukotriene synthesis, and downregulates inducible nitric oxide synthase (iNOS) to limit nitrosative stress. Suppression of NLRP3 inflammasome assembly, demonstrated in models of non-alcoholic steatohepatitis (NASH), further curtails IL-1 β -driven hepatocellular injury.^[31]

5.3 Antifibrotic Effects

Hepatic fibrosis, the penultimate stage preceding cirrhosis, is driven principally by activated hepatic



stellate cells (HSCs) that transdifferentiate into myofibroblastic cells under stimulation by transforming growth factor- β 1 (TGF- β 1). Silybin specifically inhibits TGF- β 1 signalling through the Smad2/3 axis, reducing the transcription of collagen type I, fibronectin, and α -smooth muscle actin in activated HSCs.^[32] Silymarin also reduces hepatic expression of connective tissue growth factor (CTGF/CCN2) and tissue inhibitor of metalloproteinase-1 (TIMP-1), shifting the balance toward matrix metalloproteinase (MMP)-mediated extracellular matrix degradation.^[33]

5.4 Hepatocyte Regeneration

Stimulation of hepatocyte proliferation represents a distinctive feature of silymarin's hepatoprotective profile. Silybin activates ribonucleic acid polymerase I (RNA Pol I) in hepatocytes but not in hepatoma cell lines, enhancing ribosomal RNA synthesis and accelerating cellular regeneration—an effect that does not extend to malignant cells, where silymarin instead promotes apoptosis.^[34] Upregulation of the epidermal growth factor receptor (EGFR) signalling pathway by silybin may further contribute to regenerative capacity.

5.5 Modulation of Bile Salt Transport

Silymarin exerts choleretic effects by increasing the expression and membrane localisation of the bile salt export pump (BSEP/ABCB11) and the multidrug resistance protein 2 (MRP2/ABCC2), facilitating biliary secretion of organic anions. Inhibition of the ileal apical sodium-dependent bile acid transporter (ASBT) reduces intestinal reabsorption of cytotoxic bile acids, complementing the hepatic export mechanisms.^[35] These actions confer protection against cholestatic liver injury and form the rationale for its application in intrahepatic cholestasis of pregnancy and primary biliary cholangitis.^[36]

6. Pharmacological Activities Beyond Hepatoprotection

6.1 Anticancer Properties

6.1.1 Molecular Mechanisms

The anticancer activity of silybin is multifaceted, engaging complementary mechanisms across the hallmarks of cancer. Silybin inhibits epidermal growth factor receptor (EGFR), insulin-like growth factor type-1 receptor (IGF-1R), and vascular endothelial growth factor receptor (VEGFR) signalling; suppresses cell cycle progression by downregulating cyclin D1 and CDK4/6 while upregulating p21Waf1/Cip1 and p27Kip1; promotes intrinsic apoptosis through Bcl-2/Bax ratio alteration and cytochrome c release; inhibits topoisomerase I and II; and abrogates epithelial–mesenchymal transition (EMT) by targeting E-cadherin/vimentin and the Wnt/ β -catenin axis.^[37]

6.1.2 Prostate Cancer

Silybin reduces androgen receptor (AR) transcriptional activity and decreases serum prostate-specific antigen (PSA) levels in both androgen-sensitive and castration-resistant prostate cancer cell lines. In a phase I clinical trial, silybin-phytosome (Siliphos) demonstrated a dose-dependent reduction in PSA velocity in men with biochemically recurrent prostate cancer, with a maximum tolerated dose of 13 g/day.^[38]

6.1.3 Colorectal Cancer

Colorectal cancer (CRC) represents the second-leading cause of cancer-related mortality globally. Silymarin and silybin inhibit proliferation and induce G2/M phase arrest in HCT116 and HT29 CRC cell lines. In azoxymethane/dextran sulphate sodium (AOM/DSS) murine models of CRC, oral silymarin significantly reduced tumour multiplicity, load, and colonic expression of

cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2).^[39]

6.1.4 Breast and Ovarian Cancers

In oestrogen receptor-positive (ER+) breast cancer cells, silybin inhibits aromatase activity and blocks oestrogen receptor α (ER α) signalling, reducing proliferative responses to exogenous oestrogen. Synergistic cytotoxicity with cisplatin and doxorubicin has been documented, with silybin concurrently attenuating nephrotoxicity and cardiotoxicity—a valuable protective attribute in platinum-based regimens.^[40]

6.2 Antidiabetic and Metabolic Effects

Silymarin addresses multiple pathogenic components of type 2 diabetes mellitus (T2DM). It inhibits aldose reductase, limiting accumulation of polyols in peripheral nerves; suppresses gluconeogenic enzyme expression (PEPCK, G6Pase) in hepatocytes; enhances insulin receptor substrate-1 (IRS-1) phosphorylation and GLUT-4 translocation, improving peripheral glucose uptake; and reduces pancreatic β -cell apoptosis induced by oxidative stress.^[41] A meta-analysis of nine RCTs involving 487 patients with T2DM demonstrated that silymarin supplementation significantly reduced fasting blood glucose (FBG), glycated haemoglobin (HbA1c), and HOMA-IR scores compared with placebo, without clinically significant adverse effects.^[42]

6.3 Cardioprotective Effects

Emerging evidence supports a cardioprotective role for silymarin. In experimental models of doxorubicin-induced cardiomyopathy, silybin pretreatment reduced myocardial lipid peroxidation and preserved left ventricular ejection fraction.^[43] Silymarin inhibits LDL oxidation, suppresses foam cell formation in vascular macrophages, and reduces vascular smooth muscle cell proliferation stimulated by platelet-derived growth factor (PDGF),

mechanistically supporting its antilipidaemic and anti-atherosclerotic potential. In a randomised open clinical trial involving 14 patients with type II hyperlipidaemia, 420 mg silymarin daily for seven months reduced total cholesterol, LDL-cholesterol, and triglycerides while increasing HDL-cholesterol.^[44]

6.4 Neuroprotective Effects

Neurological applications of silymarin are an expanding research frontier. In transgenic mouse models of Alzheimer's disease, oral silymarin decreased amyloid- β (A β) plaque burden, reduced tau hyperphosphorylation, and improved spatial memory in the Morris water maze—effects attributed to inhibition of β -secretase (BACE1), suppression of neuroinflammation via NF- κ B, and Nrf2-mediated reduction of mitochondrial oxidative stress.^[45] In Parkinson's disease models, silybin protected dopaminergic neurons in the substantia nigra against 6-OHDA and MPTP-induced toxicity. A phase II clinical trial in patients with Parkinson's disease is currently exploring silymarin as neuroprotective adjunct therapy.^[46]

6.5 Dermatological Applications

Topical and oral silymarin preparations have been investigated for psoriasis, photocarcinogenesis prevention, and wound healing. The antipsoriatic effect is mediated by inhibition of leukotriene B4 synthesis, reduction of keratinocyte hyperproliferation, and improved hepatic detoxification that limits endotoxin-driven keratinocyte activation.^[47] In UV-induced murine skin carcinogenesis models, topical silybin significantly reduced tumour incidence, multiplicity, and burden, with human clinical trials of topical silybin against UV-induced epidermal damage currently ongoing.^[48]

6.6 Renal Protective Effects



Silymarin has demonstrated nephroprotective activity in cisplatin-induced and gentamicin-induced models of acute kidney injury, reducing urinary biomarkers of tubular damage (NGAL, KIM-1) and preserving histological renal architecture.^[49] This nephroprotective property is mechanistically consistent with its antioxidant and anti-inflammatory profile and provides a rationale for its co-administration with nephrotoxic chemotherapeutic regimens.^[50]

7. Clinical Evidence for Hepatic and Non-hepatic Indications

7.1 Alcoholic Liver Disease

Several RCTs have evaluated silymarin in ALD with heterogeneous results. A landmark study by Ferenci et al. reported a statistically significant improvement in survival in patients with alcoholic cirrhosis who received silymarin 420 mg/day for two years compared with placebo, particularly in Child-Pugh A patients and non-drinkers.^[28] A subsequent large multicentre RCT (SILC trial, n = 200) failed to replicate this survival benefit; however, methodological differences in patient selection, degree of hepatic decompensation, and alcohol abstinence rates limit cross-study comparison.^[29]

7.2 Non-Alcoholic Fatty Liver Disease

NAFLD/MAFLD has emerged as the most common liver disease in industrialised nations. In patients with NAFLD, silymarin at 280–420 mg/day significantly reduced serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in multiple RCTs. A prospective observational study of 179 NAFLD patients demonstrated that a 12-month regimen of silymarin combined with vitamin E reduced hepatic steatosis scores on ultrasound and improved insulin sensitivity.^[30] A 2017 meta-analysis of silymarin in chronic liver disease concluded that reductions in transaminases,

though statistically significant, were modest and of uncertain clinical relevance, underscoring the need for trials powered to hard endpoints such as liver-related mortality and fibrosis regression.^[31]

7.3 Viral Hepatitis

In chronic hepatitis C, the largest relevant clinical trial—the SyNCH trial (n = 154)—found that high-dose intravenous silybin significantly reduced HCV RNA levels over 7 days compared with placebo, suggesting direct antiviral activity through inhibition of NS5B RNA-dependent RNA polymerase.^[32] Oral silymarin has not demonstrated consistent antiviral efficacy in chronic hepatitis C patients receiving standard-of-care therapy, though its hepatoprotective and anti-inflammatory effects may still provide symptomatic benefit. For chronic hepatitis B, preclinical studies suggest inhibition of HBsAg secretion, warranting clinical investigation.^[33]

7.4 Drug-induced and Toxin-induced Liver Injury

The most compelling clinical evidence for acute hepatoprotection derives from studies of *Amanita phalloides* (death cap mushroom) poisoning, where intravenous silibinin (Legalon SIL®) has been adopted as standard of care in many European centres based on retrospective series demonstrating reduction in liver transplantation and mortality.^[34] In paediatric haematology, silymarin significantly reduced chemotherapy-induced hepatotoxicity (elevated ALT/AST) in children with acute lymphoblastic leukaemia (ALL) receiving hepatotoxic regimens, without compromising antileukemic efficacy.^[35]

7.5 Antidiabetic Clinical Trials

An RCT by Huseini et al. in 51 type 2 diabetic patients demonstrated that silymarin 200 mg three times daily for four months significantly reduced FBG, HbA1c, total cholesterol, LDL-cholesterol, and triglycerides relative to placebo, with



concomitant reductions in serum transaminases reflecting amelioration of diabetic hepatopathy.^[36]

8. Safety Profile and Adverse Events

8.1 General Safety

Silymarin is widely regarded as a safe and well-tolerated herbal preparation, with an adverse event profile broadly comparable to placebo in controlled trials. The German Commission E monograph for milk thistle fruit extract specifies no contraindications, drug interactions, or adverse effects at recommended doses.^[37] In a systematic review and meta-analysis of 36 RCTs, adverse event rates in silymarin-treated groups (3.5%) did not differ significantly from placebo (4.4%), confirming its favourable safety profile across diverse patient populations.^[38]

8.2 Adverse Events at Therapeutic Doses

At oral doses of 420 mg/day (standardised to 70–80% silymarin), adverse events are predominantly gastrointestinal, including nausea, abdominal bloating, mild laxative effect, and, rarely, diarrhoea—the last attributable to enhanced bile secretion and flow. Headache and dizziness have been reported in isolated trials. Mild allergic reactions, manifesting as urticaria or pruritus, occur rarely and may reflect cross-reactivity with other Asteraceae family members in atopic individuals.^[39]

8.3 High-dose and Long-term Safety

In a phase I dose-escalation trial of silybin-phytosome in patients with advanced hepatocellular or biliary carcinoma, dose-limiting toxicity occurred at 10–20 g/day in the form of asymptomatic hyperbilirubinaemia and grade 2 ALT elevation. Below these suprapharmacological doses, the preparation was well-tolerated for up to 12 months.^[40] Intravenous silibinin (Legalon SIL®) at 5–30 mg/kg/day in Amanita poisoning and HCV patients produced no

clinically significant haematological, renal, or hepatic toxicity. Data on safety in children is available for intravenous routes (20–50 mg/kg for mushroom poisoning) and orally for childhood leukaemia; no paediatric-specific toxicities have been reported.^[41]

8.4 Drug Interactions

Silymarin and silybin interact with cytochrome P450 (CYP) enzymes and drug transporters. In vitro studies indicate inhibition of CYP2C9, CYP2D6, CYP3A4, and the efflux transporter P-glycoprotein (P-gp); however, in vivo pharmacokinetic interaction studies in healthy volunteers have generally demonstrated only modest or clinically insignificant effects on probe drug exposure at therapeutic silymarin doses.^[42] Clinically relevant interactions with indinavir (antiretroviral) and tamoxifen (oncological) have been reported and warrant caution. Co-administration with anticoagulants (warfarin) should be monitored given theoretical CYP2C9 inhibition. Clinicians should exercise caution when recommending silymarin to patients on narrow therapeutic index medications.^[43]

8.5 Use in Special Populations

Silymarin has been administered safely to pregnant women with intrahepatic cholestasis at doses up to 560 mg/day without adverse foetal outcomes in available case series. The estrogenic activity of silymarin flavonolignans warrants theoretical caution in oestrogen-sensitive neoplasms, though no definitive clinical evidence of harm in breast cancer patients has been published. There are no studies providing adequate safety data in severe renal impairment; dose adjustment based on pharmacokinetic principles may be prudent.^[44]

9. Current Research Landscape and Future Directions



9.1 Formulation Innovations

The most immediate translational opportunity lies in exploiting advanced formulation technologies to overcome silymarin's bioavailability barrier. SEDDS, lipid nanosystems, and co-amorphous dispersions offer scalable manufacturing pathways to enhance C_{max} and AUC without escalating administered dose. Head-to-head clinical pharmacokinetic comparison of these platforms is a recognised priority.

9.2 Combination Therapy Strategies

The multi-target pharmacological profile of silymarin positions it as an attractive partner for combination regimens. Preclinical evidence supports synergistic antiproliferative effects with sorafenib in hepatocellular carcinoma, with direct-acting antivirals in HCV, and with metformin in NAFLD.^[45] Formalised investigation of these combinations in well-powered RCTs is a priority emerging from recent systematic reviews.^[46]

9.3 Standardisation and Quality Control

Post-market surveillance data consistently reveal that a significant proportion of commercial milk thistle products contain substantially lower flavonolignan concentrations than labelled.^[47] Integration of validated UHPLC-MS/MS methods into pharmacopoeial standards, alongside mandatory DNA barcoding authentication, would provide a robust analytical framework to ensure product integrity and support meaningful inter-trial comparisons.

9.4 Precision Medicine and Biomarker Development

The identification of pharmacogenomic predictors of silymarin response—particularly polymorphisms in OATP1B1/B3, UGT1A9, SULT1A1, and nuclear receptor genes (NRF2, FXR)—could enable stratification of patients most likely to derive hepatoprotective or anticancer benefit. Development of validated, non-invasive

fibrosis biomarkers (e.g., ELF score, FIB-4) as surrogate endpoints will accelerate meaningful clinical evaluation.

9.5 Priority Clinical Trial Agenda

The following represent the most urgently needed areas for high-quality RCT investigation: (i) silymarin in NASH/MAFLD with histological fibrosis regression as primary endpoint; (ii) silybin IV in acute liver failure of toxic aetiology; (iii) silybin-phosphatidylcholine in prostate cancer recurrence; (iv) silymarin as adjunctive neuroprotection in Parkinson's disease; and (v) dose–response characterisation of silymarin's antidiabetic effects in prediabetes, employing next-generation standardised preparations.^[48,49,50]

CONCLUSION

Silybum marianum and its constituent silymarin complex represent one of phytomedicine's most scientifically investigated natural product platforms. The convergence of mechanistic clarity—encompassing antioxidant, anti-inflammatory, antifibrotic, pro-regenerative, and multi-pathway anticancer activities—with a favourable safety record and expanding clinical evidence across hepatic, metabolic, oncological, and neurological domains justifies continued scholarly and clinical investment.

Nevertheless, translating this promise into definitive clinical benefit demands resolution of several persistent challenges: the bioavailability limitations of conventional oral preparations, the heterogeneity of commercial products that impedes cross-study comparability, the methodological shortcomings (small sample sizes, surrogate endpoints, inadequate blinding) of many existing RCTs, and the absence of robust data in paediatric and geriatric populations. The accelerating development of advanced drug delivery platforms, combined with stricter regulatory and pharmacopoeial quality standards,



provides a realistic pathway to overcome these hurdles.

Looking forward, silymarin's multi-target pharmacology positions it as a promising precision adjuvant in combination regimens for chronic liver disease, metabolic syndrome, and certain malignancies, provided that trials are designed with adequate power, standardised interventions, validated endpoints, and appropriate pharmacogenomic stratification. The scientific community, regulators, and industry stakeholders share a collective responsibility to generate the evidence that patients and clinicians deserve.

Declarations

Author Contributions

[Author 1]: Conceptualisation, original draft preparation, literature search. [Author 2]: Review and editing, critical revision. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

No new datasets were generated during this study. All data analysed are derived from previously published peer-reviewed literature cited within the manuscript.

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