

# Silymarin and Its Role in Chronic Diseases

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**Abstract** Silymarin is the active constituent of *Silybum marianum* (milk thistle) which is a C-25 containing flavonolignan. Milk thistle has a lot of traditional values, being used as a vegetable, as salad, as bitter tonic, and as galactogogue in nursing mothers and in various ailments such as liver complications, depression, dyspepsia, splenic congestions, varicose veins, diabetes, amenorrhea, uterine hemorrhage, and menstrual problems. In this present chapter, a comprehensive attempt has been made to discuss the potential of silymarin in chronic disorders. An insight into modulation of cellular signaling by silymarin and its implication in various disorders such as liver disorders, inflammatory disorders, cancer, neurological disorders, skin diseases, and hypercholesterolemia is being provided.

**Keywords** *Silybum marianum* · Silymarin · Silybin · Isosilybin · Hepatitis · Cancer · Oxidative stress · Immunomodulation

## 1 Introduction

The commonly known plant milk thistle (*Silybum marianum* L. Gaertn., *Cardus marianus* L., Compositae/Asteraceae) is an ancient plant which is used over 2000 years for the treatment of various disorders [1]. Milk thistle is a tall, biennial herb up to 5–10 ft. with large prickly leaves, large purple flowering heads, and strongly spinescent stems (Fig. 1). The plant derives its name due to the presence of milky veins on the leaves [2]. The plant grows in Kashmir, southern and Western Europe, Southern America, and North America [3]. Traditionally, milk thistle was used as a vegetable in Europe. Leaves were used as salad, and seeds were used as galactogogue in nursing mothers, bitter tonic, and antidepressant, in liver complications (including gallstones), dyspepsia, splenic congestions, varicose veins,

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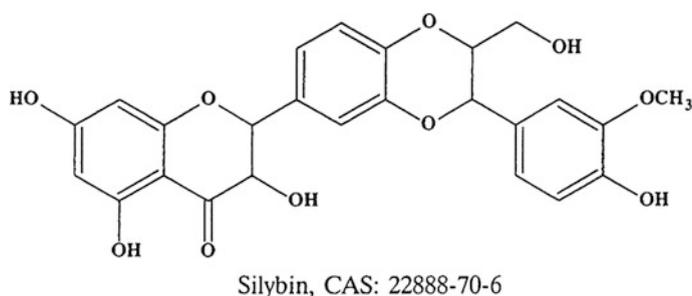
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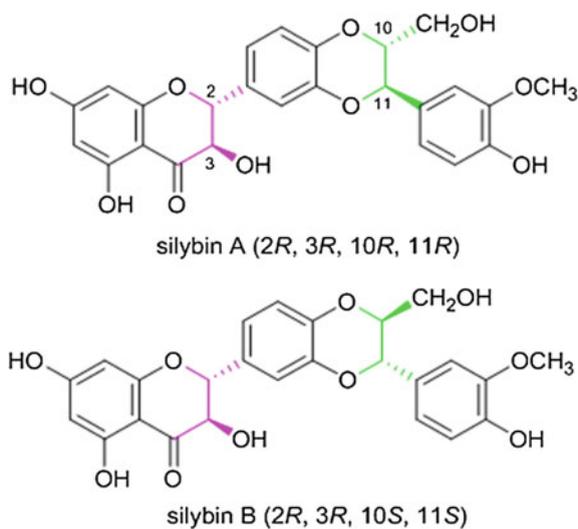
**Fig. 1** Milk thistle (*Silybum marianum*) plant with large prickly leaves, purple flowering heads, and spine scent stems



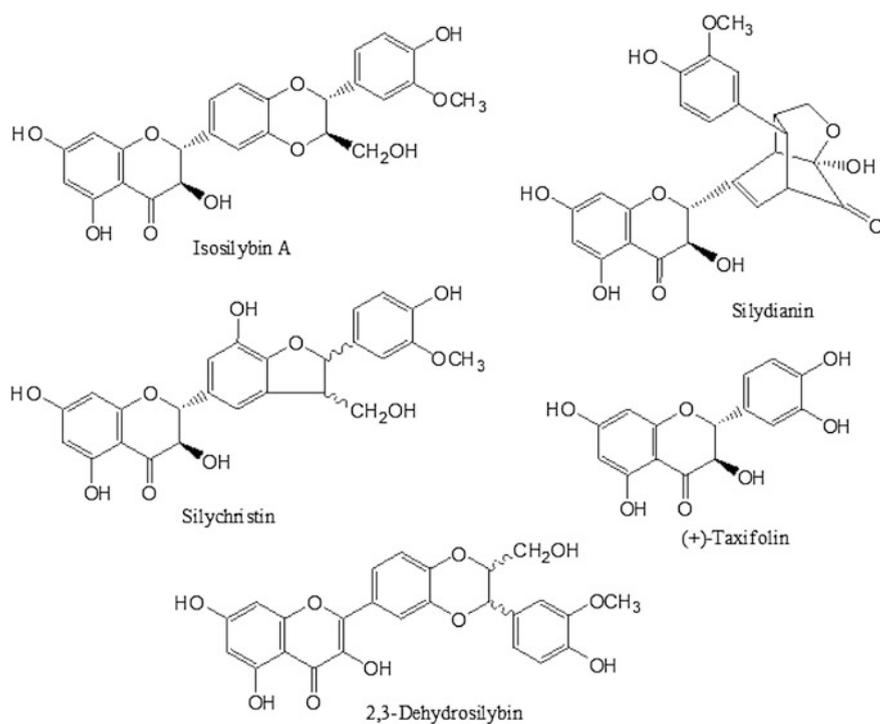
diabetes, amenorrhea, uterine hemorrhage, and menstrual problems [4]. Presently, milk thistle seed, its purified extracts, and its active constituents are mainly used in liver diseases. The active constituent of *S. marianum* (milk thistle) is silymarin, which is a C-25 containing flavonolignan. It is a mixture of 65–80 % of flavonolignans, i.e. silybin A and silybin B, isosilybin A, isosilybin B, silychristin and silydianin, small amounts of flavonoids, and 20–30 % of fatty acids, betaine, apigenin, silybonol, proteins, fixed oil, and polyphenolic compounds (Figs. 2, 3 and 4) [5]. Among these chemical constituents, silybin is the biological active component. Silybin is a mixture of two diastereomers A and B in approximately 1:1 proportion. Silymarin is insoluble in water so usually given in capsule form. It is excreted in bile and its half-life is 6–8 h [6].



**Fig. 2** Chemical structure of silybin



**Fig. 3** Chemical structures of silybin A and silybin B



**Fig. 4** Chemical structures of isosilybin A, silychristin, silydianin, taxifolin, and 2,3-dehydrosilybin

**Table 1** Physicochemical properties of *Silybum marianum*

Characteristics	Value (%)
Saponification value	180.9
Ester value	193.9–195
Acid value	1.82
Iodine value	109.57
Peroxide value	14.97–17.37
Free fatty acid value	16.62–19.22
Refractive index	1.452
Color/optical density	0.3413
Anisidine value	1.8979
Chlorophyll content	0.55

## 2 Physicochemical Properties of Silymarin

Silymarin is extracted from the seeds of *S. marianum* after the isolation of fatty oils. Seeds are rich in fatty acid composition. The concentration of fatty oils is about 17–31 % and has similar fatty acid composition, i.e. linoleic acid > oleic acid > palmitic acid > stearic acid [7]. It has been reported that seeds of milk thistle have very low moisture content in the range of 4.24–4.72. The physicochemical properties of *S. marianum* oil are described in Table 1 [8]. From Table 1, it has been reported that *S. marianum* is rich in oil and fatty acids which is important from medicinal point of view. The seeds could be utilized as edible oil and proteins [9].

## 3 Modulation of Cell Signaling Pathways by Silymarin

Apart from its hepatoprotective and antioxidant effects, the use of silymarin has been broadened to other actions such as cardioprotection, skin protection, neuroprotection, and chemoprotection. This mounting attention in use of silymarin is due to its effect on cellular and molecular levels. The modulation of various cell signaling pathways is described as follows:

### 1. Modulation of steroid hormone receptors

Many compounds have been reported to inhibit or activate the expression of nuclear receptors. Polyphenolic compounds inhibit the steroid receptors due to their anti-androgenic and anti-estrogenic activities. Reports suggest that silymarin partially activates estrogen receptors (ER) whereas silybin has weak ER-mediated activity and diastereomer silybin A was found to be inactive [10]. It has been reported that both silymarin and silybin showed an anti-androgenic activity in prostate cancer cells [11].

## 2. Modulation of drug transporters

Multidrug resistance (MDR) occurs as a result of prolonged exposure of cells to a single drug. This causes a problem in the treatment of various bacterial infections and cancers. This resistance may occur via a number of mechanisms. Among these, the drug depletion in cells by membrane efflux proteins such as P-glycoprotein (Pgp) is an important mechanism. Pgp is a phosphorylated glycoprotein of size 170 kDa encoded by human MDR1 gene. This Pgp is important for the systemic disposition of various lipophilic, amphipathic drugs, toxins, carcinogens, etc. [12]. Reports suggest that silymarin is inhibitor of Pgp. Silymarin augments the doxorubicin cytotoxicity in Pgp-positive cells [13]. Silymarin has been reported to inhibit the Pgp-mediated efflux of digoxin and vinblastine resulting in their accumulation in intestinal Caco-2 cells [14]. Reports indicate that silymarin increases the accumulation of daunomycin and vinblastine by inhibiting the other drug transporter such as MRP1 (multidrug resistance-associated protein 1) [15]. Silybin was reported to be a potent, non-competitive inhibitor of trypanosomal purine transporter TbAT1. Silybin also inhibited melarsen-induced lysis of bloodstream form trypanosomes. This makes silybin a good contender for anti-parasital and/or adjuvant anti-parasite treatment [16].

## 3. Modulation of inflammation and apoptosis

Silymarin modulates inflammation by the inhibition of transcription factor NF- $\kappa$ B that is involved in the production of interleukins (IL-1, IL-6), tumor necrosis factor (TNF- $\alpha$ ), lymphotoxin, interferon (IFN- $\gamma$ ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [17]. Silymarin inhibits TNF- $\alpha$ -induced activation of NF- $\kappa$ B which is mediated through the inhibition of phosphorylation and degradation of inhibitory protein I $\kappa$ Ba [18]. Silymarin also inhibits TNF- $\alpha$ -induced activation of mitogen-activated protein kinase and c-Jun N-terminal kinase. Silybin has been reported to depress the growth and induce the apoptosis of ECV 304 cells. This occurs as a result of DNA fragmentation, cleaved and condensed nuclear chromatin, and DNA hypoploidy. Silymarin decreases the nuclear level of p65 subunit of NF- $\kappa$ B and change in the ratio of Bax/Bcl-2 that favors apoptosis. It also induces the release of cytochrome c and activation of caspase-3, caspase-9, cleavage of poly (ADP-ribose) polymerase (PARP), and inhibition of cell growth [19]. These results propose that silybin may exert its anti-cancer effect by inhibiting angiogenesis through induction of endothelial apoptosis via modulation of NF- $\kappa$ B, Bcl-2 family of proteins, and caspases.

## 4. Modulation of $\beta$ -catenin signaling

It has been reported that nuclear  $\beta$ -catenin accumulation results in tumor progression and metastasis. Non-phosphorylated  $\beta$ -catenin interacts with T-cell factor transcription factor and controls the target genes such as cyclins, c-myc, and matrix metalloproteinases that are involved in cellular proliferation and migration [20]. Presence of mutated  $\beta$ -catenin is related to the tumor progression [21]. It has been reported that silymarin increases the expression of GSK-3 $\beta$  and CK-1 $\alpha$  that leads to

phosphorylation of  $\beta$ -catenin. This results in degradation of  $\beta$ -catenin and decline in nuclear accumulation [22]. Many reports also indicate that silymarin increases the binding of  $\beta$ -TrCP to phosphorylated  $\beta$ -catenin which results in degradation or inactivation of  $\beta$ -catenin [23].

### **5. Modulation of EGFR-MAPK/ERK1/2/AKT/mTOR/PP2A signaling**

It has been evidenced that silymarin treatment inhibits transforming growth factor  $\alpha$ -mediated activation of erbB1 in human prostate carcinoma cells. Along with this, it also inhibits the tyrosine phosphorylation of an adaptor protein Shc which is the immediate downstream target erbB1 [24]. It is reported that silymarin treatment inhibits activation of ERK1/2 that further impairs the activation of erbB1 [25]. Silymarin is suggested to be involved in suppressing the PP2Ac/AKT Ser473/mTOR pathway in colorectal cancer [26].

### **6. Modulation of IGF receptor Signaling**

Silymarin is documented to increase accumulation of insulin-like growth factor binding protein-3 (IGFBP-3) in androgen-independent prostate cancer PC-3 cells. In addition to this, silybin is suggested to decrease insulin receptor substrate 1 (IRS-1) tyrosine phosphorylation that indicates the inhibitory effect on the IGF-R1 receptor-mediated signaling pathway [27].

### **7. Modulation of PPAR-Gamma Pathway**

One of the components of silymarin extract such as isosilybin is reported to act as a PPAR-gamma agonist [28]. Therefore, it is suggested as a good candidate for the treatment of diabetes. Isosilybin causes transactivation of PPAR-gamma-dependent luciferase reporter in a concentration-dependent manner. This effect is reversed by PPAR-gamma antagonist T0070907 that indicates agonistic activity of isosilybin [28].

### **8. Modulation of LXR pathway**

Administration of silymarin has been reported to increase the expression of peroxisome proliferator-activated receptor gamma coactivator (PGC)-1 $\alpha/\beta$ , peroxisome proliferator-activated receptor (PPAR)- $\alpha$ , forkhead box protein O1 (FOXO1), sterol regulatory element-binding protein (SREBP)-1c, liver X receptor (LXR)- $\beta$ , and fatty acid synthase (FAS) [29].

### **9. Modulation of nitric oxide pathway**

Silymarin is reported to have restorative potential in endothelial damage and vascular tone which is dependent on nitric oxide [30]. Silymarin is reported to inhibit the iNOS gene expression and NO production that is responsible for its anti-inflammatory action.

## 4 Role of Silymarin in Chronic Diseases

Silymarin is being explored for a wide variety of disorders such as oxidative stress, inflammatory disorders, cancer, liver disorders, gastrointestinal disorders, dyspepsia, splenic congestions, varicose veins, diabetes, amenorrhea, uterine hemorrhage, and menstrual problems. The exhaustive role of silymarin in various disorders is described below (Fig. 5):

### 1. Silymarin and oxidative stress

Many evidences report that silymarin is powerful antioxidant. It acts as a free radical scavenger and inhibits lipid peroxidation. It protects from oxidative stress by decreasing the levels of reduced glutathione [31]. It has been reported that silibinin is a powerful iron chelator, thereby inhibiting the oxidation of linoleic acid catalyzed by  $Fe^{2+}$  salts [32]. Silymarin maintains the normal membrane fluidity by directly interacting with cell membrane components, thereby preventing alteration in the content of lipid fraction [33].

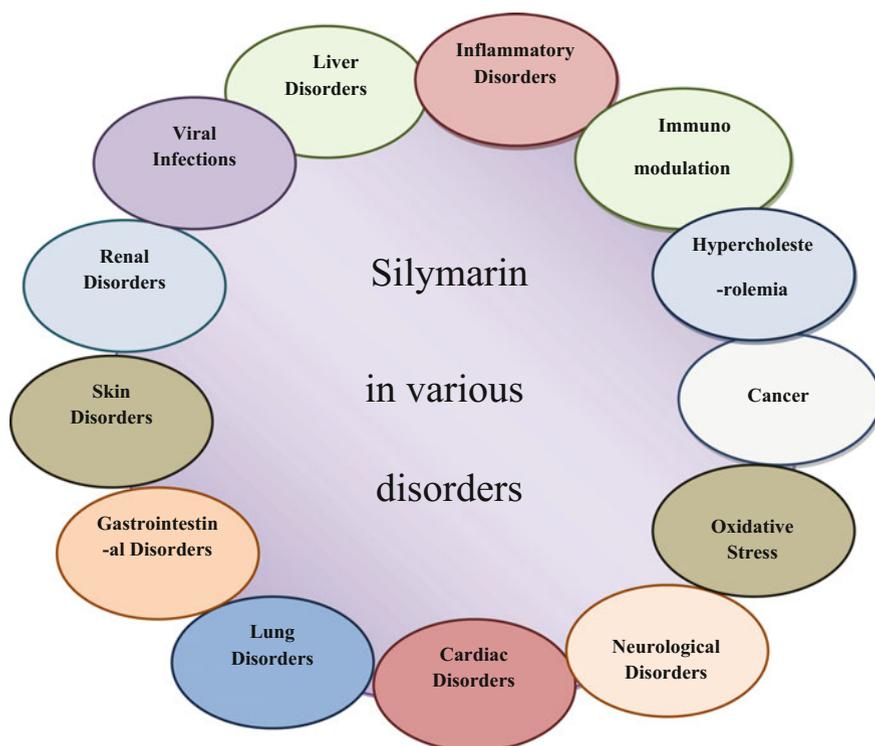


Fig. 5 Therapeutic profile of silymarin in various disorders

## 2. Silymarin and inflammatory disorders

Silymarin acts as an anti-inflammatory agent in the treatment of arthritis. It acts as an anti-inflammatory agent as it inhibits the migration of neutrophils to the site of inflammation [34]. It inhibits the Kupffer cells, prostaglandins, leukotrienes, and transcription factor NF- $\kappa$ B which regulates various genes involved in the inflammatory process [35–37]. Silymarin has been reported to inhibit the tumor necrosis factor-alpha (TNF- $\alpha$ ), interferon- $\gamma$ , IL-2, and inducible nitric oxide synthase (iNOS) [38, 39].

## 3. Silymarin and cancer

Silymarin has been used in variety of cancers. Silymarin has been to inhibit the growth of tumors and regression of established tumors. The chemoprotective effect of silymarin is due to its antioxidant and free radical scavenger activity. It has also been reported to modulate the multiple signaling pathways such as NF- $\kappa$ B, EGFR-MAPK/ERK 1/2 signaling, and IGF signaling [40]. The use of silymarin in various types of cancers is explained as follows:

- ***Bladder carcinoma***

Silymarin has been reported to arrest G2/M phase in transition cell carcinoma-human bladder cancer cell lines (TCC-SUP). It also modulates CDK1-CDK cyclin cascade pathway and activates caspase-3 resulting in growth inhibition and apoptotic death of TCC cells [41].

- ***Hepatocellular carcinoma***

Silymarin inhibits the increase in  $\beta$ -catenin which will suppress the proliferation of hepatocellular carcinoma HepG2 cells. It has also been reported to inhibit mitochondrial membrane potential of HepG2 cells that causes disruption in membrane permeability [42]. Reports indicate that silybin inhibit the growth of Hep3B hepatocellular carcinoma cells by arresting both G1 and G2-M phases. Silymarin also modulates the activity of CDK-2, CDK-4, and CDC-2 kinase activity [43].

- ***Cervical cancer***

Silibinin leads to significant inhibition of cell growth and DNA synthesis along with loss of cell viability in cervical cancer [44]. Silymarin has been reported to induced and augmented human cervical cancer cell apoptosis through p38/JNK MAPKs [45].

- ***Prostate cancer***

Silymarin acts as anti-proliferative, pro-apoptotic, and anti-angiogenic in prostate tumor. It inhibits the growth of prostate cancer cells both in vitro and in vivo. Silymarin also modulates MAPK, ERK 1/2, and IGF signaling pathways [46].

- ***Skin cancer***

Skin cancers occur due to ultraviolet light-induced immunosuppression and oxidative stress. It has been noticed that topical and dietary administration of silymarin to mouse prevents photocarcinogenesis. This can occur by inducing apoptosis, increase in catalase activity, and induction in cyclo-oxygenase and ornithine decarboxylase activity [47].

- ***Lung cancer***

Silibinin significantly induces growth inhibition, a moderate cell cycle arrest, and a strong apoptotic cell death in small-cell and non-small-cell human lung carcinoma cells [48]. Treatment of human lung cancer A549 cells with silymarin inhibits phosphorylation of ERK 1/2 and reduces the level of MMP-2 and u-PA [49].

#### 4. Silymarin and Liver disorders

Liver plays a major role in detoxification of drugs and homeostasis. Exposure to toxins and pharmaceutical drugs may lead to liver damage. Silymarin has been reported to be effective in a variety of liver disorders. This effect is attributed due to its antioxidant, anti-inflammatory, anti-fibrotic activity, and many others. The role of silymarin in various liver disorders is as follows:

- ***Anti-hepatotoxic potential***

Silymarin is one of the common plant extracts used for the treatment of liver diseases. Silymarin has shown its efficacy in toxin-induced liver damage such as acetaminophen [50], arsenic [51], and carbon tetrachloride [52]. Silymarin has been reported to protect from hepatic injury induced by *Amanita phalloides*, phenothiazines, and butyrophenones [53]. These toxins disrupt liver membrane and block hepatic protein synthesis. Silymarin blocks the binding sites of these toxins.

- ***Alcoholic liver disease/cirrhosis***

Much evidence suggests that metabolism of ethanol results in the production of free radicals leading to oxidative stress in liver. Silymarin restores the normal liver function due to its antioxidant and hepatoprotective activities [54]. In addition to this, it has also been noticed that silymarin lowers the level of bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels in alcoholic cirrhosis while the level of gamma glutamyl transferase and procollagen III peptide level decreased [55].

- ***Hepatitis***

Silymarin is reported to be effective in both acute and chronic hepatitis. Silymarin decreases the serum bilirubin, AST, and ALT levels. Liver function tests and histological improvement are noted after the administration of silymarin in chronic hepatitis [56].

- ***Liver Fibrosis***

In liver fibrosis, the hepatic stellate cells start converting into myofibroblasts leading to remodeling in the liver structure. Silymarin has been reported to inhibit the conversion of stellate cells into myofibroblasts, indicating the downregulation gene expression involved in fibrosis [57].

- ***Liver tissue regeneration***

Silymarin acts not only on the cell membrane, but also on the nucleus where it increases the formation of ribosomes and DNA synthesis resulting in protein synthesis by stimulating RNA polymerase I and the transcription of rRNA. This is an important step in the repair of cellular injury and is essential for restoring structural proteins and enzymes damaged by toxins [58].

### **5. Silymarin and Immunomodulation**

Silymarin exhibits immunomodulatory effect by inhibiting the activation of human T-lymphocytes, human polymorphonuclear leukocyte, inflammatory mediators (IFN- $\gamma$ , IL-2, 4, TNF- $\alpha$ , and nitric oxide), expression of histocompatibility complex, and nerve cell damage [59]. Silymarin has also been reported to suppress ultraviolet radiation-induced immune suppression [60].

### **6. Silymarin and Hypercholesterolemia**

Reports suggest that silymarin affects the metabolism of cholesterol in different ways. Silybin has been reported to inhibit the key enzyme HMG-CoA reductase involved in the synthesis of cholesterol [61]. Silymarin inhibits the synthesis of phospholipids and triacylglycerols which is the major mechanism behind its anti-atherosclerotic and anti-hypocholesterolemic activities. Silymarin also inhibits lipids peroxidation and thereby inhibits the synthesis of triglycerides. It has been reported to reduce the level of biliary cholesterol and phospholipids in both rats and humans [62]. Silymarin decreases the plasma level of cholesterol and low-density lipoproteins (LDL) in hyperlipidemic rats. In type II hyperlipidemic patients, silymarin reduces the total cholesterol and high-density lipoproteins [63, 64].

### **7. Silymarin and Neurological disorders**

Silymarin has been used in a number of neurological disorders due to its antioxidant activity and various other mechanisms. Silymarin inhibits the activation of microglia, TNF- $\alpha$ , NF- $\kappa$ B, and nitric oxide, thereby protecting the dopaminergic neurons from lipopolysaccharide-induced neurotoxicity [65]. A comparative 8-week pilot double-blind study on 35 patients suffering from obsessive compulsive disorder was conducted to evaluate the efficacy of silymarin. Results indicated that silymarin has positive effects on obsession and compulsion starting from the fifth week [66].

## 8. Silymarin and Cardiac Disorders

During chemotherapy some drugs such as doxorubicin results in cardio-toxicity mediated by oxidative stress and apoptosis. Silymarin has been reported to protect from cardio-toxicity due to its antioxidant activity [67]. Silymarin has been reported to be involved in cardiac preconditioning and hence protects the cardiac tissue from ischemia [68]. Amiodarone is an anti-arrhythmic drug, but due to some serious side effects, its use has been limited. Amiodarone leads to toxicity due to free radical generation, direct cytotoxicity, development of lysosomal phospholipids, indirect immunologically mediated toxic effects, and membrane destabilization. Silymarin administration along with amiodarone decreases the development of lysosomal phospholipids [69].

## 9. Silymarin and Lung Disorders

Silymarin has shown activity against bronchial anaphylaxis, post anaphylactic, or platelet-activating factor-induced hyper-reactivity in guinea pigs. Silymarin has been reported to be effective in asthmatic disorders by decreasing responsiveness to histamine [70]. In addition to this, silymarin has been used in lung cancer which is discussed above.

## 10. Silymarin and Gastrointestinal Disorders

Silymarin has been reported to exhibit anti-ulcer activity in rats. Reports suggest that silymarin undergoes excessive entero-hepatic circulation which forms a loop between intestine and liver. This prevents the disturbance in the secretion of bile resulting in the increased secretion of bile, cholate, and bilirubin excretion. It has been observed that alloxan induces diabetes mellitus. Alloxan results in the production of hydrogen peroxide and free radicals. Administration of silymarin along with alloxan prevented high plasma glucose levels and damage in pancreatic cells [71]. Silymarin has shown its efficacy in colitis and colon cancer.

## 11. Silymarin and Skin Disorders

Exposure to UV radiation results in a number of skin disorders such as erythema, edema, sunburn, cell formation, hyperplasia, immune suppression, DNA damage, photoaging, melanogenesis, and skin cancers. This may be due to the generation of free radicals, which causes oxidative stress in skin cells. It has been noticed that topical and dietary administration of silymarin to mouse prevents photocarcinogenesis. This can occur by inducing apoptosis, increase in catalase activity, and induction in cyclo-oxygenase and ornithine decarboxylase activity [59]. Silymarin has been reported to shown efficacy in psoriasis because it inhibits cAMP phosphodiesterase and leukotriene synthesis [72]. Silymarin decreases intracellular production of hydrogen peroxide, nitric oxide, and catalase activity in UVB-irradiated mouse skin. It also inhibits COX-2, PGE<sub>2</sub>, PGF<sub>2</sub>, PGD<sub>2</sub> expression which plays a major role in tumor production [73]. Silymarin has been reported to inhibit the skin edema, formation of sunburn and apoptotic cells, and infiltration of inflammatory mediators [74]. Many experiments suggest that silymarin is

effective against sunburn response, DNA damage, and immunosuppression. Moreover, further studies need to be investigated to determine the effect of silymarin on skin.

## 12. Silymarin and Renal Disorders

Silymarin helps to maintain normal renal function. Alloxan-induced diabetes mellitus in rats produces free radicals which damage renal tissues. Administration of silymarin along with alloxan protects the renal tissues from oxidative damage via increase gene expression of antioxidant enzymes. Therefore, silymarin is useful in the treatment of diabetic nephropathy [75]. Silymarin inhibits the expression of NF- $\kappa$ B, which is involved in the activation of oncogenic process. Therefore, silymarin is useful in the treatment of renal carcinoma [76]. It has been noticed that silymarin (210 mg/day for 8 weeks) in peritoneal dialysis patients inhibits the effect of pro-inflammatory cytokines such as TNF- $\alpha$  [77].

## 13. Silymarin and Viral Infections

Silymarin does not affect viral replication, but it has beneficial role in viral hepatitis due to its inhibitory action on inflammatory and cytotoxic processes induced by viral infection. It has also been reported to inhibit mitochondrial membrane potential of HepG2 cells that causes disruption in membrane permeability [54]. Reports indicate that silybin inhibit the growth of Hep3B hepatocellular carcinoma cells by arresting both G1 and G2-M phases. Silymarin also modulates the activity of CDK-2, CDK-4, and CDC-2 kinase activity [55]. Silymarin exerts anti-viral effect by inhibited expression of TNF- $\alpha$  and NF- $\kappa$ B in human hepatocellular carcinoma cells [78].

# 5 Biological Activities of Silymarin in Animal Models

### (a) Cardiovascular effects

It has been reported that silymarin is effective in carbon tetrachloride-induced cardiac damage [79]. It has been found that silymarin ameliorates the inflammatory response-induced cardiac infarction as well as oxidative DNA damage and apoptosis caused by the toxic effects of CCl<sub>4</sub>.

### (b) Renal effects

Silymarin has been reported to prevent cisplatin-induced glomerular and tubular nephrotoxicity in rats [80]. Silymarin has been reported to protect the kidney tissues of rat from ischemic reperfusion injury [81]. Silymarin is shown to prevent tubular dilatation and vacuolization, pelvic inflammation, interstitial inflammation, perirenal adipose infiltration, and tubular and glomerular necrosis in Sprague Dawley rats. Along with this, Silymarin prevented I/R-induced renal damage on the basis of various kidney markers such as serum creatinine, urea, and cystatin C

concentrations, serum enzymatic activity of glutathione peroxidase and serum and tissue MDA and NO levels [81].

(c) **Hepatoprotection and hepatitis**

Many reports indicate that administration of silymarin to rats, mice, rabbits, and dogs showed a significant protection against *Amanita* mushroom poisoning [82]. Before exposure to chemical hepatotoxins, pretreatment of rats and mice with silymarin attenuates lipid peroxidation and hepatotoxicity [83]. It has also been evidenced that silymarin protects the liver from alcohol toxicity. In rats with bile duct obstruction, silymarin protects due to its anti-fibrotic effect [84].

(d) **Anti-lipemic effects**

Treatment of silymarin to rats fed with cholesterol-enriched diet increases hepatic LDL clearance, which indicates silymarin has protective role in diet-induced hypercholesterolemia [85]. Silymarin has been reported to be useful in high-fat diet-induced dementia in mouse [86].

(e) **Anti-diabetic and pancreatic protectant**

Silymarin has been reported to protect the pancreas from damage in experimentally induced diabetes mellitus [87]. Silymarin and Silibinin stimulate insulin secretion from  $\beta$ -pancreatic cells of rats which is attributed to its anti-diabetic potential. It has been found that silymarin induces insulin resistance in Wistar rats through an increase of PTEN (Phosphatase and Tensin Homolog) [88].

(f) **Anticancer**

Silymarin has been used in different mouse models of cancer. Reports suggest that silymarin treatment protects the mice from chemical and UVB tumors [89]. The chemoprotective effect of silymarin is due to its antioxidant and free radical scavenger activity. It has also been reported to modulate the multiple signaling pathways such as NF- $\kappa$ B, EGFR-MAPK/ERK 1/2 signaling, and IGF signaling [40]. Silymarin inhibits the increase in  $\beta$ -catenin which suppresses the proliferation of hepatocellular carcinoma HepG2 cells.

(g) **Antioxidant**

Pretreatment of rats with silymarin has efficacy against ischemia-induced gastric ulcers [90]. Silymarin has been reported to act as antioxidant in three ways, i.e., by direct free radical scavenging activity, by preventing the free radical formation by inhibiting specific enzymes responsible for free radical production, and by maintenance of optimal redox status of the cell by activating a range of antioxidant enzymes and non-enzymatic antioxidants, mainly via transcription factors, including Nrf2 and NF- $\kappa$ B [90].

## 6 Biological Activities of Silymarin in Humans

As we know the use of herbal drugs is increasing throughout the world and among these herbal preparations many formulations are derived from milk thistle. Mainly this drug is used in the treatment of liver diseases from Greco-Roman era, but till now no convincing clue is obtained on its clinical efficacy. A number of clinical trials have been carried out, but these trials fail due to the number of shortcomings such as small sample size, lack of etiology, and severity of disease. Some of the biological activities of silymarin in humans are described as follows:

### (a) **Hepatoprotection**

Silymarin is the most commonly used drug when liver damage and alcohol are the major factors for the liver cirrhosis. It has been observed that Europeans use silymarin in larger extent to cure liver damage due to different factors. It has been noticed that administration of milk thistle extract (Legalon) in an open label study of 2367 patients in different liver disorders for eight weeks showed a significant decline in increased liver enzymes [91]. Administration of silybin to *Amanita* mushroom poisoning protects from severe liver damage [92]. It has been evidenced that administration of silymarin in alcohol-induced liver disease in 300 patients showed a significant improvement in liver enzymes within 4 weeks [93].

### (b) **Hepatitis**

Reports showed that administration of silymarin to patients with chronic hepatitis twice daily for two months results in a significant decrease in AST and ALT levels [94]. In other study, 57 patients with viral hepatitis receiving silymarin at the dose of 140 mg thrice a day for three weeks indicates lowering of bilirubin, AST, and ALT levels in 3–4 weeks as compared to the placebo-treated humans [95].

### (c) **Anti-lipemic**

Reports indicate that silymarin inhibits the hepatic synthesis of cholesterol. On the basis of this, the efficacy of silymarin has been investigated in hypercholesterolemia. Studies showed that patients receiving silymarin (420 mg daily for 1 month) had significant decrease in biliary cholesterol when compared to placebo indicating inhibition of hepatic cholesterol synthesis [96].

### (d) **Anti-diabetic**

In a study comprising 60 patients with hepatic cirrhosis and insulin-resistant/insulin-dependent diabetes, administration of silymarin (200 mg thrice a day daily) is observed to result in a decrease in fasting glycemia, blood glucose, glycosuria, and insulin levels within 6 months of treatment [97].

### (e) **Anti-inflammatory**

Silymarin has shown anti-inflammatory potential in some clinical studies. In a double-blind placebo-controlled trial involving 40 patients with alcoholic cirrhosis,

treatment of silymarin is reported to elevate lectin-induced lymphoblast transformation, and attenuate percentage of OKT8<sup>+</sup> cells [98]. Silymarin has also been reported to enhance leukocyte motility.

(f) **Anticancer**

It has been indicated that self-medication with 450 mg silymarin daily to 52-year-old man with hepatocellular carcinoma is resolved spontaneously [99]. Silymarin and silybin demonstrated chemopreventive effects in human epidermal, prostate, and breast and cancer cell lines.

(g) **Antioxidant**

Silymarin showed an antioxidant effect by increasing the levels of superoxide dismutase in erythrocyte and lymphocytes in patients with alcoholic cirrhosis [100]. In human mesangial cell cultures incubated with glucose, silybin acts as an antioxidant by inhibiting the formation of malondialdehyde. In human leukocytes, silymarin protected against hydrogen peroxide-induced DNA damage. Silymarin has also shown antioxidant effects in human platelets.

## 7 Conclusion

Since herbal drugs are used for a number of approaches as they are safer and better than the standard medical drugs. Extensive research has been carried to use herbal drugs for the treatment of number of disorders. Silymarin is a well-researched drug and nowadays being explored in a variety of disorders due to its number of properties such as antioxidant, anti-inflammatory, and anti-carcinogenic. It is shown to be quite safe, has less serious side effects, and well tolerated in humans. Sufficient data are now available that document silymarin as an important therapeutic agent with lot of potential in the treatment of liver disorders, cancer, inflammatory disorders, renal disorders, skin disorders, lung disorders, and many more. Nonetheless, more effective clinical trials are required to fully explore the benefits of silymarin in these chronic disorders.

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