Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31768

Progress in Pharmacological Research on Silibinin

Jiaqi Chen

School of Health Science and Engineering, Hubei University, Wuhan, China
3051955429@qq.com

Abstract. **:** Silibinin is a flavonoid compound from Silybum marianum. It has gotten a lot of attention because it works on many targets and pathways. Recent studies show that silibinin has significant bioactivity in many systems. These include hepatoprotection, anti-fibrosis, metabolic regulation, anti-tumor, anti-infective, cardiovascular, and dermatological protection. Its main mechanisms involve inhibiting lipid peroxidation and modulating key signaling pathways like NF-κB, AMPK, and Wnt/β-catenin. It also maintains mitochondrial homeostasis and energy metabolism and regulates cell cycle and apoptotic pathways. This is how it intervenes in tissue damage and pathological processes. At the same time, new drug delivery systems are being developed. These include nanocrystals, liposomes, and phospholipid complexes. They offer new ways to improve bioavailability and targeting. However, there are still challenges. These include poor solubility, low bioavailability, and not enough high-quality clinical trials. These problems limit the clinical translation and broader application of silibinin.

Keywords: Silibinin, Hepatoprotection, Metabolic Regulation, Anti-tumor Activity, Antioxidant and Anti-inflammatory Effects

1. Introduction

1.1. Chemical characteristics and sources of silibinin

Silibinin is the principal bioactive compound extracted from the seeds of Silybum marianum, a member of the Asteraceae family, and belongs to the flavonoid lignans class. Its chemical structure comprises a dihydroflavonol backbone linked to a phenylpropanol moiety, containing multiple phenolic hydroxyl groups that confer potent free radical scavenging and antioxidant properties.

1.2. Background and clinical significance of the study

Chronic diseases, including liver disorders—such as non-alcoholic fatty liver disease, liver fibrosis, and drug-induced liver injury—and cancers have become a significant global public health burden, highlighting the urgent need for multi-target therapeutic strategies.

• Epidemiological Status: Approximately 38.7% of the global population exhibits abnormal liver function indicators, with the prevalence of fatty liver rising to 25.2%. Moreover, the incidence of drug-induced and alcoholic liver injury continues to increase, representing a major public health concern.

DOI: 10.54254/2753-8818/2026.PJ31768

• Limitations of Traditional Applications: Silymarin-based formulations have long been employed for hepatoprotection; however, their therapeutic efficacy is often limited due to single-ingredient composition and poor oral bioavailability. For instance, the bioavailability of conventional hepatoprotective tablets is only 1/26 that of newer formulations.

• Opportunities for Drug Repurposing ("Old Drugs for New Uses"): Recent studies indicate that, beyond hepatoprotection, silibinin exhibits potential efficacy in anti-tumor activity, metabolic regulation, and radioprotection. These findings suggest that silibinin could be repurposed from a liver-protective agent to a multi-target, multi-indication therapeutic candidate.

2. Hepatoprotective effect and mechanism integration

2.1. Hepatocyte protection and repair mechanism

Silibinin inhibits lipid peroxidation, thereby improving hepatocyte membrane fluidity and maintaining functional integrity [1]. Additionally, it can competitively block the binding of mycotoxins to specific membrane receptors and inhibit their transmembrane transport, thus modulating hepatointestinal toxin circulation and significantly enhancing cellular stability [2].

In residual liver tissue following hepatocyte injury or partial hepatectomy, silibinin binds to and activates estrogen receptors, enhancing RNA polymerase I activity in hepatocyte nuclei. This promotes ribosomal RNA transcription and cytosolic ribosome biogenesis, accelerating the synthesis of enzymes and structural proteins. Consequently, hepatocyte repair and regeneration are facilitated through the indirect promotion of DNA synthesis. Clinical studies have further confirmed that silibinin administration can protect residual liver tissue and support functional recovery after hepatectomy [3].

2.2. Anti-fibrosis and anti-irrhosis mechanism

Liver fibrosis is a pathological repair response triggered by chronic liver injury and represents a critical step in the progression of various chronic liver diseases toward cirrhosis. It is also a key determinant of liver disease prognosis. Hepatic stellate cells (HSCs) play a central role in fibrogenesis. Silibinin has been shown to inhibit HSC proliferation and induce apoptosis [4], while concurrently suppressing collagen synthesis and deposition and blocking pro-fibrotic signaling pathways [5].

In liver diseases like NASH, silibinin reduces liver inflammation and slows disease progression. It does this by scavenging reactive oxygen species (ROS) and inhibiting overactivation of the NF-κB signaling pathway. It also downregulates tumor necrosis factor-α (TNF-α). This disrupts the positive feedback loop between NF-κB and TNF-α [6].

2.3. Mitochondrial homeostasis and energy metabolism regulation

Silibinin improves mitochondrial respiratory chain function. This is done by upregulating optic atrophy 1 (OPA1). It promotes mitochondrial fusion and repairs the structure of the mitochondrial cristae. Experiments show silibinin can increase mitochondrial complex II activity by about 1.8 times. It also boosts ATP production by around 30%. This shows its role in maintaining energy metabolism.Also, silibinin activates the PPARα signaling pathway. This speeds up the breakdown of fatty acids. It reduces liver triglyceride (TG) levels by over 40%. At the same time, it stops the creation of new fats and suppresses inflammation. So, it improves fatty liver disease through several mechanisms [7].

DOI: 10.54254/2753-8818/2026.PJ31768

3. Metabolic regulation and insulin sensitivity improvement

Glucolipotoxicity refers to the synergistic deleterious effect of excessive free fatty acids (FFAs) and glucose on pancreatic islet β cells in hyperglycemic conditions, leading to intracellular lipid accumulation, impaired insulin secretion, and apoptosis. Silibinin has been shown to upregulate the expression of insulin-induced gene-1 (Insig-1) and enhance its binding to SREBP cleavage-activating protein, thereby inhibiting the transport and activation of SREBP-1c. This suppresses intracellular lipid synthesis, effectively alleviating glucolipotoxicity, improving β-cell function, and reducing apoptosis [6,8].

Silibinin also enhances glucose metabolism issues in type 2 diabetes by activating the AMPK signaling pathway. It greatly increases AMPK phosphorylation in skeletal muscle and liver. This helps move glucose transporter 4 (GLUT4) to the cell membrane. This increases how well cells take in glucose by about 30%. So, it improves insulin sensitivity in peripheral tissues.Additionally, silibinin lowers the expression of key gluconeogenic enzymes. These are PEPCK and G6Pase. It reduces their expression by about 45% and 38% respectively. This decreases the liver's glucose output and stops new glucose production. Together, these actions help maintain stable blood sugar levels [9].

Insulin resistance (IR) is a key problem in metabolic syndrome. It shows up as reduced insulin sensitivity, poor blood sugar control, and frequent issues with fat metabolism. Research shows silibinin significantly improves insulin sensitivity and how tissues use glucose. It does this by boosting glycogen production in the liver and skeletal muscle. At the same time, it lowers triglyceride (TG) buildup in the liver and other tissues. This helps improve insulin tolerance [10].

4. Anti-tumor effects and molecular mechanisms

4.1. Tumor microenvironment intervention

The tumor inflammatory microenvironment is a complex pathological system shaped by the coordinated actions of various inflammatory cells and their secreted cytokines and chemokines. Within this microenvironment, reactive oxygen species (ROS), reactive nitrogen species (RNS), and other inflammatory products can induce gene damage and malignant transformation in normal cells. Concurrently, inflammatory cells such as macrophages and lymphocytes promote tumor cell proliferation and angiogenesis by secreting TNF-α, TNF-β, interleukins, and chemokines [11], and they induce epithelial-mesenchymal transition, thereby enhancing tumor cell invasion and metastasis. Collectively, these observations indicate that the tumor microenvironment is a critical factor in tumor maintenance and progression.

Experimental evidence demonstrates that silibinin selectively binds to the substrate-binding site of monocarboxylate transporter 1 (MCT1) and inhibits its conformational changes, thereby blocking lactate efflux and significantly lowering the extracellular pH of hepatocellular carcinoma cells. By disrupting the acidic microenvironment adapted by tumor cells, silibinin further induces apoptosis and suppresses tumor growth [12].

During abnormal tumor proliferation, inadequate oxygen supply creates a hypoxic microenvironment, which triggers metabolic reprogramming and the activation of angiogenesis-related enzymes and growth factors to sustain energy production and promote neovascularization [13,14]. Hypoxia-inducible factor 1 (HIF-1) is a key transcription factor mediating the cellular hypoxia response [15]. HIF-1 is a heterodimer composed of the oxygen-sensitive subunit HIF-1α

DOI: 10.54254/2753-8818/2026.PJ31768

and the constitutively expressed subunit HIF-1β. While HIF-1β expression is stable and not regulated by oxygen levels, HIF-1α stability is closely dependent on oxygen availability.

Further studies revealed that silibinin can suppress HIF-1α expression by downregulating the phosphorylation of mammalian target of rapamycin (mTOR), thereby inhibiting tumor cell proliferation [6].

4.2. Intracellular anti-tumor mechanism

The results of the studydemonstrated that silibinin exhibits significant anti-cancer activity against human hepatocellular carcinoma (HCC) cells, primarily by modulating cell cycle mechanisms [16]. Fluorescence-activated cell sorting (FACS) analysis confirmed that silibinin treatment induces G1 phase arrest in HCC cell lines. Cyclin E, expressed in late G1 phase, forms an active complex with cyclin-dependent kinase 2 (CDK2), which is essential for G1-S phase transition and the initiation of DNA synthesis [17,18]. Further experiments revealed that silibinin treatment decreases the expression levels of cyclin E and CDK2, as well as CDK2-related kinase activity in HCC cells, resulting in G1 phase arrest and inhibition of S phase entry.

Progression from G2 to M phase requires activation of cyclin-dependent kinase 1 (CDK1), which is facilitated by binding to cyclin B116. Experimental evidence indicated that silibinin treatment reduces cyclin B1 expression and decreases both the phosphorylation and total protein levels of CDK1 and the cyclin 25 isoenzyme C (CDC25C), causing Hep3B cells to arrest in G2-M phase. Notably, G2-M phase blockade is often associated with enhanced cytotoxicity [19]. Consistent with these findings, silibinin increased cytotoxicity in Hep3B cells, which is correlated with the induction of apoptosis.

S Mechanistically, silibinin typically upregulates the expression of pro-apoptotic protein Bax while downregulating anti-apoptotic proteins such as Bcl-2 and Bcl-XL, thereby decreasing the Bcl-2/Bax ratio, disrupting mitochondrial membrane potential, and promoting cytochrome C release [20]. The released cytochrome C interacts with apoptotic protease-activating factor 1 (Apaf-1) to form apoptosomes, activating initiator caspase-9 and subsequently effector caspases, including caspase-3 and caspase-7. Activated caspase-3 cleaves various substrates, including poly (ADP-ribose) polymerase (PARP), ultimately leading to apoptosis [21].

4.3. Combination therapy potential

Regarding combination therapy, silibinin may exert synergistic anti-cancer effects and potentially allow for dose reduction of chemotherapeutic agents, thereby minimizing associated side effects. In terms of formulation improvement, the oral bioavailability of silibinin remains low. Research on novel drug delivery systems, including nanocrystals and liposomes, holds promise for enhancing both bioavailability and tumor-targeting efficiency.

5. Antibacterial and immunomodulatory effects

5.1. Direct antibacterial effect

Studies have demonstrated that silibinin exerts significant inhibitory activity against Staphylococcus aureus by disrupting bacterial cell walls and suppressing bacterial protein expression [22]. Further investigations revealed that silibinin markedly inhibits bacterial soluble protein synthesis, reduces DNA and RNA content, attenuates topoisomerase activity, inhibits biofilm formation, and compromises biofilm structural integrity [2].

DOI: 10.54254/2753-8818/2026.PJ31768

Specifically, silibinin may interfere with bacterial division by targeting FtsZ and SSD proteins in S. aureus, resulting in abnormal bacterial morphology [22].

5.2. Host immune defense enhanced

Silibinin significantly enhances phagocytic activity by stabilizing intracellular sulfhydryl (-SH) levels and mitigating oxidative stress-mediated inhibition of macrophage function. Experimental results showed that silibinin treatment increased macrophage phagocytic activity by approximately 3.5-fold, accompanied by modulation of inflammatory factors, including IL-6 and IL-1Ra, suggesting that it may improve immune clearance through redox balance regulation [23].

6. Cardiovascular protective effect

6.1. Anti-atherosclerotic (AS) effect

Atherosclerosis (AS) is a major contributor to severe cardiovascular and cerebrovascular diseases, including myocardial infarction and cerebral infarction, primarily by inducing vascular stenosis and occlusion. Studies have demonstrated that silibinin reduces cholesterol ester accumulation in macrophages and inhibits the formation of macrophage-derived foam cells by promoting the expression of the macrophage cholesterol efflux receptor ABCG1 and enhancing its protein stability. These findings suggest that silibinin exerts a protective effect by maintaining intracellular cholesterol ester homeostasis within atherosclerotic lesions [24].

Oxidative stress is a key factor in the start and progression of AS. Silibinin lowers reactive oxygen species (ROS) and malondialdehyde (MDA) levels. It also boosts the activity of antioxidant enzymes like superoxide dismutase (SOD). This reduces the formation of oxidized low-density lipoprotein (ox-LDL). It also protects endothelial cells from oxidative damage [25].

6.2. Protection of cardiomycytes and resistance to ischemia-reperfusion injury (IRI)

Anestopoulos et al. studied the heart-protecting effects of silibinin. They used an in vitro model of embryonic rat heart-derived H9C2 cells. They tested it against hydrogen peroxide (H_2O_2)-induced oxidative stress and norepinephrine-induced myocardial hypertrophy. The results showed that silibinin pretreatment greatly improved cell survival under H_2O_2 exposure. It also reduced apoptosis and kept the cell structure normal. Also, silibinin stopped norepinephrine-induced hypertrophy and lowered ROS overproduction. This shows it protects heart muscle cells by boosting free radical scavenging and reducing oxidative stress damage [26].

Moreover, Yi-He Chen et al. reported that silibinin showed strong heart-protective effects in rat cardiac ischemia-reperfusion models. This works by inhibiting IKKα phosphorylation. It also prevents IκBα degradation and suppresses p65 NF-κB nuclear translocation. This blocks the abnormal activation of the NF-κB signaling pathway [27].These findings further confirm the potential value of silibinin in the treatment of oxidative stress-related myocardial injury.

7. Antioxidant and barrier function repair of skin

Under ultraviolet (UVB/UVA) radiation and environmental stress, the skin generates excessive reactive oxygen species (ROS), which can disrupt intracellular antioxidant defense systems and induce oxidative damage. Studies have shown that silibinin can inhibit the overactivation of UVB-

DOI: 10.54254/2753-8818/2026.PJ31768

induced MAPK/NF-κB inflammatory signaling and modulate autophagy in both epidermal and dermal cells, thereby effectively alleviating UVB-induced skin inflammation [28].

In addition, silibinin attenuates UV-induced apoptosis by regulating signaling pathways such as IGF-1R and ATM-p53 and stimulating relevant caspase family proteins, thereby protecting both epidermal and dermal cells from photodamage [29].

8. Conclusions and prospects

8.1. Summary of pharmacological activity

Silibinin is a natural flavonoid lignan. It shows multi-system and multi-target pharmacological activities. Its mechanisms are complex and wide. Its main actions involve antioxidant, anti-inflammatory, and metabolic regulatory effects. It protects cells by scavenging free radicals and reducing oxidative stress. It controls inflammatory signaling pathways like NF-κB. This stops the release of pro-inflammatory factors and creates anti-inflammatory effects. At the metabolic level, it regulates lipid and glucose metabolism. This shows potential for treating cardiovascular diseases, cancers, and metabolic disorders. Overall, its effects are systemic and work together. This shows its significant potential for managing complex diseases.

8.2. Current research questions

Preclinical studies have made progress, but silibinin faces challenges in clinical use. High-quality clinical evidence is still limited. There are few large-sample, multicenter trials. This limits strong clinical recommendations. Also, silibinin has low water solubility and bioavailability. Current formulations cannot fully use its pharmacological potential. This limits how well it works. Most mechanism studies use cell and animal models. There is limited verification in human systems. How it works across different organ systems is still unclear. This blocks systematic development and use.

8.3. Future research directions

Future studies should focus on several areas. Research should strengthen the study of cross-system mechanisms. It should use multi-omics and systems pharmacology. This will fully explain silibinin's multi-target, multi-pathway networks. New formulations should be made, like nanoparticles and phospholipid complexes. This will improve bioavailability and tissue targeting. It will make the drug work better while using less. Clinical applications should test combination strategies with chemotherapy or immunotherapy. This could reduce toxicity. They should also look at comprehensive treatments for metabolic diseases like fatty liver disease and diabetes. These approaches aim to expand clinical uses, improve evidence, and help move from basic research to clinical practice.

References

[1] F, W. et al. Preparation of C-23 esterified silybin derivatives and evaluation of their lipid peroxidation inhibitory and DNA protective properties. Bioorg. Med. Chem. 17, (2009).
[2] Jl, P.-F. et al. A Comprehensive Review on the Antibacterial, Antifungal, Antiviral, and Antiparasitic Potential of Silybin. Antibiot. Basel Switz. 13, (2024).
[3] C, L. & D, F. Silybin and the liver: from basic research to clinical practice. World J. Gastroenterol. 17, (2011).
[4] Ec, F., R, W. & Oh, W. Effects of silibinin and of a synthetic analogue on isolated rat hepatic stellate cells and myofibroblasts. Arzneimittelforschung. 47, (1997).

DOI: 10.54254/2753-8818/2026.PJ31768

[5] X, L. et al. Silybin Meglumine Mitigates CCl4-Induced Liver Fibrosis and Bile Acid Metabolism Alterations. Metabolites 14, (2024).
[6] Sh, L. et al. Activation of PI3K/Akt/mTOR signaling pathway triggered by PTEN downregulation in the pathogenesis of Crohn's disease. J. Dig. Dis. 14, (2013).
[7] Mq, L. et al. Alleviation of metabolic dysfunction-associated steatotic liver disease by silymarin is associated with maintaining mitochondrial homeostasis via regulation of optic atrophy 1. J. Pharmacol. Exp. Ther. 392, (2025).
[8] K, C. et al. Overexpression of Insig-1 protects β cell against glucolipotoxicity via SREBP-1c. J. Biomed. Sci. 18, (2011).
[9] J, C. et al. Liposomal Silybin Improves Glucose and Lipid Metabolisms in Type 2 Diabetes Mellitus Complicated with Non-Alcoholic Fatty Liver Disease via AMPK/TGF-β1/Smad Signaling. Tohoku J. Exp. Med. 261, (2023).
[10] S, Y., F, Z., Y, L. & Q, C. Effects of silymarin on insulin resistance and sensitivity: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res. Clin. Pract. 220, (2025).
[11] I, C., R, A. & R, G. Exploring the Crosstalk between Inflammation and Epithelial-Mesenchymal Transition in Cancer. Mediators Inflamm. 2021, (2021).
[12] S, S. et al. Transport mechanism and drug discovery of human monocarboxylate transporter 1. Acta Pharmacol. Sin. 46, (2025).
[13] H, M., Rp, H., M, K. & Bg, W. Hypoxia signaling and the metastatic phenotype. Curr. Mol. Med. 14, (2014).
[14] M, D., L, P., M, S. & J, S. Influence of hypoxia inducible factors on the immune microenvironment in ovarian cancer. Anticancer Res. 34, (2014).
[15] Ja, S., L, W., Le, H. & Cj, H. Hypoxia regulates alternative splicing of HIF and non-HIF target genes. Mol. Cancer Res. MCR 12, (2014).
[16] L, V., C, A., A, T., Rp, S. & R, A. Silibinin efficacy against human hepatocellular carcinoma. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 11, (2005).
[17] A, D., P, S. & Pw, H. Cyclins and cdks in development and cancer: a perspective. Oncogene 24, (2005).
[18] O, C. Linking cyclins to transcriptional control. Gene 299, (2002).
[19] M, C., Jl, P., T, R. & G, K. Cyclin-dependent kinase-1: linking apoptosis to cell cycle and mitotic catastrophe. Cell Death Differ. 9, (2002).
[20] Hj, W., S, T., S, O. & T, I. Inhibition of insulin-like growth factor 1 receptor signaling enhanced silibinin-induced activation of death receptor and mitochondrial apoptotic pathways in human breast cancer MCF-7 cells. J. Pharmacol. Sci. 107, (2008).
[21] D, T., R, K., Tv, B., P, V. & G, K. The molecular machinery of regulated cell death. Cell Res. 29, (2019).
[22] P, B. et al. Staphylococcus aureus major cell division protein FtsZ assembly is inhibited by silibinin, a natural flavonolignan that also blocked bacterial growth and biofilm formation. Int. J. Biol. Macromol. 279, (2024).
[23] M, T., J, D., U, T., K, H. N. & S, A. Restoration of the cellular thiol status of peritoneal macrophages from CAPD patients by the flavonoids silibinin and silymarin. Free Radic. Res. 34, (2001).
[24] L, W. et al. Silymarin Constituents Enhance ABCA1 Expression in THP-1 Macrophages. Mol. Basel Switz. 21, (2015).
[25] R, L., Pm, S., R, W. & W, V. Inhibitory action of silibinin on low density lipoprotein oxidation. Arzneimittelforschung. 48, (1998).
[26] I, A. et al. Silibinin protects H9c2 cardiac cells from oxidative stress and inhibits phenylephrine-induced hypertrophy: potential mechanisms. J. Nutr. Biochem. 24, (2013).
[27] Yh, C. et al. Protective role of silibinin against myocardial ischemia/reperfusion injury-induced cardiac dysfunction. Int. J. Biol. Sci. 16, (2020).
[28] Rp, S., S, D., S, M., C, A. & R, A. Silibinin inhibits UVB- and epidermal growth factor-induced mitogenic and cell survival signaling involving activator protein-1 and nuclear factor-kappaB in mouse epidermal JB6 cells. Mol. Cancer Ther. 5, (2006).
[29] W, L. et al. Silibinin protects murine fibroblast L929 cells from UVB-induced apoptosis through the simultaneous inhibition of ATM-p53 pathway and autophagy. FEBS J. 280, (2013).