

## Silymarin's Potential in Countering Drug-induced Cardiotoxicity, Nephrotoxicity, and Hepatotoxicity: A Narrative Review

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### Abstract

According to availability of natural products, lower cost and less toxic effects compared to synthetic drugs make them an easy and excellent choice in the treatment of diseases. Silymarin “milk thistle” has been used for many years. Silymarin has antioxidant, anti-lipid peroxidation, anti-fibrotic, anti-inflammatory, and immunomodulatory properties. These effects are due to the addition of endogenous antioxidant enzymes, inhibition of neutrophil infiltration, and a reduction in serum malondialdehyde as an end product of myocardial lipid peroxide. The antioxidant and anti-inflammatory properties of silymarin may also have a protective role against carcinogens. Studies have shown that Silymarin can have protective effects against hepatotoxicity, nephrotoxicity and cardiotoxicity caused by chemical agents. A notable feature is the prowess of silymarin in shielding against reperfusion injury and inflammation, sustained by its unwavering support of anti-inflammatory and antioxidant functions. This review provides a comprehensive survey of the potentials of silymarin in cardio-protection, nephroprotection, and hepatoprotection.

**Keywords:** Silymarin, Nephrotoxicity, Hepatotoxicity, Cardiotoxicity

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### 1. Introduction

The use of medicinal plants in the treatment of diseases has been reported since ancient times. In the case of liver disease, some species like *Silybum Marianum* have been shown to improve liver damage (1). Silymarin, a natural compound found in species derived from *Silybum Marianum*, contains at least seven flavolignans along with the flavonoid taxifolin. Notable among them are silybin, silydianin, and silychristin, with silybin accounting for a substantial 50- 70% of the silymarin extract. Silymarin is clinically utilized in cirrhosis, viral hepatitis, and protection against poisoning induced by *Amanita phalloides* (2-4). The antioxidant and anti-inflammatory properties of silymarin may also have a protective role against carcinogens (5). Studies have shown that

silymarin can have protective effects against hepatotoxicity, nephrotoxicity, and cardiotoxicity caused by chemical agents (4, 6, 7).

Silymarin contributes to antioxidant protection in a variety of ways. First, it acts through direct free radical scavenging. Second, it prevents the formation of free radical material by inhibiting specific enzymes that generate free radical material or maintaining integrity under stress conditions in the mitochondrial electron transport chain (8). Third, it contributes mainly to the maintenance of the optimal redox state of the cell by activating several antioxidant enzymes and non-enzymatic antioxidants, including Nrf2 and NF- $\kappa$ B. Finally, it activates various defensive molecular vitamins responsible for synthesis, such as HSP, thioredoxin (Trx), and sirtuins, and provides additional protection against chemical agents (4, 8). Administration of silymarin before or after the chemical-induced injury has prevented or reduced toxicity (3, 6, 8).

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Thus, Silymarin seems to have the potential as a protective agent against drug toxicity due to its antioxidant, anti-inflammatory, and anti-apoptotic activities. This review summarizes the existing literature that has examined the nephroprotective, cardioprotective, and hepatoprotective effects of silymarin against drug-induced toxicity.

## 2. Methods

### 2.1 Comprehensive Review Approach

This review evaluates and criticizes studies that examine the use of silymarin as a protective agent. Materials for this review were collected by searching Medline, PubMed, and the Scopus database. Keywords used as search terms include "silymarin", "milk thistle", "Silybum Marianum", "silybin", "silibinin", "nephrotoxicity", "hepatotoxicity", "nephroprotective", "cardiotoxicity", "cardioprotective", "hepatotoxicity", and "hepatoprotective". The findings extracted from the scientific literatures are summarized in Table 1.

## 3. Result

### 3.1 Silymarin and its role in preventing Drug-induced Cardiotoxicity

Cytotoxic agents used in cancer therapy can detrimentally impact the cardiovascular system. Cardiotoxicity is one of the most important side effects of cancer treatment and is responsible for significant morbidity and mortality. The most common and serious adverse effects of chemotherapeutic agents on the cardiovascular system are heart failure with ventricular systolic dysfunction. Other toxic effects include hypertension, thromboembolic disease, arrhythmias, and myocardial ischemia (9). Cardiotoxicity has limited their clinical use (9, 10). Silymarin can significantly ameliorate the cardiotoxicity induced by cisplatin and doxorubicin (11).

Doxorubicin is a potent chemotherapeutic agent, and its therapeutic efficacy comes with a challenge with adverse consequences such as oxidative stress, mitochondrial dysfunction, and cardiotoxicity (8). Oxidative stress and the formation of free radicals are thought to play an essential role in the mechanism of doxorubicin toxicity. Although the adverse effects of doxorubicin extend to multiple organs, its cardiotoxicity is a limiting factor in cancer treatment (12). The cardioprotective effects of silymarin against doxorubicin-

induced cardiotoxicity have been demonstrated through cell membrane stabilization, free radical scavenging, and iron chelation effects. Doxorubicin-induced cardiotoxicity is demonstrated by increased plasma creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) activity and confirmed by severe cardiac histopathological lesions. The results showed that these changes were associated with hyperlipidemia, a significant increase in cardiac malondialdehyde (MDA) levels, and a decrease in glutathione content. Pretreatment with silymarin significantly improved all toxic effects of doxorubicin in the rat heart tissue except for hyperlipidemia (12). Co-administration of silymarin/silibinin could reduce elevated serum levels of cardiac damage-related enzymes (cholesterol, CPK, CK-MB, LDH, and AST) and cardiac troponin I in the doxorubicin-treated groups (13-16) and also may attenuate doxorubicin-induced biochemical changes in cardiac cells/tissues of treated patients (7, 17). In a study by Psotova et al., silymarin and its three components, including silybin, silydianin, and silychristin, showed protection of the rat heart microsomes and mitochondria against iron-dependent doxorubicin-induced lipid peroxidation. The lipid antioxidant activity of silymarin may be due to the presence of taxifolin with chelating and antioxidant activities, and the ability of chemically unidentified polyphenols, including 30% silymarin, to bind to transition metal and quenching reactive oxygen species (ROS) (17). Accordingly, silymarin may have great potential as a novel therapeutic agent to prevent cardiotoxic effects caused by anti-cancer medications (11).

Cisplatin is an effective chemotherapeutic agent for various cancers. Although cisplatin is very effective in the treatment of testicular and ovarian cancer, it causes a large number of toxic side effects. The main side effects of cisplatin are nephrotoxicity, ototoxicity, hepatotoxicity, and gastrointestinal toxicity (18). Cardiac events, reported in numerous case reports, may include ECG (electrocardiogram) changes, arrhythmias, myocarditis, cardiomyopathy, and congestive heart failure (19). Silymarin (100 mg/kg orally, for 10 days) has been used as an antioxidant to protect the heart from cisplatin-induced myocardial damage by reducing the activity of serum biochemical markers, including LDH and CK-MB (20). Silymarin stabilizes the pericardium and prevents the

leakage of cardiac enzymes. In addition, silymarin increases the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) (11).

Silymarin inhibits lipid peroxidation due to the presence of free C5 and C7 hydroxyl groups that react with peroxy radicals. This effect leads to a significant increase in cellular antioxidant defenses. Silymarin also reduces oxidative damage of mitochondrial DNA due to its free radical scavenging properties (21). With different mechanisms and documented efficacy, silymarin assumes a leading role in the fight against cardiotoxicity associated with chemotherapeutic agents such as cisplatin. Silymarin shows promise in reducing treatment-related cardiovascular adverse effects on improving patient outcomes (11). Accordingly, silymarin may have great potential as a novel therapeutic agent to prevent cardiotoxic effects caused by anticancer drugs.

### *3.2 Silymarin and prevention of Drug-induced Nephrotoxicity*

Drug-induced nephrotoxicity (DIN) is a major cause of acute renal failure. DIN is associated with 20% of hospitalization of patients and 8-60% of hospital admissions. Drug-induced kidney disease is recognized as a leading cause of morbidity and mortality (22). Several common mechanisms have been proposed for DIN, including changes in glomerular hemodynamics, tubular cytotoxicity, inflammation, rhabdomyolysis, and microvascular disease. In addition, patient- or drug-related factors may predispose some patients to drug-induced kidney injury (6).

Numerous classes of therapeutic drugs, such as chemotherapeutic agents, aminoglycosides, amphotericin B, contrast agents, calcineurin inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs), and vancomycin are also commonly recognized as nephrotoxic drugs. Silybin and silychristin have been shown to increase proliferation, protein and DNA biosynthesis, and lactate dehydrogenase activity in the renal cells damaged *in vitro* by paracetamol, cisplatin, or vincristine. Administration of silybin before or after chemical trauma has prevented or reduced nephrotoxic effects (23). Thus, silymarin appears to have the potential to become a protective agent against nephrotoxic drugs due to its antioxidant, anti-

inflammatory, and anti-apoptotic effects.

To date, the protective effect of silymarin against drug-induced nephrotoxicity has been studied mainly in animals, and many cases of protection against cisplatin and gentamicin have been reported (24, 25)

The aminoglycosides are broad-spectrum, bactericidal antibiotics that are generally recognized as the most potent nephrotoxic medications. Absorption of aminoglycosides occurs via internalization by megalin transporters. After internalization, aminoglycosides initiate a series of reactions that eventually lead to cell death. To date, increases in intracellular sodium levels, reactive oxygen species and proinflammatory cytokines and apoptosis, decreased glucose, and depletion of adenosine triphosphate (ATP) stores have been suggested as responsible for aminoglycoside-induced renal tubular, glomerular, and vascular injury (26). Moreover, an increase in vasoconstrictor mediators, including angiotensin-II, endothelin-I, thromboxane A2, and ROS, and decreased vasodilatory prostaglandins, have been proposed to explain aminoglycoside-induced vascular dysfunction. Aminoglycoside nephrotoxicity may manifest with non-oliguric renal failure, and its clinical manifestations include increased serum creatinine and urea concentrations, proteinuria, hypomagnesemia, hypocalcemia, and hypokalemia. (27). Varzi and colleagues evaluated the effects of silymarin on gentamicin-induced nephrotoxicity in a study on five groups of dogs. Total serum antioxidant activity was also evaluated as a marker of antioxidant capacity. Dogs that received silymarin concomitantly with gentamicin showed lower increases in serum creatinine and urea and a higher glomerular filtration rate (GFR) than the group that received gentamicin alone. Serum accumulation of MDA, a marker of lipid peroxidation, was also significantly lower, and total serum antioxidant activity was higher in silymarin-treated dogs (28). In a study, Mahi et al. investigated the protective effects of silymarin on hospitalized patients who had received gentamicin. Patients treated with silymarin, unlike those treated with placebo, showed no nephrotoxicity on days 3 and 5. Furthermore, the silymarin-treated group exhibited less nephrotoxicity even on day 7, with a substantially lower increase in serum creatinine levels during gentamicin treatment compared to the placebo group.

Also, the increase in the serum Cr level on days 2, 3, 5, and 7 of gentamicin treatment was higher in the placebo group than in the silymarin group (25).

Cyclosporine is a calcineurin inhibitor, used as an immunosuppressant medication, and is the mainstay of immunosuppressive regimens in transplantation centers. Cyclosporine-induced renal dysfunction is manifested in asymptomatic serum creatinine elevations, acute renal failure, impaired transplant rehabilitation, and even hemolytic uremic syndrome. While antioxidants have been suggested as possible protective agents against cyclosporine-induced nephrotoxicity, more human studies need to be conducted (29).

Zima et al. hypothesized a possible role for silybin in preventing cyclosporine-induced nephrotoxicity. They induced nephrotoxicity with cyclosporine in a rat model. After administering silybin to rats before cyclosporine exposure, they observed reduced concentrations of plasma and renal MDA compared to cyclosporine treatment alone. However, silybin could not prevent the decrease in GFR induced by cyclosporine administration (30).

In the same line, Satyanarayana and colleagues also examined a possible protective role of quercetin, one of the bioflavonoid components of silymarin, against cyclosporine-induced nephrotoxicity (31).

In a rat model of cyclosporine nephrotoxicity, quercetin administration showed a significant renoprotective effect. The quercetin group showed significantly preserved renal function and structure, based on an assessment of plasma creatinine and urea concentrations. The antioxidant properties of quercetin have been implicated in the underlying renal protective mechanism (31).

Vancomycin is a tricyclic glycopeptide antibiotic, used to treat serious infections, is associated with nephrotoxicity and should be limited. According to Guzel et al.'s study on Wistar albino rats, concurrent vancomycin and silymarin administration led to reduced concentrations of MDA, serum urea, and creatinine than in the vancomycin group. Silymarin, especially at increased doses, exerted a potential nephroprotective effect against vancomycin-induced nephrotoxicity due to its antioxidant, anti-inflammatory, and anti-apoptotic properties (32). To maintain the integrity of the kidney against nephrotoxic agents, plant com-

pounds such as silymarin, silybin, and quercetin appear to provide renal protection.

### *3.3 Silymarin and Prevention of Drug-induced Hepatotoxicity*

Silymarin has both hepatoprotective and regenerative effects. It effectively scavenges free radicals, a product of membrane-damaging toxins, and performs competitive inhibition by modifying the outer membrane of hepatocytes. In addition, silymarin stimulates hepatocyte metabolism and activates ribosomal RNA synthesis to stimulate protein formation (33–35). Silymarin is perhaps the most frequently used natural compound to treat liver diseases worldwide due to its antioxidant, anti-inflammatory, and anti-fibrotic activities (36).

Notably, the hepatoprotective effects of silymarin have been investigated in previous studies. It is effective in preventing hepatotoxicity caused by acetaminophen (37), carbon tetrachloride (38), ethanol (39), and the toxins produced by *Amanita phalloides* (40). Most of these results were found in animal models, although some studies have been done on humans and showed the effectiveness of silymarin.

In a study conducted by Sandoval et al., the authors observed a protective effect of silymarin in rat hepatocytes when they used it as a comparator to measure the liver weight per animal (hepatomegaly)(41). Silymarin enhances glutathione production in the liver by increasing cysteine availability and inducing cysteine synthesis while inhibiting its catabolism to taurine. Regulation of cysteine synthesis may then contribute to antioxidant protection (42).

In a study, Marjani et al. evaluated the potential hepatoprotective effects of silymarin in treated cases of tuberculosis. Participants were randomly assigned to a treatment group and a placebo group. Usage of silymarin tablets for two weeks was shown to reduce liver damage caused by anti-tuberculosis medications. Although mild elevations in liver enzymes were observed, these effects were transient, and overall adverse events were not significantly different from those in the placebo group (43). Furthermore, in a comprehensive mouse model undertaken by Aminzadeh et al., simultaneous administration of silymarin with isoniazid, rifampin, and pyrazinamide significantly reduced the risk of anti-tuberculosis drugs hepato-

**Table 1.** The characteristics of the included studies.

Medications	Model	Silymarin dosage and protocol of usage and administration route	Silymarin co-administration outcomes	Ref
Doxorubicin	In vitro/rat heart microsomes and mitochondria	9.66 mg/L (IC50 for microsomes) and 4.90 mg/L (IC50 for mitochondrial)	↓LPO (TBARS)	(17)
	In vitro/rat cardiomyocytes	9.5, 39.0, and 78.0 mg/L and 1 h before DOX incubation and #25, 50, and 100 μM and 1 h before DOX incubation	LDH released activity, ↑ATP formation	(46)
	Clinical study/acute lymphoblastic leukemia patients	20 mg/day for one week after each doxorubicin administration and in the form of a Legalon tablet or Hepaticum syrup	↑ejection fraction, ↑fractional shortening, ↑tissue Doppler peak mitral annulus systolic velocity, ↓serum troponin I levels	(47)
Cisplatin	In vitro/rat cellular and subcellular changes in kidneys	cisplatin (5 mg/kg); silymarin (50 mg/kg) 2 h after cisplatin injection; and silymarin (50 mg/kg) 2 h before cisplatin injection]	Post-treatment of silymarin: ↑body weight returning to normal value, failed in complete protection against the pathological alteration caused by cisplatin Pre-treatment with silymarin: ↓histological and ultrastructural changes	(48)
	Clinical trial/patients with malignancy	Silymarin tablet 140 mg/bid 7 days before Cisplatin administration together with Cisplatin	↓BUN and serum Cr; ↑ in the control group two weeks after Cisplatin administration.	(24)
Gentamicin	In vitro/dog nephrotoxicity	gentamicin sulfate was administrated intramuscularly at a dosage of 20 mg/kg once daily for 9 days. silymarin was administered orally at a dosage of 20 mg/kg once daily for 9 days.	no significant difference in serum creatinine, ↑serum MDA concentration, ↑TSAO activity	(28)
	Clinical Study/ Infectious Patients	Gentamicin is administered for at least 7 days. Patients in the treatment group received, in addition to gentamicin, 140 mg of Silymarin tablets (Livergol®, Goldaru Pharmaceutical Laboratories, Iran) administered orally three times per day with meals up to completing the gentamicin treatment course.	No nephrotoxicity on days 3 and 5. renal toxicity three times less than those treated with a placebo on day 7.	(25)
Cyclosporin	In vitro/male rats nephrotoxicity	silymarin-treated group was orally (200 mg/kg bw/day), cyclosporine treated group was orally supplemented with cyclosporine (5 mg/kg bw/day) and a combination of cyclosporine and silymarine-treated group (Sil+Cyc) were orally supplemented with cyclosporine (5mg/kg, bw/day) and silymarin (200 mg/kg, bw/day).	↓serum creatinine and urea nitrogen in both the Silymarin and Silymarin+Cyclisporin group	(49)
Vancomycin	In vitro/ Wistar albino rats nephrotoxicity	Vancomycin 400mg/kg-day, Silymarin 100mg/kg-day, Vancomycin + Silymarin 50mg/kg-day, Vancomycin + Silymarin 100mg/kg-day and Vancomycin + Silymarin 200 mg/kg-day	↓caspase activities in Vancomycin+Silymarin 200,MDA, ↓serum BUN, and creatinine levels in Vancomycin+Silymarin (50, 100, and 200)	(32)

toxicity. This effect was shown by evaluating histopathological changes caused by anti-tuberculosis drugs and biochemical tests such as AST, ALT,

alkaline phosphatase, and bilirubin levels (44). However, it should be noted that not all studies have shown a protective effect of silymarin against

anti-tuberculosis drugs hepatotoxicity (45).

#### 4. Conclusion

In conclusion, natural plant compounds have recently garnered attention from researchers for their potential in protecting against oxidative stress. The availability of natural products, their lower cost, and fewer toxic effects compared to synthetic drugs make them an appealing choice in diseases treatment.

Silymarin extracted from *S. marianum* has particularly received much attention for its anti-oxidant,

Antitumor, and anti-inflammatory properties. This narrative review underscores the potential of silymarin in protecting against drug-induced cardiotoxicity, nephrotoxicity, and hepatotoxicity, as evidenced by in vivo and in vitro studies. To date, the protective effect of silymarin against drug-induced toxicity has been primarily studied in animals, and further exploration in clinical trials is warranted for more definitive results.

According to the investigations, there is a growing body of evidence confirming the beneficial effects of silymarin on various diseases.

Several mechanisms, including anti-inflammatory properties, free radical scavenging, enhancement of antioxidant defenses, membrane

stabilization, chelating activity, and inhibition of apoptosis, are associated with the cardioprotective effects of silymarin.

Silymarin exhibited numerous cardioprotective activities against chemical-induced toxicity. However, due to the scarcity of human reports, further studies are necessary to establish the utility of silymarin in protecting against cardiotoxicity.

Most studies on silymarin demonstrate promising positive effects on drug- or chemical-induced kidney disease. Given the significant burden that drug-induced nephropathy imposes on patients' morbidity, mortality, and health-related costs, silymarin may be recommended as a nephroprotective agent to mitigate the toxicity of certain medications.

There is substantial evidence from animal studies suggesting that treatment with silymarin improves liver diseases. Therefore, further investigations are warranted to elucidate the mechanisms of action of these compounds. Additionally, concerning patients taking anti-tuberculosis drugs, the use of silymarin did not appear to reduce hepatotoxicity, as indicated by current research.

#### Conflict of Interest

The authors declare no conflict of interest.

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