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# Translational Potentials of Silymarin: A Comprehensive Narrative Review of Chemistry and Pharmacology

**Joseph O.T. Emudainohwo[1,2]*, Frank Samuel[2], Benneth Ben-Azu[1,3], Israel O. Bolanle[4], Raymond I. Ozolua[2]**

*[1]DELSU Joint Canada-Israel Neuroscience and Biopsychiatry Laboratory, Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Delta State University, Abraka, Nigeria. [2]Department of Pharmacology & Toxicology, Faculty of Pharmacy, University of Benin, Benin City 300001, Nigeria. [3]School of Medicine, Faculty of Health, University of Victoria, Victoria, Canada. [4]Center for Biomedicine, Hull York Medical School, University of Hull, Hull HU6 7RX, United Kingdom.*

***Corresponding Author:** jot.emudainohwo@delsu.edu.ng*
***Phone:** +234 703 314 7570*
***ORCID:** 0009-0007-3784-3342*

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## ABSTRACT

**Background and Purpose:** Silymarin, a flavonolignan complex derived from *Silybum marianum* (L.) Gaertn. (milk thistle), has been extensively studied for its therapeutic potential in metabolic, neuropsychiatric, and neurodegenerative diseases. Despite over four decades of research and more than 12,000 PubMed-archived records on *Silybum marianum* and its constituents, of which over 3,000 relate specifically to silymarin and its flavonolignans, existing reviews predominantly focus on specific disease states, often overlooking the comprehensive structure-activity relationships and mechanistic foundations. This comprehensive narrative review provides an integrated, up-to-date analysis of silymarin's chemistry, pharmacological actions, underlying mechanisms, and translational potential.

**Methods:** This involved a comprehensive narrative review rather than a systematic review. We identified relevant articles published between 1981 and 2026 through PubMed, Scopus, and Google Scholar using keywords related to silymarin, flavonolignans, pharmacological actions, mechanisms, and clinical applications, supplemented by hand-searching reference lists. We selected articles for relevance and quality without a pre-registered protocol, standardized Boolean strings, predefined inclusion criteria, formal risk-of-bias assessment, or PRISMA reporting.

**Results:** The literature demonstrates that silymarin exerts multifaceted pharmacological effects, including hepatoprotective, anticancer, cardioprotective, neuroprotective, and immunomodulatory activities. These actions are mediated by integrated mechanistic pathways: Nrf2-driven antioxidant defense, NF-κB/NLRP3 anti-inflammatory signaling, mitochondrial protection, upregulation of neurotrophic factors (BDNF/GDNF), and modulation of cholinergic and monoaminergic systems. Structure-activity relationship analysis reveals that the flavonolignan scaffold, particularly the phenolic hydroxyl groups and 1,4-benzodioxane ring system, underlies these diverse activities. Notable translational challenges, such as poor oral bioavailability, are being addressed through advanced formulation strategies, including liposomes, nanoemulsions, and phytosomes.

**Conclusion:** Silymarin has evolved beyond traditional hepatoprotection and shows therapeutic potential across diverse diseases. While preclinical evidence is compelling, well-designed randomized controlled trials are needed to validate clinical utility and optimize therapeutic applications. Integrating novel formulations with mechanistic understanding holds promise for translating silymarin's potential into clinical practice.

## INTRODUCTION

Plants have been central to traditional medical systems, many of which modern scientific research has validated. Plants have also been a plentiful source of bioactive compounds that are either utilized directly as drugs or as templates for drug discovery (Chaachouay and Zidane, 2024; Chihomvu *et al*., 2024). Many plant secondary metabolites have a wide range of biological properties, including antimicrobial, anticancer, anti-inflammatory, antiviral, antioxidant, and antidiabetic activities. Some of these metabolites have central nervous system effects with potential for a variety of illnesses, including anxiety, depression, psychosis, epilepsy, and Alzheimer's disease. Flavonoids have attracted particular interest in recent years because of their diverse pharmacological activities, attributed to their polyphenolic structure and high antioxidant activity, which are linked to cardiovascular diseases, cancer, neurodegenerative diseases, diabetes, and aging-related diseases (Panche *et al*., 2016; Ullah *et al*., 2023). Flavonolignans are a class of flavonoids that contain a lignan component. This additional moiety drives their interactions with cellular targets and their strong antioxidant and membrane-stabilizing properties (Bijak, 2022). The most well-known flavonolignans occur in a naturally bioactive complex called silymarin, found in the dried achenes or seeds of *Silybum marianum* L., Gaertn. In English, this plant is commonly known as milk thistle (Abenavoli *et al*., 2023). In European medical traditions and other systems, it has been used since ancient times to treat hepatic and biliary disorders. It is one of the most studied phytochemical compounds for protecting, rejuvenating, and restoring liver function (Loguercio and Festi, 2011; Abenavoli *et al*., 2023; Zhang *et al*., 2024; Selçuk *et al*., 2024). Apart from liver diseases, scientific evidence has been found for its anti-diabetic effect (Said *et al*., 2022) and its calming effect in neuropsychiatric illnesses like anxiety and depression, neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis (Vargas-Mendoza *et al*., 2024). It is also known to have a cardioprotective and neuroprotective effect (Jubaidi *et al*., 2021; Cai *et al*., 2024; Liu *et al*., 2025).

In contrast with most conventional drugs, which are composed of one active ingredient, silymarin is made of various flavonolignans: silybin (silibinin), isosilybin, silychristin and silydianin (Křen and Walterová, 2005; Loguercio and Festi, 2011; Abenavoli *et al*., 2023). Of these, silybin is the most prevalent, accounting for about 50-70% of the extract and contributing significantly to the beneficial pharmacological activity of silymarin (Polyak *et al*., 2013; Bijak, 2017). Lesser amounts of taxifolin and other phenolics are also found in the extract, and these could play a role in the biological activities (Křen and Walterová, 2005; Bijak, 2017).

Silymarin is one of the most studied bioactive natural products, with more than 3,000 PubMed-archived articles published from 1981 to 2026. Some reviews exist, but most focus on sources, chemistry, pharmacological actions, and safety; however, no recent review focuses on all aspects. This review includes complete, scientifically sound, and up-to-date data on its pharmacological actions, underlying mechanism, safety, pharmacokinetics, and therapeutic relevance and translation.

### Botanical Source and Distribution

*Silybum marianum* (Milk Thistle) of the family Asteraceae, subfamily Carduoideae, and tribe Cardueae, is the primary botanical source of silymarin (Figure 2). The genus Silybum has two accepted species: *Silybum marianum* L., an annual or biennial with a wide distribution, and *Silybum eburneum* Coss. & Durieu, a perennial, geographically restricted plant, which is the subject of controversy because of its taxonomic rank, both in classical and modern floristic research data (Greuter, 2003; Abid and Qureshi, 2022). *S. marianum* is easily recognized morphologically by its large spiny and glabrous leaves with prominent white venation, large purple capitula, and stiffly branching bracts. It is native to the Mediterranean basin, North Africa, and Western Asia, and has become naturalized across temperate regions globally, often as an agricultural weed in disturbed, high-nitrogen soils (Hegazy *et al*., 2018; Khan *et al*., 2023).

## CHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF SILYMARIN

#### Chemical Composition and Structural Characteristics

Silymarin is a heterogeneous mixture of structurally related flavonolignans (Selçuk *et al.*, 2024), as shown in Figure 2. The major flavonolignan constituents include silybin, isosilybin, silychristin, isosilychristin, and silydianin, along with minor oxidized and dehydrogenated derivatives (Gillessen and Schmidt, 2020; Akhtar *et al.*, 2023). Of these, silybin (silibinin) is the most abundant, accounting for about 50–60% of the flavonolignan fraction, and is the main contributor to silymarin's pharmacological properties (Wadhwa *et al*., 2022; Surai, 2024). The commercial products are usually a mixture of the diastereoisomers silybin A and B in roughly equal amounts (Wadhwa *et al*., 2022; Fenclová *et al*., 2023).

Silybin is (2R,3R)-3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]chroman-4-one. It has a molecular formula $C_{25}H_{22}O_{10}$ and a molecular weight of 482.44 g/mol (Wadhwa *et al*., 2022; Fenclová *et al*., 2023).

It also contains a flavonol nucleus connected to a phenylpropanoid moiety by a unique benzodioxane ring system, providing the characteristic flavonolignan framework found in silymarin and other flavonoids (Akhtar *et al*., 2023; Surai, 2024). The molecule features several phenolic hydroxyl groups, a ketone functionality, and several stereogenic centers, all of which play a key role in its biological and antioxidant activities (Zhao *et al*., 2011; Fenclová *et al*., 2023). Table 1 summarizes the key molecular features that contribute to its biological actions.

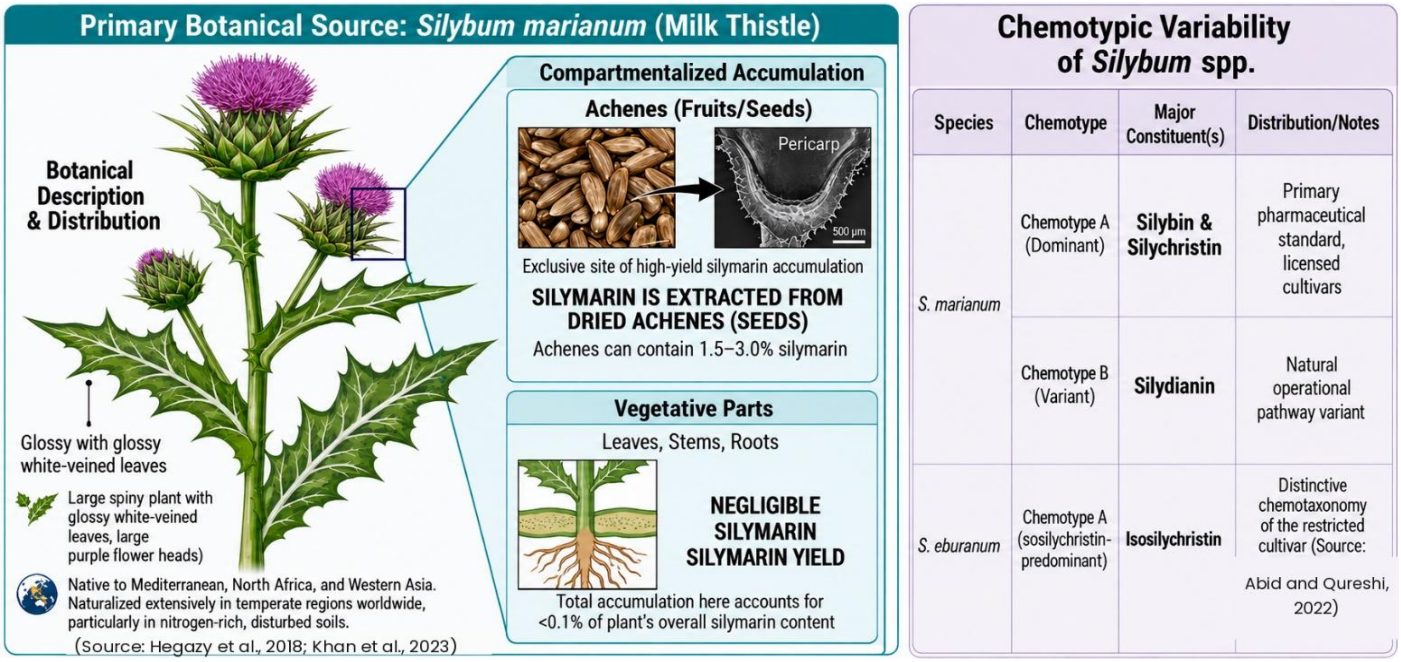


**Figure 1:** Natural sources of silymarin, including plant parts, extraction sites, and species-specific chemotypes (adapted from Wellington and Jarvis, 2001).

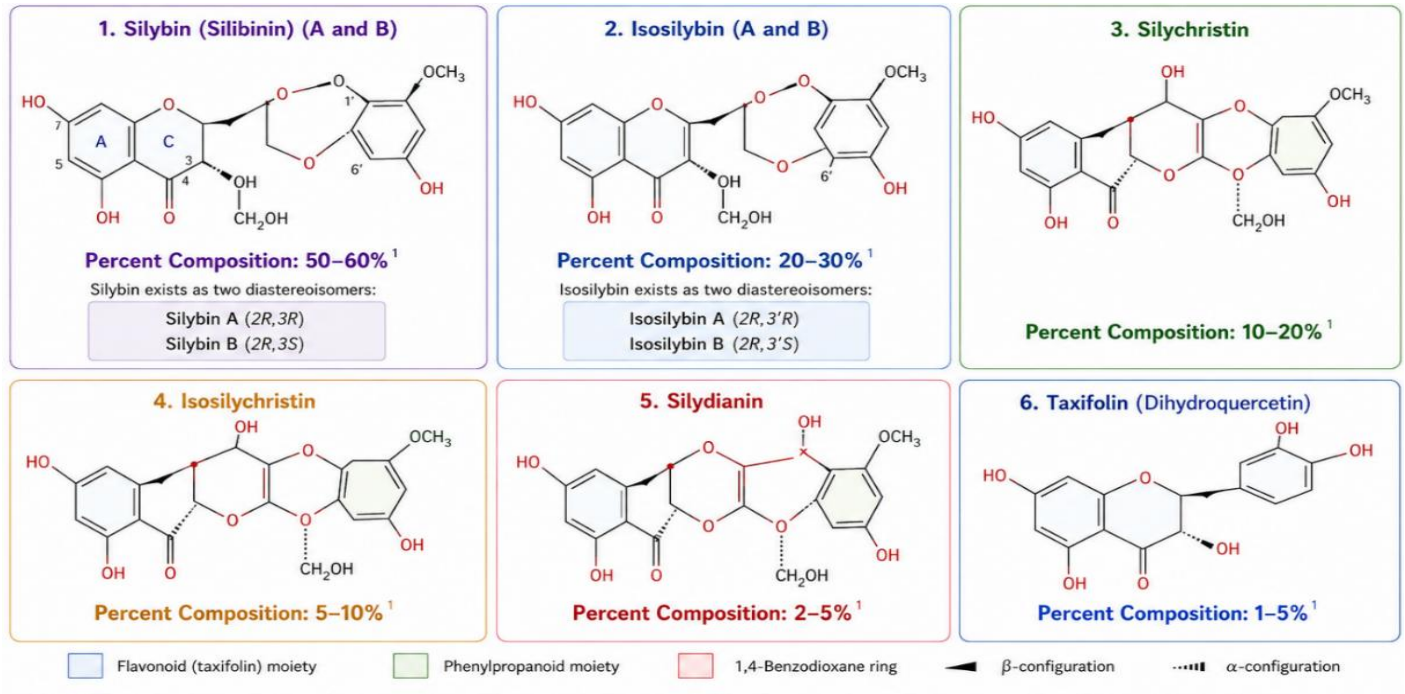


**Figure 2:** Chemical structures of the major flavonolignan constituents of silymarin and their percentage composition (adapted from Wellington and Jarvis, 2001).

**Structure-Activity Relationship**

Table 1 presents the structure-activity relationship (SAR) describing the pharmacological actions associated with silymarin's backbone and functional groups.

**Table 1: Important Structure-Activity Relationship of Silymarin.**

| Structural Feature | Structural Determinant | SAR Observation | Pharmacological Consequence | References |
|---|---|---|---|---|
| Flavonolignan hybrid backbone | Taxifolin + coniferyl alcohol conjugation (flavonoid–lignan hybrid) | Hybridization creates a unique scaffold distinct from classical flavonoids | Confers baseline hepatoprotective, antioxidant, and cytoprotective activity | Křen and Walterová, 2005; Polyak *et al.*, 2010 |
| Phenolic hydroxyl groups (general) | Multiple free OH groups across A, B, and C rings (C-5, C-7, C-2′, C-3′, etc.) | Free phenolic OH groups strongly enhance hydrogen donation; methylation/acetylation reduces activity | Potent radical scavenging, inhibition of lipid peroxidation, anti-inflammatory, and hepatoprotective effects | Surai, 2015; Zhao *et al.*, 2011 |
| 3,5,7-trihydroxyl system | A-ring and C-ring hydroxyl pattern | Essential for electron donation and ROS neutralization | Strong antioxidant activity and interruption of the oxidative chain reactions | Wellington and Jarvis, 2001; Surai, 2015 |
| Catechol-like B-ring dihydroxylation (3′,4′-OH in taxifolin moiety) | Ortho-dihydroxyl arrangement on aromatic B-ring | Enhances electron delocalization and redox cycling stability | Potent inhibition of lipid peroxidation and free radical scavenging | Flora *et al.*, 1998; Křen and Walterová, 2005 |
| 3-OH / 4-keto system (flavanonol core) | C-3 hydroxyl + C-4 carbonyl motif | Critical metal-binding pharmacophore; disruption reduces activity | Chelation of $Fe^{2+}/Fe^{3+}/Cu^{2+}$ → suppression of Fenton reaction and oxidative injury | Zhao *et al.*, 2011 |
| 1,4-benzodioxane ring system | Oxidative coupling bridge between flavonoid and lignan units | Increases structural rigidity and membrane affinity | Enhances hepatocyte membrane stabilization and signal pathway modulation (NF-κB, TGF-β, Hsp90) | Polyak *et al.*, 2010 |
| Conjugated aromatic system/planarity | Extended π-electron delocalization | Improves radical stabilization and electron resonance | Enhances antioxidant, cytoprotective, and anti-inflammatory effects | Flora *et al.*, 1998 |
| C-7 hydroxyl group | Specific phenolic OH on A-ring | Critical for hydrogen bonding and enzyme interaction | Enhances the inhibition of enzymes such as lipoxygenase and CYP450 modulation | Wellington and Jarvis, 2001 |
| C-23 hydroxymethyl group (primary alcohol) | Terminal $–CH_2OH$ substituent | Major site for derivatization (esterification, glycosylation, phosphorylation) | Modulates solubility, membrane permeability, bioavailability, and anticancer potency | Zhao *et al.*, 2011; Polyak *et al.*, 2010 |
| Stereochemistry (C-2, C-3 chiral centers) | Diastereomers (Silybin A, Silybin B, isosilybin forms) | Alters spatial orientation and receptor/enzyme binding affinity | Different anticancer potency, enzyme inhibition profiles, and pharmacokinetics | Ferenci *et al.*, 1989; Hahn *et al.*, 2012 |
| Isosilybin structural rearrangement | Positional and stereochemical variation of flavonolignan core | Changes 3D pharmacophore alignment | Enhanced antiproliferative activity in some cancer cell lines | Polyak *et al.*, 2010 |

**Table 1: Important Structure-Activity Relationship of Silymarin (Cont'd).**

| Structural Feature | Structural Determinant | SAR Observation | Pharmacological Consequence | References |
|---|---|---|---|---|
| Methoxy substitution (–$OCH_3$) | Replacement or masking of phenolic OH groups (in derivatives) | Reduces polarity and hydrogen donation capacity | Decreased antioxidant activity; increased lipophilicity | Křen and Walterová, 2005 |
| Absence of glycosylation (aglycone form) | Non-glycosylated flavonolignan structure | Increases lipophilicity but decreases aqueous solubility | Poor oral bioavailability but better membrane penetration | Li *et al.*, 2013 |
| Overall hydroxyl density | High total phenolic OH content | Correlates with antioxidant strength | Strong hepatoprotective, antifibrotic, and anti-inflammatory activity | Surai, 2015 |

## PHARMACOLOGICAL ACTIONS AND MECHANISMS OF SILYMARIN

Over the decades, much has been added to the knowledge of silymarin's pharmacological actions. Used since ancient times to treat liver-related diseases, its pharmacological actions have expanded to include neuropsychiatric, neurodegenerative, and neoplastic conditions, as discussed below. To avoid repetition with the section on core mechanisms, the disease-specific subsections here emphasize phenotypic and functional outcomes, while the shared underlying molecular pathways (Nrf2/ARE, NF-κB/NLRP3, mitochondrial protection, neurotrophic and monoaminergic signaling, and estrogen receptor modulation) are consolidated and discussed in depth in the core mechanisms.

### Anticancer Actions

Many studies have shown that silymarin has activity against a variety of cancers such as gastric, prostate, hepatocarcinoma, laryngeal carcinoma, lung, glioblastoma, breast cancer, multiple myeloma, glioma, colorectal, malignant melanoma, bladder, skin, nasopharyngeal, cervical, and leukemia (Frassová and Rudá-Kučerová, 2017; Wadhwa *et al*., 2022; Bjørklund *et al*., 2025; Sharma *et al*., 2025). Silymarin has specific anti-neoplastic properties against important survival targets of oncogenic cells. In human studies using NSCLC cell lines (A549, H292, and H460), silymarin was shown to downregulate the JAK/STAT and PI3K/Akt/mTOR signaling pathways, and reduces activity of epidermal growth factor receptor (EGFR) (Rugamba *et al*., 2021), just as evidence from human, rodents (*in vivo*), and cell culture models have equally shown that, silymarin blocks expression of important gene products involved in proliferation such as cyclin D1, STAT3, AKT1, and Bcl-2 (Rugamba *et al*., 2021; Wadhwa *et al*., 2022). Silybin is a natural inhibitor of STAT3 activity and blocks the development of STAT3-dependent cancer drug resistance in the clinic through a multi-pronged effect: it re-sensitizes resistant tumor cells, interferes with drug efflux, and throws a wrench into critical survival signaling networks like JAK/STAT, PI3K/Akt/mTOR, and STAT3 (Bosch-Barrera *et al*., 2017). Silybin has been shown to arrest HepG2 cells in $G_1$ phase of the cell cycle and upregulate miR223-3p and miR16-5p (Bektur Aykanat *et al*., 2020). Many localized tumors have high glucose turnover, and glucose starvation is a promising anticancer strategy (Cui *et al*., 2023; Agrawal *et al*., 2024). Silybin and 2,3-dehydrosilybin have been identified as inhibitors of glucose uptake in cells by binding to the glucose transporters (GLUT) (Zhan *et al*., 2011). Silybin modulates $\beta_1$-integrin and downstream molecules such as Cdc42, Raf-1, and D4GDI, inhibiting migration and adhesion in MDA-MB-231 cells (Binienda *et al*., 2020). Cyclin D1 is downregulated, and the corresponding upregulation of the cyclin-dependent kinase inhibitors p21 and p27 leads to cell cycle arrest at the $G_1$/S transition (Srivastava *et al*., 2025; Wang *et al*., 2023). Apoptotic cell death occurs through either the extrinsic death receptor pathway or the intrinsic mitochondrial pathway, with an increased Bax/Bcl-2 ratio, cytochrome c release, and activation of caspase-9/caspase-3 (Srivastava *et al*., 2025). Anti-angiogenic effects are mediated by downregulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) (Wang *et al*., 2023). Moreover, evidence supports the use of silymarin as an adjuvant chemotherapeutic agent to enhance anticancer effects and mitigate chemotherapy-related side effects in humans.

### Hepatoprotective Actions (Anti-fibrotic and Metabolic)

Silymarin is a popular medicinal plant that has been employed in the treatment of liver diseases such as alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and drug toxicity. Silymarin's classical hepatoprotective pharmacology has multiple complementary mechanisms. The first proposed mechanism of action of silymarin is membrane stabilization, achieved by physically incorporating

flavonolignans into hepatocyte lipid bilayers, making them more rigid and blocking the entry of hepatotoxins such as carbon tetrachloride, acetaminophen, ethanol, and phalloidin (Bahmani *et al*., 2015; Jaffar *et al*., 2024).

In an *in vitro* model of hepatic steatosis, silybin inhibited the lipid overload that free fatty acids typically trigger in human HepG2 liver cells. Mechanistically, fatty acid transport protein 5 (FATP5), sterol regulatory element-binding protein 1 (SREBP1), and stearoyl-CoA desaturase 1 (SCD1) are all attenuated, effectively cutting off both fat import and new fat synthesis (Dhami-Shah *et al*., 2018).

The protective effect of silymarin on NAFLD in vivo has also been demonstrated by its ability to downregulate liver cholesterol (Colletta *et al*., 2020; Li *et al*., 2024). Isosilybin A was identified as the first flavonolignan PPARγ agonist and was shown to facilitate cholesterol efflux from THP-1 macrophages. Further, isosilybin, silychristin, and isosilychristin were shown to stimulate ABCA1 expression in THP-1 cells (Wang *et al*., 2020a). Anti-fibrotic activity suppresses transforming growth factor-$\beta_1$ (TGF-$\beta_1$) / SMAD signaling in hepatic stellate cells (HSCs), preventing HSC transdifferentiation into myofibroblasts and inhibiting type III procollagen synthesis (Kim *et al*., 2012; Bahmani *et al*., 2015). Silybin exhibits antioxidative and anti-inflammatory effects by suppressing NF-κB and activating Nrf2 signaling pathways, as well as by reducing CYP2E1 expression (a key generator of reactive oxygen species), and also lowers the levels of 4-hydroxynonenal (4-HNE) (a cytotoxic end-product of lipid peroxidation that drives cell damage and inflammation) (Ou *et al.*, 2018; Wang *et al.*, 2020b). Finally, silymarin's regenerative capacity is attributed to the physiological stimulation of RNA polymerase I in hepatocytes, increasing ribosomal RNA synthesis and protein anabolism necessary for tissue recovery - an effect observed specifically in injured hepatocytes (Bahmani *et al.*, 2015; Saller *et al.*, 2008).

**Cardioprotective Property**

Cardiovascular diseases are currently the leading cause of death in the elderly and are usually associated with ischemic injury (Liu *et al.*, 2024; Cai and Lin, 2025). Pathological mechanisms generally believed to be the primary mechanisms of cardiovascular diseases, such as heart failure, myocardial infarction (MI), and arrhythmia (Donia and Khamis, 2021), include inflammation, oxidative stress, and cell death. In pig models of MI, silymarin enhanced myocardial salvage by maintaining mitochondrial function through antioxidant mechanisms during the acute stage of MI (Cai *et al*., 2024). Moreover, *Silybum marianum* improved cardiac healing and heart contractility post-MI by decreasing cardiac reactive fibrosis in the border zone by inhibiting TGFβ1−TβR−Smad2/3 signaling pathways (Liu *et al*., 2025). Silybin protects the cardiac myocytes from isoproterenol-induced injury by improving mitochondrial function and regulating Silent Information Regulator 1 (SIRT1) and Bcl-2 (Jubaidi *et al*., 2021). Interestingly, 2,3-dehydrosilybin exhibits excellent inotropic effects without the side effects of β-agonists, supporting its use as a novel inotropic agent for both acute and chronic heart failure (Gabrielová *et al.*, 2019).

**Immunomodulatory and Metabolic Homeostatic Actions**

Silymarin exerts broad immunomodulatory effects beyond its anti-neuroinflammatory actions. As for psoriasis, a TLR4-mediated autoimmune skin disease model, silymarin is shown to inhibit the activation of TLR4/NF-κB and PI3K/Akt/mTOR signaling, decrease the production of pro-inflammatory IL-23 and IL-17A cytokines, and induce the polarization of macrophages from the pro-inflammatory M1 to anti-inflammatory M2 phenotype (Azimi *et al*., 2025). Silybin specifically blocks dendritic cell activation and Th17 cell differentiation, thereby attenuating the autoimmune cascade involved in central demyelination in multiple sclerosis (MS) models (Abbasirad *et al*., 2021). From a metabolic homeostasis perspective, silymarin inhibits the vasoactive peptide urotensin II (U-II) and its receptor (UTR), leading to activation of AMP-activated protein kinase (AMPK) and facilitating peripheral glucose uptake while inhibiting hepatic gluconeogenesis (Rahimi *et al*., 2018). Increased PPAR-α expression also restores lipid homeostasis and insulin sensitivity (Jaffar *et al*., 2024). These metabolic actions are directly relevant to type 2 diabetes mellitus, gestational diabetes, and metabolic dysfunction-associated steatotic liver disease (MASLD/NAFLD) (Jaffar *et al.*, 2024).

**Protective Effects against Chronic Neurodegenerative Diseases**

***Alzheimer's Disease***

Alzheimer's disease (AD) is a neurodegenerative disorder marked by a gradual cognitive decline, along with synapse and nerve damage, Aβ peptide aggregation, and cholinergic deficits (Selkoe and Hardy, 2016; Du *et al*., 2018; Hampel *et al*., 2018). Silybin has been found to both inhibit Aβ aggregation in hippocampal cells and suppress acetylcholinesterase (AChE) activity, which consequently lifts acetylcholine levels (Duan *et al*., 2015; Wang and Yang, 2025). In an *in vitro* model of Aβ-induced oxidative damage, isosilybin protected mouse hippocampal HT-22 cells against Aβ25–35 toxicity. This protection occurs via Nrf2/ARE-dependent antioxidant mechanisms detailed in the core mechanisms (Zhou *et al*., 2016). Silymarin reduces Aβ aggregation by directly interfering with Aβ self-assembly—an effect independent of BACE1-mediated cleavage (Almutary *et al*., 2025). Silymarin also raises the levels of key neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), particularly in the hippocampal subfields (Dentate Gyrus, CA1, and CA3) as

well as interconnected cortical structures (including the entorhinal and prefrontal cortices) to promote neuronal survival and synaptic plasticity. Consistent improvements in cognitive and memory function have been documented across various preclinical AD animal models (Ranjan and Gautam, 2023; Almutary *et al*., 2025). In AD patients with dyslipidemia, a double-blind, placebo-controlled randomized trial showed that silymarin combined with rosuvastatin increased SOD activity, which was directly correlated with Aβ1-42/Aβ1-40 load but inversely related to changes in lipid profiles such as triglyceride levels (Rustamzadeh *et al*., 2024).

***Parkinson's Disease***

In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, silymarin significantly reduced the number of apoptotic cells and preserved dopaminergic neurons in the substantia nigra pars compacta (SNpc), attenuating both oxidative stress and neuroinflammatory damage (Ullah and Khan, 2018). Like selegiline, an antiparkinsonian drug, monoamine oxidase-B (MAO-B) inhibition increases the availability of dopamine in the synapse (Ullah and Khan, 2018). In patients with Parkinson's disease (PD), the neuroprotective and symptom-modifying effects of silymarin were assessed at Tanta University, Egypt, and registered in a clinical trial with the identifier NCT07001150 (Ranjan and Gautam, 2023).

***Huntington's Disease***

In the 3-nitropropionic acid (3-NPA) rat model of Huntington's disease (HD), a neurodegenerative disease characterized by degeneration of the medium spiny neurons in the basal ganglia, notably the striatum and cerebral cortex, and by dopamine and GABA depletion, associated with hyperkinetic movement known as chorea (Irfan *et al*., 2022), the dynamic equilibrium of the direct and indirect basal ganglia pathways is disturbed, with the indirect pathway becoming more prominent than the direct pathway, leading to increased thalamic disinhibition and clinically evident jerky, involuntary writhing that is characteristic of chorea. Silymarin effectively prevented motor coordination deficits and weight loss, along with striatal oxidative stress, as shown by decreased malondialdehyde (MDA) and nitrite levels and increased GSH, catalase, and SOD activity (Chandolia *et al*., 2022).

***Multiple Sclerosis***

In the experimental autoimmune encephalomyelitis (EAE) murine model of multiple sclerosis, a chronic autoimmune-mediated neurological disease characterized by widespread inflammation, demyelination, and enduring axonal loss, which together alter neurological disability (Boutitah-Benyaich *et al*., 2025), silymarin significantly decreased clinical symptom scores and the incidence of EAE as well as inflammatory infiltration and severe demyelination (Boutitah-Benyaich *et al*., 2025; Ranjan and Gautam, 2023). Silybin efficiently blocks dendritic cell activation and Th17 lymphocyte differentiation, suppressing the autoimmune pathway that causes central demyelination (Abbasirad *et al*., 2021). These preclinical findings are supported by a double-blind, placebo-controlled clinical trial (Abbasirad *et al.*, 2021) that demonstrated significant immunomodulatory and hepatoprotective effects of silymarin in MS patients who also received interferon-β therapy.

**Ameliorative Actions on Neuropsychiatric and Mood Disorders**

***Depression, Anxiety and Schizophrenia***

Depression and anxiety have been associated with an increased risk of developing AD and schizophrenia. In depressed patients, both BDNF receptor TrkB and phosphorylated TrkB are deficient in the brain. Silymarin and silybin activate the BDNF/TrkB pathway, promoting neurogenesis, inhibiting the inflammatory response and oxidative stress, and inhibiting autophagy, leading to improved anxiety/depression-related behaviors (Song *et al*., 2016; Jin *et al*., 2016). The systematic review of 17 preclinical studies revealed that there was a consistent increase in BDNF, neural stem cell proliferation, 5-HT, DA, and NE levels, and a decrease in MDA and an increase in SOD, CAT, and GSH, as well as attenuation of neuroinflammatory cytokines (IL-6, IL-1β, IL-12β, TNF-α) (Rostamian *et al*., 2023). These behavioral effects parallel the MAO-B inhibition, BDNF-TrkB/PI3K/Akt-mediated neurogenesis, HPA-axis normalization, and NF-κB suppression (Rostamian *et al*., 2023) detailed in the core mechanisms described below. Silymarin has been shown to reduce anxiety-/depression-like behaviors in amyloid precursor protein transgenic mice (Song *et al*., 2016). In a schizophrenia model, silymarin was effective in preventing and reversing the hyperlocomotion and stereotypy induced by ketamine, a repetitive, ritualistic, meaningless motor behavior and one of the main features of schizophrenia (Ben-Azu *et al*., 2024). In a parallel study, silymarin also reduced social withdrawal and memory deficits in mice injected with ketamine by acting on dopaminergic and serotonergic pathways, particularly in the striatum and prefrontal cortex (Ben-Azu *et al*., 2024). Additionally, silymarin's antischizophrenic effect correlates with reduced pro-inflammatory cytokines, such as TNF-α and IL-6, and myeloperoxidase, which may link to silymarin's ability to mitigate negative and cognitive symptoms of schizophrenia (Ben-Azu *et al*., 2026).

***Post-Traumatic Stress Disorder and Chronic Stress***

Experimental results show that silybin treatment can improve learning and memory impairment in lipopolysaccharide (LPS)-treated rodents, a model for depression- and anxiety-related behavioral changes and can also decrease neuroinflammatory signaling and oxidative stress (Song *et al*., 2016). Moreover, silybin prevents nitrosative stress in rat pheochromocytoma cell lines (PC12) and reduces hippocampal neuronal damage in animals exposed to LPS. This is consistent with the neurotrophic signaling mechanisms detailed in in the core mechanisms (Song *et al*., 2016; Wang *et al*., 2020b). In the single prolonged stress (SPS) mouse model of PTSD, two studies by Emudainohwo *et al*. (2026a and 2026b) showed that 21-day treatment with silymarin (25–100 mg/kg, p.o.) reversed PTSD-associated impairments in recognition and working memory, in addition to suppressing anxiety- and depressive-like behaviors, via several overlapping pathways: reducing oxidative stress; inhibiting brain region–dependent expression of the proapoptotic protein caspase-3; reducing serum corticosterone levels; enhancing neurotransmission by monoamines; and reducing the expression of the astrocytic neurotoxic protein glial fibrillary acidic protein (GFAP) in the prefrontal cortex and Cornu Ammonis 3 (CA3) subregion of the hippocampus. The activities of silymarin in various aspects of PTSD-related diseases are summarized in Table 2.

**Table 2: Actions of silymarin relevant to PTSD pathophysiology.**

| Silymarin's Property | Key Molecular/Cellular Actions | Relevant PTSD Pathophysiological Target | Supporting References |
|---|---|---|---|
| Potent Antioxidant | Free radical scavenging; ↑ GSH, SOD, CAT, GST; ↓ MDA | Oxidative/nitrergic stress in prefrontal cortex, hippocampus, striatum | Galhardi *et al.*, 2009; Chtourou *et al.*, 2010; Ben-Azu *et al.*, 2020 |
| Anti-inflammatory | Inhibits NF-κB; ↓ TNF-α, IL-6, iNOS; ↓ MPO | Chronic neuroinflammation and microglial/astrocyte activation | Lu *et al.*, 2009; Cohen *et al.*, 2011; Almutary *et al.*, 2025 |
| Neuroprotective | Prevents protein/lipid oxidation; protects mitochondria; ↓ Aβ aggregation | Neuronal degeneration and synaptic loss in corticolimbic circuits | Murata *et al.*, 2010; Raza *et al.*, 2011; Goh *et al.*, 2021 |
| Anti-apoptotic | Modulates p53, apaf-1, caspase-9; stabilizes mitochondrial function | Stress-induced neuronal apoptosis (e.g., in the hippocampus) | Raza *et al.*, 2011; Shokouhi *et al.*, 2020 |
| Cholinergic Modulation | Regulates AChE activity; may ↑ acetylcholine availability | SPS-induced cholinergic dysfunction and memory impairment | Chtourou *et al.*, 2010; El-Marasy *et al.*, 2018 |
| Estrogenic Activity | Binds to and ↑ ER-β expression; neurotrophic support | Hippocampal neuroprotection, learning, and memory | Baluchnejadmojarad *et al.*, 2010; Seidlova-Wuttke *et al.*, 2003 |

**Protective Effects against Acute Central Nervous System Injury**

A systematic review of 17 preclinical studies documented consistent neuroprotective and antioxidant benefits of silymarin and silibinin across models of acute CNS injury; the underlying antioxidant, anti-inflammatory, mitochondrial, and anti-apoptotic mechanisms are summarized in the core mechanisms below (Mardani Nafchi *et al*., 2025). In experimental intracerebral hemorrhage (ICH), silymarin was shown to inhibit an increase in oxidative stress markers and suppress NF-κB p65 expression, as well as NLRP3 inflammasome activation (caspase-1 and IL-1β expression), and promote microglial M2 polarization (Yuan *et al*., 2017). By exerting antioxidant and anti-inflammatory effects, silymarin was found to significantly improve sensorimotor functions and neuropathic pain outcomes in intrathecal administration in a rat model of compression spinal cord injury (SCI) (Bahmani *et al*., 2025). Generally, the effect of silymarin on cognitive impairments and hippocampal TNF-α and BDNF levels after mTBI was sex-dependent, which may be due to ER-β-mediated neuroprotective signaling (Shokouhi *et al*., 2020; Ranjan and Gautam, 2023).

**Metabolic and Toxic Neurological Disorders**

Silymarin suppresses hyperglycemia-linked oxidative stress and neuroinflammation in the diabetic brain by enhancing the activity of antioxidant enzymes and increasing the level of BDNF, which improves learning and memory performance in cognitively impaired diabetic rodents (Ranjan and Gautam, 2023; Almutary *et al*., 2025).

In a preclinical study of chemobrain in rats, El Sayed *et al*. (2025) also showed that intranasal administration of silymarin nanoemulsion (200 times lower in dose compared to oral administration) improved cognitive deficits caused by chemotherapy, protected brain structure, decreased AChE and caspase-3 activity, and increased mitochondrial biogenesis through the Nrf2/HO-1 axis. A triple-blinded, randomized clinical trial by Karbasforooshan *et al*. (2024) investigated the effects of nano-silymarin micelles on the severity of FOLFOX6/XELOX chemotherapy-induced peripheral neuropathy and hand–foot syndrome in metastatic colorectal cancer patients and demonstrated significant reductions.

## CORE MOLECULAR MECHANISMS OF SILYMARIN

Silymarin's mechanism of action is complex and operates at multiple levels. Several key mechanistic axes underlie the multi-pronged pharmacologic actions of silymarin, which are summarized below and schematically illustrated in Figure 3.

### Antioxidant Cascades: Nrf2/ARE Activation

Silymarin exerts potent antioxidant effects through a dual-action mechanism. First, it directly scavenges radicals and chelates metals. Silymarin's flavonolignan components donate hydrogen atoms to neutralize superoxide, hydroxyl, and peroxyl radicals, and chelate redox-active transition metals such as $Fe^{2+}$ and $Cu^{2+}$ to help stop lipid peroxidation chain reactions (Ranjan and Gautam, 2023; Li *et al*., 2025). Second, it indirectly activates endogenous defenses by modifying specific cysteine residues on the cytoplasmic inhibitor of Nrf2, Kelch-like ECH-associated protein 1 (KEAP1), disrupting the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex responsible for Nrf2 degradation by the proteasome (Li *et al*., 2025; Fath *et al*., 2024). Once released, Nrf2 translocates to the nucleus, heterodimerizes with small Maf proteins and binds to antioxidant response elements (AREs) in the promoter regions that leads to the upregulation of other cytoprotective target genes such haem oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) and simultaneously elevates reduced glutathione (GSH) levels (Mardani Nafchi *et al*., 2025; Ranjan and Gautam, 2023). These antioxidant effects are further supported by its ability to stabilize mitochondrial membrane potential and inhibit the mitochondrial permeability transition pore (mPTP), which prevents bioenergetic failure due to mitochondrial ROS (Mardani Nafchi *et al*., 2025).

### Anti-inflammatory Pathways: NF-κB and NLRP3 Inhibition

Silymarin suppresses neuroinflammation and systemic inflammation through several interdependent molecular mechanisms. Its primary anti-inflammatory effects are by the inhibition of NF-κB light chain enhancer. Silymarin is known to block the activation and degradation of inhibitory protein IκB-α, preventing the p50/p65 NF-κB heterodimer from entering the nucleus and inhibiting the transcription of pro-inflammatory target genes such as tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-12 (IL-12), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and myeloperoxidase (MPO) (Zhao *et al*., 2024; Li *et al*., 2025). Additionally, silymarin inhibits the upstream activation of mitogen-activated protein kinase (MAPK) family members ERK1/2, JNK and p38 MAPK, which are key upstream regulators of NF-κB and other pro-inflammatory transcription factors (Zhao *et al*., 2024; Li *et al*., 2025). Another anti-inflammatory activity of silymarin that is mechanistically relevant is its inhibitory effect on the NOD-like receptor family pyrin domain-containing 3 (NLRP3) or cryopyrin inflammasome. Molecular docking results indicate that silibinin binds directly to internal pockets of the NLRP3 NACHT domain, which prevents its oligomerization and the binding of apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC) and also inhibits pro-caspase-1 autocleavage (Mai *et al*., 2023). Silymarin inhibits the activation of caspase-1, thereby inhibiting the maturation and release of IL-1β and IL-18; it also inhibits the expression of thioredoxin-interacting protein (TXNIP) and simultaneously activates SIRT2 while reducing mitochondrial ROS (Mai *et al*., 2023). In brain injury models, silymarin also has a neuroprotective effect and induces microglial cells to adopt the neuroprotective M2 phenotype rather than the pro-inflammatory M1 phenotype (Yuan *et al*., 2017).

### Mitochondrial Protection/Bioenergetic Preservation

Mitochondrial dysfunction is a convergence point in both acute and chronic central nervous system (CNS) injury. Silymarin has several interdependent mechanisms that prevent mitochondrial deterioration. It helps to stabilize the mitochondrial membrane potential, inhibit mPTP opening, and preserve $Na^+$-$K^+$ ATPase activity, ensuring the ionic homeostasis crucial for neuronal survival (Mardani Nafchi *et al*., 2025; Ranjan and Gautam, 2023). Silymarin upregulates PGC-1α, the master regulator of mitochondrial biogenesis; uncoupling protein 2 (UCP2), which dissipates the proton gradient and reduces mitochondrial superoxide production; and nuclear respiratory factor 1 (NRF1), which triggers transcription of nuclear-encoded mitochondrial components (Mardani Nafchi *et al*., 2025). These effects synergize with silymarin's activation of the Nrf2/HO-1 axis,

which also regulates mitophagy and mitochondrial quality control (Li *et al*., 2025).

**Anti-apoptotic Signaling**

Based on a comprehensive review article involving *in vitro* studies, Almutary *et al*. (2025) demonstrated that silymarin can modulate the critical balance between pro- and anti-apoptotic proteins of the Bcl-2 family by increasing expression of Bcl-2 and Bcl-xL and decreasing expression of Bax, which reduces the ratio of Bax to Bcl-2, a reduction

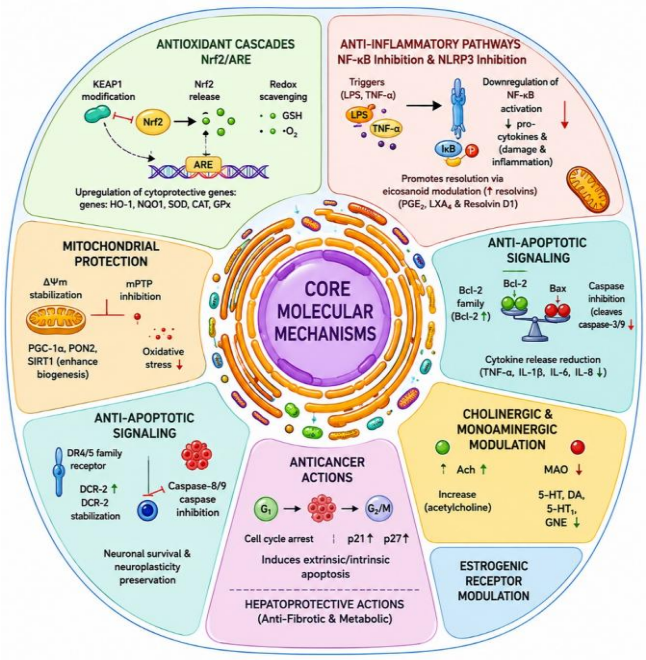


**Figure 3: Multi-Level Mechanisms of Silymarin:** The mechanistic pathways of silymarin involve multiple layers of molecular mechanisms. Its antioxidant mechanism involves a cascade of intracellular modulation of Nrf2 and KEAP1 pathways, leading to increased antioxidant scavenging capacity. The anti-inflammatory pathway involves downregulation of NFkB pathway and reduced cytokine release. Additionally, mitochondrial protection involves inhibition of oxidative stress, mPTP, and mitochondrial stabilization. Besides, its anti-apoptotic pathways also consist of suppression of apoptotic proteins while enhancing the modulation of monoamines and acetylcholine.

that prevents cytochrome c release from the outer mitochondrial membrane, inhibits assembly of the apoptosome, and downregulates the tumor suppressor p53. Interestingly, recent studies has indicated that the anti-apoptotic activity of silymarin may vary depending on the brain region and the context in which it is applied, as observed in a single prolonged stress (SPS) model of PTSD, where caspase-3 was suppressed in the hippocampal dentate gyrus, while showing differential modulation in the PFC (Rostamian *et al*., 2023; Emudainohwo *et al*., 2026b).

**Neurotrophic Signaling: BDNF, GDNF, and Downstream Pathways**

In mice, silymarin and silibinin have been shown to increase brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in the brain areas associated with the limbic system and cortex (Rostamian *et al*., 2023; Almutary *et al*., 2025). BDNF signals through its high-affinity cognate receptor, tropomyosin receptor kinase B (TrkB), to activate two major survival-promoting cascades: the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway that regulates neuronal survival, hippocampal neurogenesis, synaptic strength, and protein synthesis; and the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway that controls axonal growth and synaptic plasticity (Rostamian *et al*., 2023). The neurotrophic mechanism is responsible for the ability of silymarin to reverse cognitive and mood-related impairments both in chronic stress and PTSD models (Rostamian *et al*., 2023) and for its ability to induce neural stem cell (NSC) proliferation in both the cortex and hippocampus (Rostamian *et al*., 2023).

**Cholinergic and Monoaminergic Modulation**

Silymarin directly inhibits acetylcholinesterase (AChE), raising synaptic acetylcholine (ACh) concentrations in a mechanism similar to the approved cholinesterase inhibitors, but without the associated peripheral cholinergic adverse effects (Ranjan and Gautam, 2023; Almutary *et al.*, 2025). In monoaminergic systems, silymarin and silibinin increase the levels of serotonin, dopamine, and noradrenaline in limbic and cortical areas (Rostamian *et al*., 2023). One of the main mechanisms is the inhibition of the major enzyme that breaks down dopamine in the striatum, MAO-B. This decreases the degradation of dopamine in the striatal tissue (Ullah and Khan, 2018). All these effects are responsible for silymarin's pharmacological effects, including antidepressant, anxiolytic, and antiparkinsonian properties (Rostamian *et al*., 2023; Ullah and Khan, 2018).

**Estrogenic Receptor Modulation**

Silymarin has been shown to bind to estrogen receptor beta (ER-β), triggering neuroprotective cellular signaling cascades that mimic estrogen's CNS actions without the peripheral estrogenic side effects associated with exogenous estrogen administration (Ranjan and Gautam, 2023). This mechanism is thought to be responsible for the observed sex-dependent effects of silymarin, such as in models of traumatic brain injury and Parkinson's disease and may be of particular importance in situations of sex hormone deficiency (Ranjan and Gautam, 2023).

**Mechanistic Synchronization: A Unified Framework**

Silymarin has a wide range of pharmacological activities because of the synchronized modulation of an interconnected cellular signaling network. Table 3 illustrates this integrated overview of the main pharmacological aspects, molecular targets, and downstream effects of silymarin.

**Table 3: Unified mechanistic framework of silymarin's multi-target pharmacological actions.**

| Dimension | Key Molecular Targets | Primary Downstream Effects | Animal Species | Key Reference(s) |
|---|---|---|---|---|
| Antioxidant | Nrf2↑, KEAP1↓, mPTP blockade | HO-1, NQO1, SOD, CAT, GPx, GST upregulation; GSH restoration; MDA and 4-HNE reduction | *Rattus norvegicus* (Wistar rats) | Mardani Nafchi *et al*. (2025) |
| | | | *Mus musculus* (C57BL/6 mice) | Li *et al*. (2025) |
| | | | *Rattus norvegicus* (Sprague-Dawley rats) | Ranjan and Gautam (2023) |
| Anti-inflammatory | NF-κB (IκBα stabilization) ↓, MAPKs (p38, JNK, ERK1/2)↓, NLRP3↓ | Inhibition of TNF-α, IL-1β, IL-6, iNOS, COX-2, MPO; M2 microglial polarization | *Mus musculus* (C57BL/6 mice) | Zhao *et al*. (2024) |
| | | | *Rattus norvegicus* (Wistar rats) | Azimi *et al*. (2025) |
| | | | *Mus musculus* (BALB/c mice) | Li *et al*. (2025) |
| Mitochondrial Protection | PGC-1α↑, UCP2↑, NRF1↑; mPTP suppression | Enhanced biogenesis; reduced mitochondrial ROS; preserved mitochondrial membrane potential; maintained $Na^+$-$K^+$ ATPase | *Rattus norvegicus* (Wistar rats) | Mardani Nafchi *et al*. (2025) |
| | | | *Rattus norvegicus* (Sprague-Dawley rats) | Ranjan and Gautam (2023) |
| Anti-apoptotic | Bcl-2/Bcl-xL↑, Bax↓, caspase-3/9↓, p53↓ | Prevention of cytochrome c release; apoptosome inhibition; intrinsic apoptosis suppression | *Rattus norvegicus* (Wistar rats) | Almutary *et al*. (2025) |
| | | | *Rattus norvegicus* (Wistar rats) | Rostamian *et al*. (2023) |
| Neurotrophic | BDNF↑, GDNF↑; TrkB → PI3K/Akt/mTOR, MAPK/ERK | Neuronal survival; synaptic plasticity; hippocampal neurogenesis; axonal growth | *Rattus norvegicus* (Wistar rats) | Rostamian *et al*. (2023) |
| | | | *Rattus norvegicus* (Wistar rats) | Almutary *et al*. (2025) |
| Cholinergic / Monoaminergic | AChE↓, MAO-B↓ | Increased synaptic ACh, 5-HT, DA, NE | *Rattus norvegicus* (Sprague-Dawley rats) | Ranjan and Gautam (2023) |
| | | | *Mus musculus* (Swiss albino mice) | Ullah and Khan (2018) |
| Anticancer | STAT3↓, Akt/mTOR↓, Bax/Bcl-2↑, p21/p27↑, HIF-1α↓ | $G_1$ cell cycle arrest; extrinsic/intrinsic apoptosis; anti-angiogenesis; anti-metastasis | *Mus musculus* (Athymic nude mice) | Srivastava *et al*. (2025) |
| | | | *Mus musculus* (BALB/c nude mice) | Wang *et al*. (2023) |
| Hepatoprotective | TGF-β/SMAD↓, PPAR-α↑, HSC inactivation, RNA Pol I↑ | Anti-fibrotic; reduced steatosis; membrane stabilization; hepatocyte regeneration | *Rattus norvegicus* (Wistar rats) | Jaffar *et al*. (2024) |
| | | | *Rattus norvegicus* (Wistar rats) | Bahmani *et al*. (2015) |
| Metabolic / Immunomodulatory | AMPK↑, TLR4↓, U-II antagonism; M1→M2 shift | Improved insulin sensitivity; reduced Th1/Th17 polarization; attenuated steatohepatitis | *Rattus norvegicus* (Wistar rats) | Rahimi *et al*. (2018) |
| | | | *Rattus norvegicus* (Wistar rats) | Azimi *et al*. (2025) |
| Cardioprotective | SIRT1↑, Bcl-2↑, TGFβ1−TβR−Smad2/3↓ | Increased myocardial salvage; improved contractility; reduced cardiac fibrosis | *Mus musculus* (C57BL/6 mice) | Cai *et al*. (2024) |
| | | | *Mus musculus* (C57BL/6 mice) | Liu *et al*. (2025) |
| | | | *Rattus norvegicus* (Sprague-Dawley rats) | Jubaidi *et al*. (2021) |

**Pharmacokinetics of Silymarin**

The pharmacokinetic profile of silymarin (Figure 4) is complex and is mainly characterized by poor oral bioavailability, extensive phase II metabolism, and relatively significant enterohepatic recirculation (Gillessen and Schmidt, 2020; Li *et al.*, 2025). These processes may help explain the discrepancy between its reported *in vitro* activity and the relatively low plasma concentrations observed after oral administration (Li *et al.*, 2025) (Figure 4. Despite this, hepatic exposure is maintained to some

extent largely due to preferential liver uptake and recycling within the enterohepatic system (Gillessen and Schmidt, 2020; Li *et al.*, 2025).

Following oral intake, silymarin is poorly absorbed from the gastrointestinal tract due to its physicochemical properties of low water solubility, relatively large molecular size, pre-systemic metabolism, and active efflux via intestinal transporters, all of which appear to limit its bioavailability (Gillessen and Schmidt, 2020; Achufusi *et al.*, 2024). The bioavailability of silibinin, its primary active compound, ranges between 20% and 50%, depending on the formulation used (Li *et al.*, 2025). Silymarin flavonolignans are rapidly distributed, with a greater tendency to accumulate in the liver, its main target organ, and are efficiently transported into bile (Gillessen and Schmidt, 2020). Peak plasma levels are generally reached within 2–4 hours, and absorption is notably improved when silymarin is taken with fatty meals or formulated as phospholipid complexes (phytosomes), which enhance solubility and membrane transport (Li *et al.*, 2025).

The flavonolignans are highly plasma protein-bound (90–95%) (Gillessen and Schmidt, 2020). Concentration in the liver is high due to portal circulation and enterohepatic recycling (Gillessen and Schmidt, 2020; Li *et al.*, 2025). Cytochrome P450 mediated phase I metabolism is minimal but phase II glucuronidation and sulfation are extensive (Gillessen and Schmidt, 2020; Achufusi *et al.*, 2024).

Silymarin is eliminated primarily through the biliary-fecal route, with seemingly a small portion cleared by the kidneys (Gillessen and Schmidt, 2020). Renal excretion is relatively minimal, accounting for about 3-7% of total elimination, indicating a low renal burden and supporting its safety in patients with renal impairment (Gillessen and Schmidt, 2020). The half-life of silibinin typically ranges from 4 to 8 hours, though this can vary with formulation, dose, and individual physiological factors (Gillessen and Schmidt, 2020). The low systemic bioavailability but sustained hepatic activity is central to its therapeutic utility in disorders (Li *et al.*, 2025). The dominance of conjugated metabolites, such as glucuronide and sulfate conjugates, enterohepatic recycling, and strong hepatic uptake all favor liver exposure over systemic circulation (Li *et al.*, 2025).

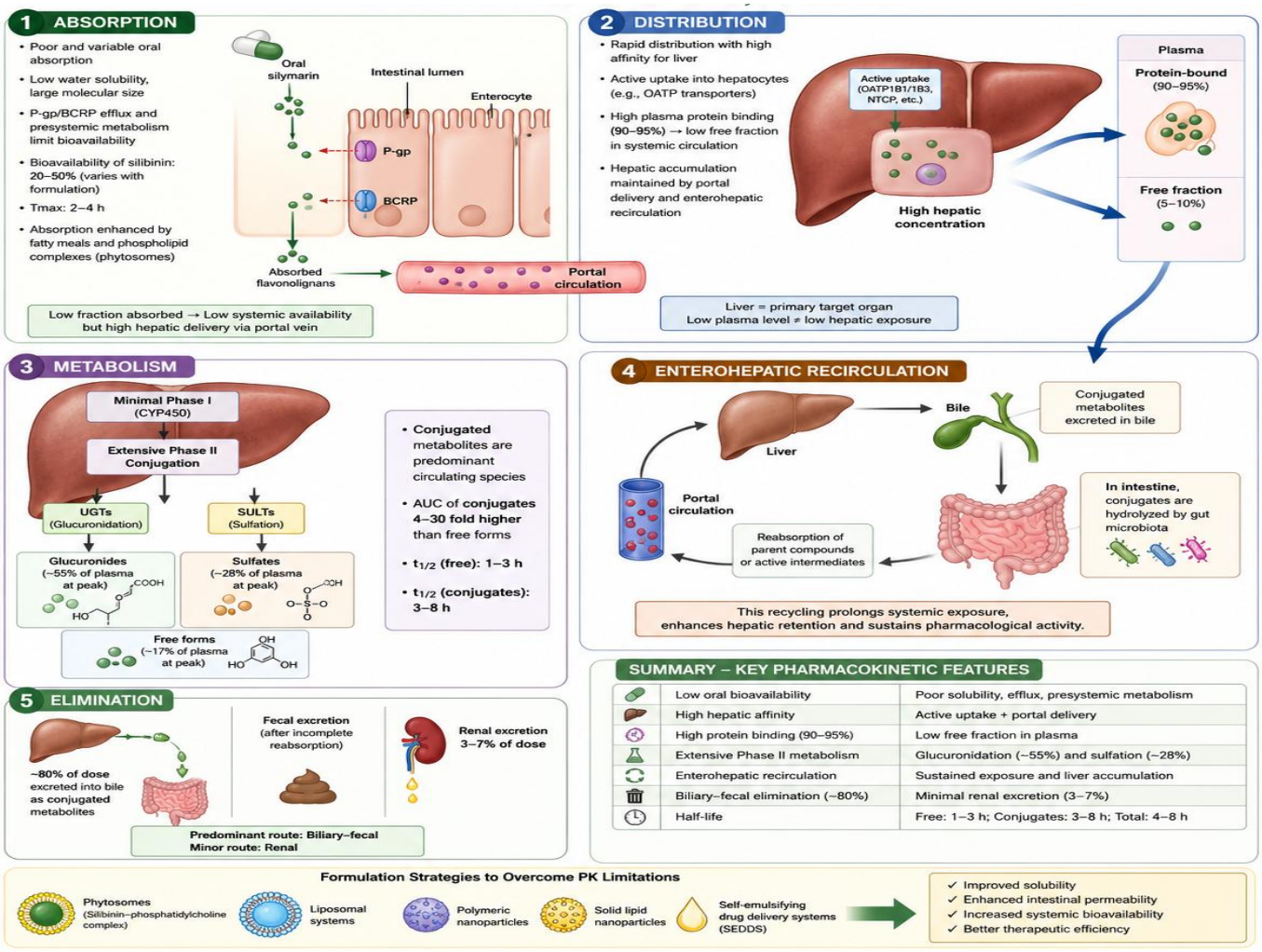


**Figure 4:** Pharmacokinetic profile of silymarin. Poor absorption due to poor solubility and P-gp-mediated efflux mechanism; rapid distribution with high hepatic accumulation and plasma protein binding; minimal phase I, but extensive phase II metabolism (glucuronidation); enterohepatic recycling and major fecal excretion.

**Addressing Pharmacokinetic Limitations**

Multiple interacting biopharmaceutical barriers, including: (a) minimal aqueous solubility (~0.4 mg/mL for silybin) (Li *et al.*, 2025); (b) active efflux by the intestinal transporters P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) (Tvrdý *et al.*, 2021); (c) gastric instability and limited membrane permeability (Li *et al.*, 2025); and (d) extensive and stereoselective phase II intestinal and hepatic glucuronidation and sulfation, account for the extremely low bioavailability of silymarin (Tvrdý *et al.*, 2021; Wu *et al.*, 2009). The blood-brain barrier (BBB) further limits central nervous system (CNS) bioavailability, a challenge that is particularly pronounced for the more hydrophilic flavonolignan constituents (Li *et al.*, 2025).

In a bid to overcome these pharmacokinetic bottlenecks, several advanced delivery methods such as liposomes (Li *et al.*, 2025), nanoemulsions (El Sayed *et al.*, 2025), polymeric micelles/phytosomes (Karbasforooshan *et al.*, 2024), and metal-organic frameworks (Yasmin *et al.*, 2024) are being introduced to substantially improve the bioavailability of silymarin (Figure 5).

**Translational Prospects**

Despite compelling mechanistic and preclinical data, well-powered randomized controlled trials in neurological populations remain comparatively limited. Some of the positive clinical trials are the nano-silymarin trial for prevention of chemotherapy-induced peripheral neuropathy (CIPN) (Karbasforooshan *et al*., 2024), the double-blind placebo-controlled immunomodulatory trial in MS patients (Abbasirad *et al*., 2021), and the Parkinson's disease trial at Tanta University (Ranjan and Gautam, 2023). These studies have expanded understanding of silymarin's therapeutic potential. Despite these trials, important limitations and unanswered mechanistic questions remain. One is the difference in neuroprotective efficacy of silymarin in response to ER-β activation for traumatic brain injury and Parkinson's disease models (Ranjan and Gautam, 2023). This requires characterization under other conditions as well, and should guide future trial design. Secondly, the differential apoptotic regulation of the brain regions, shown in the PTSD models (Emudainohwo *et al*., 2026b), suggests that similar doses of silymarin could produce contrasting effects in the different brain regions. Thirdly, there is a lack of neuroprotective efficacy in some epilepsy models; this needs to be clarified. Fourth, there is a significant lack of human dose-response and long-term safety data in neurological patients.

A further, underappreciated hurdle for clinical translation is the lack of chemotypic standardization of commercial silymarin extracts. Because silybin A and silybin B are typically present in roughly equal amounts but differ in their receptor- and enzyme-binding affinities and downstream pharmacological potency (Table 1), batch-to-batch and product-to-product variation in the silybin A:B ratio, as well as in the relative proportions of silychristin, isosilychristin, and silydianin, can materially alter the pharmacological profile of a given extract. This raw-material variability is rarely reported in clinical trials of silymarin or silibinin, yet it plausibly contributes to the inconsistent efficacy signals across studies and complicates cross-trial comparison and meta-analysis. Establishing analytically validated, chemotype-standardized extracts, with declared silybin A:B and flavonolignan ratios, is therefore a prerequisite for reproducible dose-response modeling and for meaningful comparison of outcomes across future clinical trials.

Future research priorities should include adequate powering of clinical trials in Alzheimer's disease and Parkinson's disease; testing of the ability of silybin A and B, silychristin and silydianin to produce their own specific neuroprotective effects; the application of precision medicine approaches to identify patient subpopulations most likely to benefit from treatment based on disease stage, pharmacogenomic profile or biological sex; and mechanistic dissection of the individual contributions of silybin A and B, silychristin and silydianin to specific neuroprotective outcomes.

## CONCLUSION

Overall, silymarin has clearly evolved beyond its classic role in liver protection to become a multi-target therapeutic compound. The extensive pharmacological action profile of Nrf2 activation, NF-κB/NLRP3 anti-inflammatory activity, mitochondrial biogenesis (via PGC-1α), pro-survival PI3K/Akt/mTOR and MAPK/ERK kinase signaling, cholinergic and monoaminergic modulation (AChE/MAO-B inhibition), ER-β-mediated neuroprotection, anticancer cell cycle arrest and apoptosis induction, M1→M2 immunomodulation, and metabolic homeostasis (AMPK/PPAR-α) provide a comprehensive pharmacological platform that maps onto the shared and common pathomechanisms of a wide range of diseases, such as acute CNS injuries and chronic neurodegenerative diseases, neuropsychiatric disorders, hepatic fibrosis, malignancies and metabolic disorders. Innovative formulations are steadily overcoming poor oral bioavailability, the most challenging translation hurdle, and are now clinically validated. Silymarin is therefore one of the most intriguing natural compounds to be studied in modern biomedical research: a compound that simultaneously bridges the acute neuroprotective to the chronic neuropsychiatric resilience aspects of brain health, the hepatologic to the emerging neuropharmacologic, and the preclinical mechanistic rigor to the emerging clinical validation (Almutary *et al*., 2025; Ranjan and Gautam, 2023; Jaffar *et al*., 2024; Srivastava *et al*., 2025).

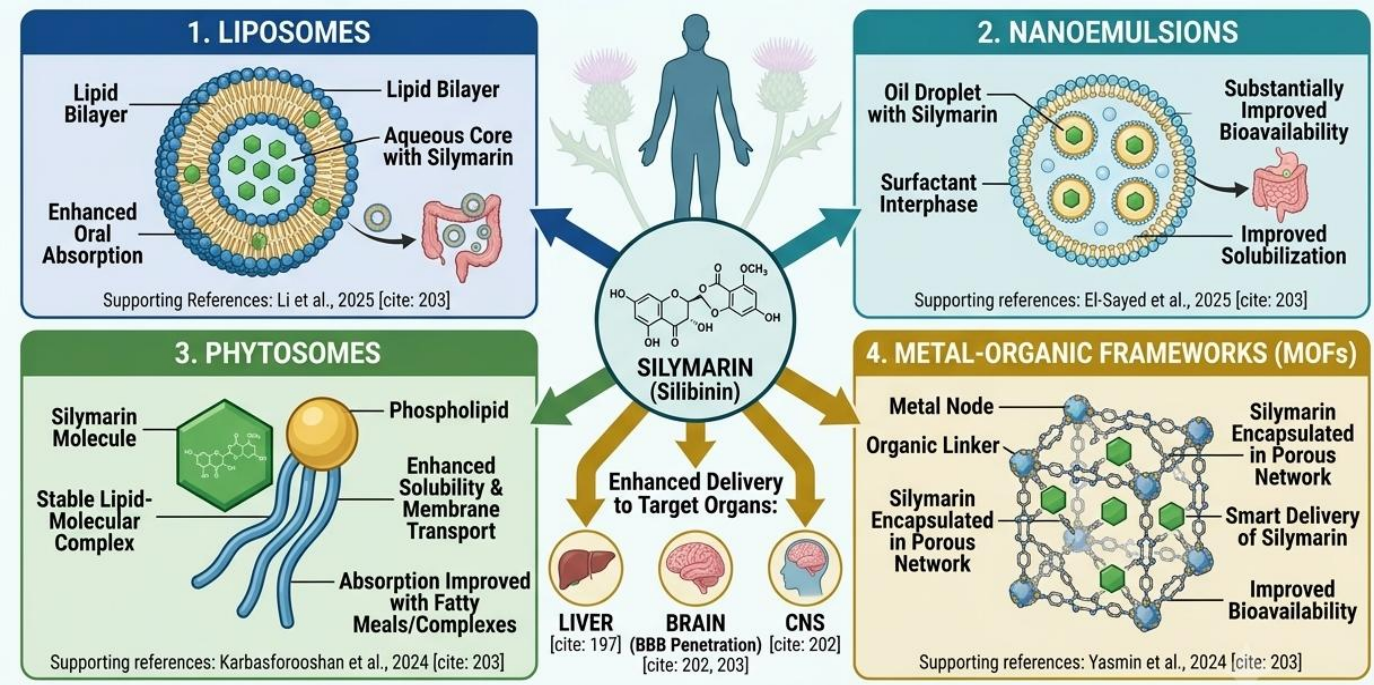


**Figure 5:** Advanced formulation strategies aimed at enhancing the bioavailability of silymarin. The formulations include liposomes, nanoemulsions, phytosomes, and metal-organic frameworks.

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None

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHORS' CONTRIBUTION

JOTE: Conceptualization, Writing - Original Draft, Review & Editing, Visualization; FS: Writing - Review & Editing; BB-A: Writing - Review & Editing, Validation; IOB: Writing - Review & Editing; RIO: Conceptualization, Supervision, Writing - Review & Editing, Validation.

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We used Grammarly software to check grammar before submission.

## AUTHORS' DECLARATION

We declare that this narrative review is original and that any liability for claims relating to its contents will be borne by us.

## ABBREVIATIONS

**5-HT:** 5-hydroxytryptamine (serotonin)

**ABCA1:** ATP-binding cassette transporter A1

**AChE:** Acetylcholinesterase

**AD:** Alzheimer's disease

**Akt:** Protein kinase B

**AKT1:** AKT serine/threonine kinase 1

**AMPK:** AMP-activated protein kinase

**ARE:** Antioxidant response element

**Aβ:** Amyloid-beta

**APP:** Amyloid precursor protein

**BACE1:** β-site amyloid precursor protein cleaving enzyme 1

**Bax:** Bcl-2-associated X protein

**Bcl-2:** B-cell lymphoma 2

**Bcl-xL:** B-cell lymphoma-extra large

**BDNF:** Brain-derived neurotrophic factor

**Caspase:** Cysteine-aspartic protease

**CAT:** Catalase

**CNS:** Central nervous system

**COX-2:** Cyclooxygenase-2

**CUL3:** Cullin 3

**CYP2E1:** Cytochrome P450 2E1

**D4GDI:** Rho GDP-dissociation inhibitor 2

**DA:** Dopamine

**ERK:** Extracellular signal-regulated kinase

**ER-β:** Estrogen receptor beta

**FOLFOX6:** Folinic acid, fluorouracil, and oxaliplatin (chemotherapy regimen)

**GDNF:** Glial cell line-derived neurotrophic factor

**GPx:** Glutathione peroxidase

**GSH:** Reduced glutathione

**GST:** Glutathione S-transferase

**HepG2 cells:** Human hepatocellular carcinoma (liver cancer) cell line

**HIF-1α:** Hypoxia-inducible factor-1 alpha

**HO-1:** Heme oxygenase-1

**HSC:** Hepatic stellate cell

**ICH:** Intracerebral hemorrhage

**IL:** Interleukin

**iNOS:** Inducible nitric oxide synthase

**IκB-α:** Inhibitor of kappa B alpha

**JAK:** Janus kinase

**JNK:** c-Jun N-terminal kinase

**KEAP1:** Kelch-like ECH-associated protein 1

**LPS:** Lipopolysaccharide

**M1:** Pro-inflammatory macrophage/microglial phenotype

**M2:** Anti-inflammatory (reparative) macrophage/microglial phenotype

**Maf:** Minor allele frequency

**MAO-B:** Monoamine oxidase B

**MAPK:** Mitogen-activated protein kinase

**MASLD:** Metabolic dysfunction-associated steatotic liver disease

**MDA:** Malondialdehyde

**MDA-MB-231:** Human breast adenocarcinoma cell line

**miR:** MicroRNA

**MPO:** Myeloperoxidase

**mPTP:** Mitochondrial permeability transition pore

**MS:** Multiple sclerosis

**mTOR:** Mechanistic (mammalian) target of rapamycin

**NACHT:** Nucleotide-binding domain shared by NAIP, CIITA, HET-E, and TP1 (the central domain of NLRP3)

**NAFLD:** Non-alcoholic fatty liver disease

**NE:** Norepinephrine

**NF-κB:** Nuclear factor kappa-beta

**NLRP3:** NOD-like receptor family pyrin domain-containing 3

**NRF1:** Nuclear respiratory factor 1

**Nrf2:** Nuclear factor erythroid 2-related factor 2

**p21:** Cyclin-dependent kinase inhibitor 1A

**p27:** Cyclin-dependent kinase inhibitor 1B

**p38:** p38 mitogen-activated protein kinase

**p50:** NF-κB subunit p50

**p53:** Tumor protein p53

**p65:** NF-κB subunit p65 (RelA)

**PGC-1α:** Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

**P-gp:** P-glycoprotein

**PI3K:** Phosphatidylinositol 3-kinase

**PPAR-α:** Peroxisome proliferator-activated receptor alpha

**PTSD:** Post-traumatic stress disorder

**Raf-1:** Rapidly accelerated fibrosarcoma-1 (proto-oncogene serine/threonine-protein kinase)

**RBX1:** RING-box protein 1

**RNA:** Ribonucleic acid

**ROS:** Reactive oxygen species

**SIRT:** Silent information regulator

**SMAD/Smad:** Signal transducers of the TGFβ family of growth factors

**SOD:** Superoxide dismutase

**SPS:** Single prolonged stress

**STAT:** Signal transducer and activator of transcription

**TGF-β:** Transforming growth factor beta

**Th:** T-helper cell

**THP-1:** Human monocytic leukemia cell line

**TLR4:** Toll-like receptor 4

**TNF-α:** Tumor necrosis factor alpha

**TrkB:** Tropomyosin receptor kinase B

**TβR:** Transforming growth factor-beta receptor

**UCP2:** Uncoupling protein 2

**U-II:** Urotensin II

**UTR:** Urotensin II receptor

**VEGF:** Vascular endothelial growth factor

**XELOX:** Capecitabine (Xeloda) plus oxaliplatin (chemotherapy regimen).

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