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Silybum marianum (L.) Gaertn. Fruits: The Earth`s Gift to the Living; A Chemical and a Biological Review

Ahmed A. Gohar*

Pharmacognosy department, faculty of pharmacy, Mansoura University, Mansoura 235516, Egypt

***Corresponding Author:** Ahmed A. Gohar, Pharmacognosy department, faculty of pharmacy, Mansoura University, Mansoura 235516, Egypt, E-mail: ahmedgohar99@yahoo.com

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Abstract

Silybum marianum (L.) Gaertn. [*Cardus marianus* (L.)] is an invasive plant indigenous to the Mediterranean region. It has many synonyms, varying according to geographical localities, such as St. Mary's thistle, Milk thistle, Blessed thistle, Holy thistle, and in Arabic countries, it`s known as Akub, Harshafbarri, Shoakennassara, Shoakeddimen, Shoaksennari, and Shoak el-gamal. The plant is an edible herb, native to the Mediterranean area, grown throughout Europe and naturalised in North and South America, with a long history in folk medicine. Since ancient times, it has been identified for snake bites, amanita poisoning, and liver disorders. It has been intensively investigated from the chemical and biological points of view. The chemical investigation led to the isolation and identification of a series of dihydroflanonolignans (thirteen compounds) collectively known as silymarin. A survey of the biological investigation has indicated that Silybum has antiviral, antioxidant, anti-inflammatory, antihepatotoxic, hepatitis, immunomodulatory, cytoprotective, antiproliferative and anticancer (human prostate carcinoma, the ovarian cells carcinoma, colorectal carcinoma, breast carcinoma, and salivary gland carcinoma), antiobesity, antihyperlipidemic, diabetes mellitus, hyperprolactinemic (galactogenic), nephroprotective, neuroprotective, anti-amnesia, anti melasma, and antifungal effects.

Keywords: Silybum Marianum; Dihdroflavolignans; Biological Activity; Antihepatotoxicity; Antioxidant

Abbreviations: ABC-Transporters: ATP-Binding Cassette Transporters; AA: Ascorbic Acid; APP: amyloid protein precursor; AIF: apoptosis induced factor; ALT: alanine transaminase; ADMA: asymmetric dimethylarginine; AST: aspartate transaminase; BUN: blood urea nitrogen; CAT: catalase; CP:carbonylated proteins, CLP: cecal ligation and puncture; DENA: diethylnitrosamine; DMSO:dimethylsulphoxide; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ECM: extracellular matrix; ERK1/2: extracellular signal-regulated kinase; FBS: fasting blood glucose; GSH: reduced glutathione; GSSG: oxidized glutathione; GGT: gamma-glutamyl transferase; HbA1c: glycosylated hemoglobin; HSC: hepatic stellate cell; HCV: hepatic virus C; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; HOMA-IR: homeostasis model assessment-IR index; Gpx: glutathione peroxidase; GSH: glutathione; GST: glutathione s- transferase; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; HIF-1α: hypoxia-inducible factor-1 alpha; IL; interleukine; LDH: lactate dehydrogenase; LGM: lipid and glucose metabolism; LOx: lipooxygenase; MDA: malondialdehyde; mTOR: mammalian target of rapamycin; MCAO: middle cerebral artery occluded; MAPK: mitogen-activated protein kinase; NADPH: nicotinamide adenine dinucleotide phosphate reduced form; NF-kB: nuclear factor-kappa B; NOx: Nitrogen oxides; PegIFN: pegylated interferon alpha; PDGF: platelet- derived growth factor; PCOS: polycystic ovarian syndrome; PTP1B: protein tyrosin phosphatase; PTEN: protein that regulates insulin signaling; PSA: prostse-specific antigen; ROS: reactive

oxygen species; a-SMA: smooth muscle actin; SOD: superoxide dismutase; SCr: Serum creatinine; TBA: thiobarbituric acid; TCA: trichloroacetic acid; trichloroacetic acid superoxide dismutase; TBARS: thiobarbituric acid reactive substance; T2DM: type 2 diabetes mellitus; TGF: transforming growth factor; TNF: tumer necrosis factor; RBV: ribavirin; XO: Xanthine oxidase.

Introduction

Silybum Adans., (tribe cynareae, family asteraceae) encompasses two plant varieties: *Silybum marianum* L. Gaertn and S. *marianum* L. Gaertn Var. albiflora Eig. It is an invasive plant indigenous to the Mediterranean region. The plant has various names, including St. Mary's thistle, E. milk thistle, blessed thistle, or holy thistle. In the Arabic countries, it's known as Akub, Harshaf barri, Shoak elnassara, Shoak eldemin, Shoak sinnari, and Shoak elgamal, and there exist other names in Europe and Asia [1-5]. The medicinal benefits of milk thistle fruits were first reported by Theophrastus of Eresos (fourth century B.C.), Pedanios Dioscorides (50 A.D.), and Plinius the Elder (first century A.D.). Dioscorides in his work "De Materia Medica" described *S. marianum* as a remedy for the bites of poisonous snakes and for melancholic depression, which was believed to be a "liver complaint" [6]. In the first century AD, Dioscorides described thistle-like plants by the term ''silybon'', while Pliny the Elder (23–79 AD), a Roman naturalist, called it ''silybum [7].

The plant was used as an emetic, it's juice mixed with honey, was used to carry off bile and it was recommended as an antidote for liver toxins. In Europe, it's used for congestion of the liver, spleen and kidney. Native Americans used the plant for boils and other skin disorders. In the United States, it`s prescribed as a food supplement and sold as a dietary supplement under the names Legalon, Silipide, and Siliphos [8]. It became medicine for hepatobiliary disease in the 16th century [141]. The German Commission E recommends the plant primarily for dyspeptic complaints, toxin-induced liver damage, hepatic cirrhosis, and for liver chronic inflammatory [9]. During cancer treatment, a possible cleansing and detoxification of liver after chemotherapy, preventing hepatotoxicity of chemotherapy drugs, and it could be an adjunctive treatment potentiating chemotherapy and radiation therapy. Milk thistle may also have applications in ameliorating long-term hepatic and cardiovascular effects of cancer treatment [10]. So, it was deemed to give a comprehensive narrative review on the chemical and biological value of *S. marianum* plant.

Development of Chemical Components in *Silybum Marianum*

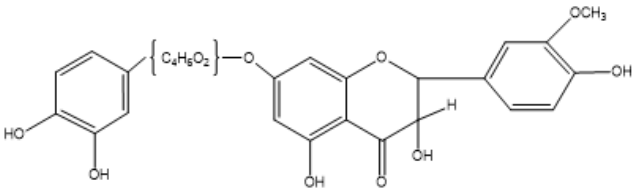
Flavanolignans: The plant has been subjected to intensive phytochemical investigation started with the first reports on the contents of dihydroflavanonol derivative which was revealed by [139], followed by the work of [152], whom confirmed 3–oxy–flavanone derivatives in the fruits of *S. Marianum*. The first suggested compound were E5 which contains one methoxyl and five phenolic OH groups and E6 which contains one methoxyl and six phenolic OH groups. The suggested E6 was identified as silybin [11]. At that time, silybin and silymarin were identified as the same compound and the two isomeric structures were suggested for the new flavolignan skeleton. This was the first suggested flavolignan structures in *S. marianum* fruits, **S1** [12, 13]. In addition to the reported silybin, another four flavonoids were isolated; 4`,5,7-trihydroxy-3`,5`- dimethoxyflavanonol **S2**, and the others were not elucidated (14). Then, a tentatively identified flavonoid was isolated from the fruits; 3`,4`-disubstituetd 5,7-dihydroxy flavonoid [15]. Later on, Silychristin and silydianin; isomers of silybin, **S3**, taxifolin and quercetin were reported [16]. At that time, [20] reported silydianin and silymarin in *S. eburneum.*

Subsequently, a flavanonol named silymarin was isolated and identified by [13]; their data suggested two isomers for silymarin **S3**; this compound was the same one previously reported as silybin and the same compound as *Silybum* substance E6. However, silymarin first appeared as silubon in the Materia medica (book four) written by the Greek physician Pedanios Dioskurides 65CE, and it was a part of traditional Chinese medicine and ancient European medicine [17]. Continued search in this area led to the separation of a series of flavonolignans by different authors, and this led to the identification of two isomers of silymarin

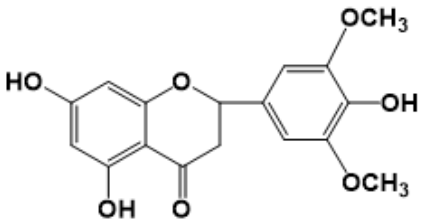
named silychristin [16, 18] and silydianin [19, 20]. Then, it was reported that silymarin is a mixture of several flavonolignans isolated from the aerial parts of *S. marianum* subsp. anatolicum, **S4**, [21]. Later on, taxifolin (dihydrofla-vonol) and dehydrosilybin were isolated and identified [127]. After that, [147] proved that silymarin was a mixture of silybin, silydianin and silychristin by HPLC analysis. Different names are applied to silybin as flavobin, silliver, silybine, silymarin I, silybina [22]. Other flavonolignans, including isosilychristin [23], silymonin and silandrin (previously named silybin) and silydianin were reported as a flavolignan mixture in *S. marianum* and anatolicum [141].The diastereomeric silybin and/or isosilybin isomers (silybins A and B, and isosilybins A and B) were isolated and identified from a crude MeOH extract of milk thistle fruits using preparative HPLC together with silychristin, isosilychristin, and silydianin, and a flavonoid taxifolin. The four diastereomeric compounds share the same chemical formula but differ in structure only with respect to the stereochemical positions of the terminal aryl (3-methoxy-4-hydroxyphenyl) and hydroxymethyl groups at the α and β carbons. A minor derivative 2,3-dehydrosilybin was isolated from seeds of the *S. marianum* subsp. anatolicum [24-27].

Later on, as a gain of progress in the isolation and spectral analysis techniques, 11 compounds were isolated by repeated column chromatography followed by HPLC analysis and their structures and stereoconfigurations were elucidated by 2D-NMR experiments; silybin A, silybin B, isosilybin A, Isosilybin B, silychristin A, silychristin B, isosilychristin A, dehydrosilychristin A, silydianin, dehydrosilydianin, and silyamandin, S4, [28], and this is the most recent report full description of the structure of *Silybum* substances.

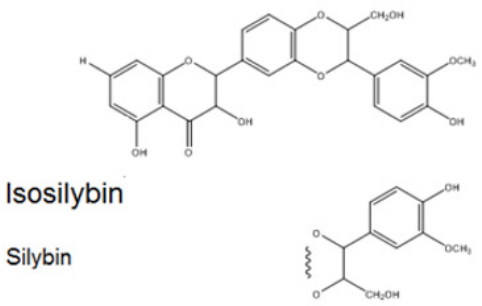
Here, it is worthwhile to mention that silibinin, the name used by pharmacopoeias, thought previously to be a single compound, is known now to be a 1:1 mixture of the diastereomers, silybin A and silybin B, and isosilybinin is a mixture of the diastereoisomers isosilybin A and isosilybin B (29, 30). Recently, sonyamandin was reported as a new flavolignan from *S. marianum* fruits collected from Jordan [31].



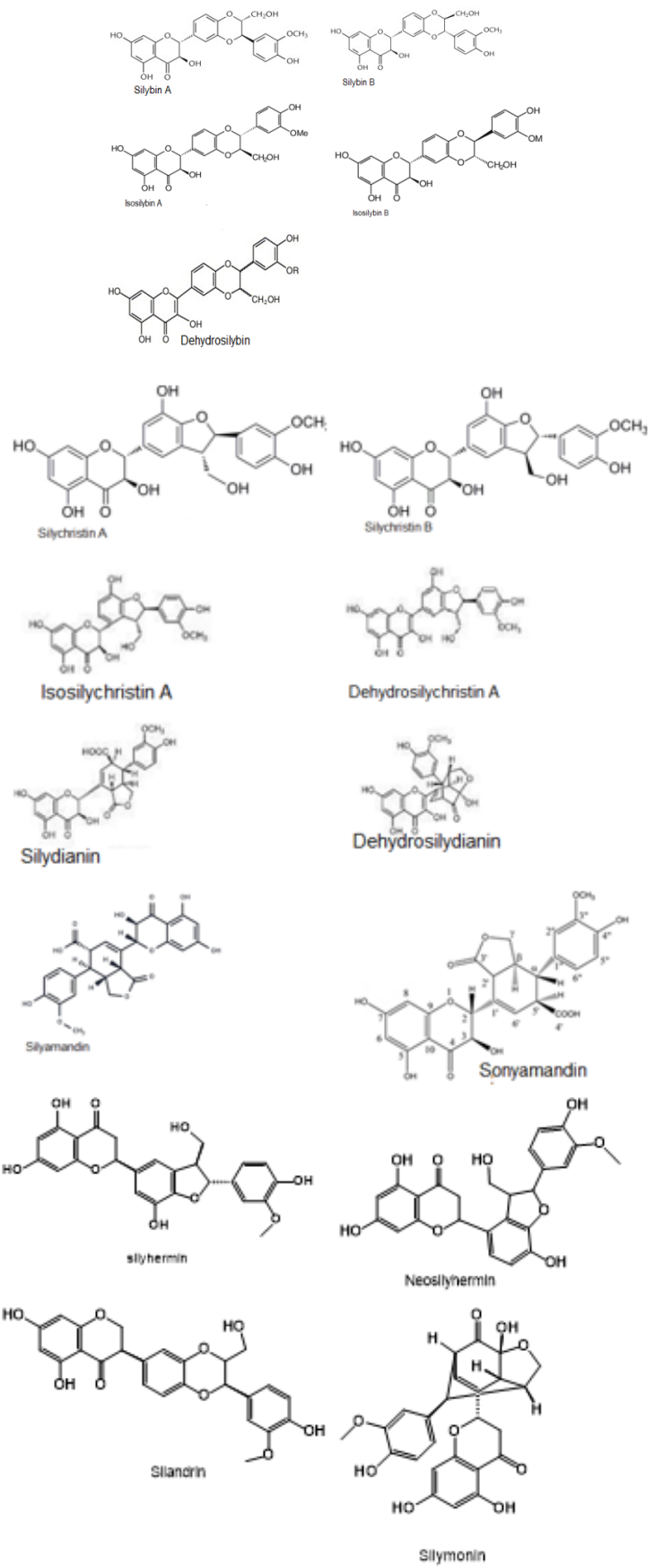
S1: The first suggested flavolignan structures in *S. marianum* fruits [11, 12, 152]



S2: Flavolignan structures in *S. marianum* fruits [14]



S3: Chemical structure of silybin and isosilybin flavolignan in *S. marianum* fruits [12-16]



S4: Refined structures of flavanolignans isolated from *S. marianum*

The flavonoid content of the white-flowered plant has been a subject of debate. Their profile in the fruits of *S. marianum* (L.)

Gaertn.Var. albiflora Eig.was found, to some extent, similar to that of *S. marianum* (L.) Gaertn. Purple-flowered- variety. It contained silybin, silydianin, silychristin, taxifolin, silandrin, and quercetin, but silymonin was not confirmed [32, 33]. But, in another study, white-flowered *S. marianum* contained 3-deoxyflavonolignans silymonin, silandrin and silyhermin [25]. These new 3-deoxy-flavonolignans possessing 2*R*- and 2*S*-configurations were identified as silyhermin, and neosilyhermins A and B. Their precursor's naringenin, eriodictyol, apigenin and chrysoeriol were detected as minor components [34]. In another study, Isosilybin [35], and another group of silybin congeners as silandrin and silymonin [141], isosilandrin [36], silyamandin [37] were isolated from *S. marianum* (L.) Gaertn. Var, albiflora. In spite of that, the albiflora variety was reported to be devoid of the flavonolignans silybin and silydianin [38].

b- ***Flavones and flavanols***: the presence of dihydrokaempferol, kaempferol, kaempferol-3-sulphate, apigenin, apigenin-7-O-glucoside and apigenin-7-O- glucouronide, naringin was confirmed by different authors in S. marianum [24, 39, 40].

c- Other Constituents in the *S. Marianum* Fruits

The *S. marianum* fruits were reported to contain edible oil known as kangal oil in the Caucasus Mountains [4]. The fruits of the variety albiflora contains 34% oil [33]. The oil contains triterpenes, and fatty acids (myrestic, palmetic, stearic, oleic, linoleic, arachidic and behenic acids), tocopherol, sterols (cholesterol, campesterol, stigmasterol, and sitosterol). Both varieties of *S. marianum* (L.) Gaertn. And white-flowered albiflora have similar lipid profile [33]. Triterpenes lupeol and lupenyl acetate, and the steroids β-sitosterol and β-sitosterol-3-O-glucoside, were isolated from the aerial parts of *S. marianum* [39, 33]. Saturated and unsaturated fatty acids were detected by GLC. Amino acids betaine, L-cysteine, L-glutamic acid, glycine, dl-2-aminobuteric acid, dl-lucine and tyramine were identified in the 70% alcohol extract of *S. marianum* L. Gaertn [41, 2]. Polyacetylenes were reported in the plant roots [42, 43]. Eriodyctiol, and chrysoeriol, 5, 7-dihydroxy chromone, dehydroconiferyl alcohol, mucilage and sugars (arabinose, rhamnose, xylose, and glucose), and proteins were reported in the plant [44, 33]

Reported Biological Activities for *S. Marianum*

a- Silymarin Antioxidant Activity: Reactive Oxygen Species (ROS) and free radicals are produced in different cells and tissues as a result of different metabolic activities. These oxidant mediators are counteracted by the antioxidant enzymes (SOD, GSH peroxidase and CAT) and non-enzyme molecules (GSH, AA, Vit. E & A). Many oxidant biological hazards and diseases are controlled by abolishing or decreasing the ROS and scavenging the free radicals. The antioxidant activity stabilises the cell membrane, regulates the GSH intracellular contents, and chelates copper and iron metal ions. It affects lipid peroxidation in liver cell walls and microsomes, which is evaluated by an increase in the level of MDA and in liver cells by the level of LDA, which damages the hepatocytes [53]. Different studies in the literature deal with the evaluation of the antioxidant activity of silymarin mixture. Different models were used to in vitro evaluate the antioxidant activity of silymarin; Lipid peroxidation, 1,1–diphenyl–2–picrylhydrazyl (DPPH), and ferric reducing power [45]. Silybin which is the main active principle of Silybum fruits active material was hypothesized to be the main antioxidants as demonstrated by free radical scavenging, inhibition of lipid peroxidation, and protection against genomic injury by suppression of the hydrogen peroxide and superoxide anions and of lipoxygenase [8]. The antioxidant mechanism of silybum substance appears by inhibition of microsomal lipid peroxidation induced by *t butylhydroperoxide*, inhibition of superoxide production [46] and restoration of the antioxidant enzymes such as CAT, SOD, GSH reductase, glutathione peroxidase (GPx), and decreasing lipid peroxidation and malondialdehyde (MDA). As an antioxidant, silymarin scavenges free radicals and directly reacts with cell membrane components to prevent oxidative damage to lipid components of the cell membrane responsible for maintaining its natural fluidity [47].

Oxidative damages have been implicated in several hepatotoxicities; damage of liver cells, hepatitis, and fibrosis followed by cirrhosis, liver cancers, and in neurodegenerative diseases; Parkinson's disease, Alzheimer, cerebral ischemia, lipopolysaccharide induced neurotoxicity and brain-related diseases. Silymarin has shown protective effects against models of hepatotoxicity and

neuronal injury which could be useful to the down progression of the neurodegenerative and hepatic diseases. A significant effect of silymarin pretreatment as cerebral protective agent in oxidative stress is shown in decreasing significantly the lipid peroxidation and improving the cellular antioxidant status in rat cerebral tissue. This was demonstrated by improvement of neurological outcomes after MCAO, increased activity of GSH, AA, and SOD which is contemporary to decreased activity of GSSG and MDA, exhibited significant attenuation in TBARS content as compared to MCAO, the activity of Na+–K+ ATPase was significantly decreased, and a restore of the activity of antioxidant enzymes in frontal cortex and increase the Caspase 8 activity [49, 50]. In murine studies, silymarin decreases the effect of heptic toxic xenobiotics and/or chemicals as demonstrated by significant abolishing the increase of ALT, AST, NO, LOx, GGT, inflammatory cytokines IL6-8, TNF-α and caspase 8. Likewise, it corrects the drop in GSH, CAT, SOD, GPX, GST and GR where they were increased with respect to the groups with hepatic damage. Inhibition of lipid peroxidation by silymarin protects against the degeneration of cell membranes and the development of liver disease. Moreover, it controls the free radical-mediated damage to liver cells by abolishing the increase in MDA, SOD, and NOx, while elevating the drop in GSH. Ameliorating oxidative-reduction factors in the liver cells acts on the HSCs, leading to their activation and the start of expressing new proteins, such as a-SMA, and new receptors, such as PDGF and TGF-β1 receptors. Therefore, activated HSCs secrete large amounts of ECM proteins, which accumulate and initiate fibrogenesis.

Moreover, silymarin inhibits the protein oxidates and hyaluronic acid in the liver cells, thus controlling liver cells fibrinogenesis. Oxidative stress is commonly associated with liver cell inflammation, which is accompanied by increased hepatic 4- hydroxyproline, TGF-β1and hepatic interleukin-6 (IL-6) levels leading to liver cell fibrosis. Regulation of cell membrane permeability and increases its stability against xenobiotics, nuclear expression by its steroid-like effect leading to tissue regeneration, this inhibits cell fibrosis and cirrhosis, and decreases cell inflammation and as a result of reduced liver tissue damage and fibrosis [51-53].

The antioxidant effect of silymarin also alleviates and protects against the toxic effects of the pollutant cadmium chloride. This was demonstrated by the significant effect of silymarin on restoring the testis diameter, wall thickness of the seminiferous tubules and nucleus diameter of spermatogonia of mice after cadmium toxicity. Moreover, histopathological changes such as increased interstitial space, irregularities, incoherence, and vacuolation of germinal epithelium, decreased sperm density in the lumen, as well as decreased seminiferous tubule wall of many seminiferous tubules were restored by silymarin. Interestingly, silymarin restored and elevated testosterone levels as a result of cadmium toxicity in mice [53].

b- Silymarin anti-inflammatory effect: One of the benefits associated with silymarin is its anti-inflammatory effects. Silymarin anti-inflammatory effect was tested by three models: carrageenan model, papaya latex model and arachidonic acid model. The results of carrageenan mode were insignificant. Silymarin exhibited significant anti-inflammatory and antiarthritic activities in the papaya latex-induced model of inflammation and in myobacterial adjuvant-induced arthritis in rats. The mechanism of the anti-inflammatory activity of SAS is through inhibition of 5-lipoxygenase for anti- inflammatory and antiarthritic activities and inhibition of the formation of 5-LO products, leukotrienes involved in inflammation (54). In studies using human T-cells, silymarin was found to inhibit TNF-α secretion and NF-κB-dependent transcription. The main reason for this response is to recruit inflammatory leukocytes, limit viral replication and spread, and ultimately eradicate the infection, indicating that silymarin may help inhibit HCV infection. SAS blocks inflammatory cytokines (TNF-α and IL-1)–induced activation of NF-kβ, causing expression of interleukin-6 in response to TNF. This effect was mediated through the inhibition of phosphorylation and degradation of Ik-β, an inhibitor of NF-kβ. NF-kβ plays the major role in the pathogenesis of chronic inflammation and insulin resistance [55, 53]. In induced polycystic ovarian syndrome in rats, silymarin inhibits the inflammatory index IL-6 and CRP (member of the pentraxin family); moreover, it is the most sensitive inflammatory index, and it inhibits 5-lipoxygenase enzyme [56].

c- Silymarin Hepatoprotective effect: Testing SAS against natural or induced toxins proved the effectiveness of SAS against nat-

ural toxins (Amanita phalloides mushroom) as demonstrated by low liver function, less prothrombin time prolongation, and reduced hemorrhagic necrosis [57, 58]. Silymarin may contribute to preventing the aflatoxicosis-induced liver cell damage by a competitive inhibition of α- amanitin uptake [132]. Although silymarin therapy of patients exposed to toxins as organophosphates, solvents, paints, and glue has no significant improvement on liver function. The available studies regarding drug-induced hepatitis or with acute alcohol hepatitis reported positive results for SAS as concluded from tested liver function parameters [59]. Silymarin exerts a hepatoprotective effect through inhibition of entry of toxins into the liver, improving liver protein production and blocking lipid peroxidation process through its antioxidant, scavenging of free radicals, increasing liver GSH level and inhibiting liver oxidative stress and the antioxidant markers [53, 60]. It also increases the activity of the antioxidant enzymes, such as SOD, CAT, and inhibits lipid peroxidation [61].

As an antioxidant, silymarin is a cell membrane stabiliser and permeability regulator, as well as a promoter of DNA, RNA polymerase I, and protein synthesis [62]. Silymarin has been shown to preserve the functional and structural integrity of hepatocyte membranes by preventing alterations of their phospholipid structure produced by carbon tetrachloride and by restoring alkaline phosphatase and γ-glutamyltransferase activities [63]. Silybin, which represents 50-70% of the extract from silymarin, has a cytoprotective effect attributed to the antioxidative activity. In addition, different factors are reported in the literature, viz., protecting against genomic injury, increasing hepatocyte protein synthesis due to activity on polymerase A in hepatocytes, decreasing the activity of tumour promoters, stabilising mast cells, chelating iron, and slowing calcium metabolism [8]. Moreover, it elevates the level of glutathione by inhibiting its metabolism into taurine. In addition, SAS correct the paracetamol toxic effect on the liver due to increased cholesterol; it significantly decreases the triglycerides (LDL) close to normal limits [64].

Although silymarin's effect on HCC is not significantly correlated to other chemotherapeutic agents, it enhances the liver chemistry and significantly reduces the serum level of alpha-fetoprotein and carcinoembryonic antigen protein synthesis. However, in some studies, most of the silymarin components exhibit no, or only weak, liver enzyme-inhibiting activity, and this was not comparable with their antihepatotoxic activity. The only exception was 3-deoxysilychristin, which produced a considerable enzyme inhibition [65]. Silymarin at the 1000 ppm dosage level can decrease the total number and multiplicity of macroscopic hepatic nodules in DENA-induced hepatocarcinogenesis in rats [66]. Silymarin interferes with the expression of the cell cycle regulators and proteins involved in apoptosis, so it can regulate the balance between apoptosis and survival of liver cells. It inhibits cell growth in HepG2 and Hep3B cells proliferation, increases the percentage of cells in G0/G1 phase and decreases cells in S-phase, up- regulates the expression of P53, Bax, RP, p21Cip1, and p27Kip1 and down-regulates the expression of antiapoptotic protein Bc1-2. It reduces the expression of cytochrome 450 2E1 (CYP2E1), TNF-α, transforming growth factor beta-1 (TGF-β1), and nuclear factor kappa-light-chain-enhancer of activated B cells-1. Silymarin inhibits proteins for transcriptional regulators of several proliferative genes in melanomas (extracellular signal-regulated kinase (ERK)-1/2 and RSK2, mitogen- activated protein kinase (MEK)-1/2, nuclear factor-kappa B (NF-κB), activator protein-1, and STAT3). In addition, it induces cell-cycle arrest at the G1 phase, which inhibits melanoma cell growth in vitro and in vivo [148].

Pure silymarin component, in combination with other natural products having a positive effect on liver syndrome (nonalcoholic fatty liver disease and nonalcoholic steatohepatitis), together with possible different mechanisms of hepatoprotective action, can inhibit hepatocellular toxicity and liver regeneration by promoting protein synthesis [29].

Given the difference in the compounds in SAS; Silbinin and silychristin increase the DNA synthesis, which is accompanied by an increase in protein synthesis, assisting cells proliferation, while isosilibinin and silydianin have a negative effect on protein synthesis and cells proliferation. The metabolic cell activity measured by LDH showed that silibinin and silychristin increased the activity of LDH, while silydianin and isosilibinin inhibited it. This was proved by counteracting the toxic effect of paracetamol in the presence of silybinin. [46].

In a clinical study to evaluate the effect of silymarin on the anti-TB drugs rifampicin (RIF), isoniazid (INH) and pyrazinamide

(PZA) on the liver, however, some reports concluded that silymarin reduced the incidence of hepatic damage caused by anti-TB drugs-reduced SOD; other reports can't support these results. The same conclusion was deduced in clinical studies conducted to assess the effect of silymarin on methotrexate in the treatment of children with acute lymphoblastic leukaemia. The clinical study to assess the silymarin effect on hepatic damage caused by type-2 diabetes drugs led to encouraging results since glycemic profile was improved as a result of significant reduction in HbA1c and GPA, LDL, triglyceride, AST and ALT. The hepatoprotective effect of silymarin was proved to be synergistic with other natural products, viz. glycyrrhizin, aloe vera, quercetin and dried grape extract [67, 68].

d- Silymarin Cytoprotective Activity: primary human hepatocytes in vitro culture is considered a good model for testing the cytoprotectivity of *Silybum* active flavolignans [69]. Silydianin and silychristin were not cytotoxic, whereas silybin and isosilybin at higher concentrations are cytotoxic. The mechanism of cytoprotection is thought to be through the antioxidant and the chemoprotectant activity [70], inhibit nuclear factor-κB and tumor necrosis factor induction, and balance the cascade of transcriptional processes affecting cell growth and apoptosis, thereby reducing inflammation and supporting the liver's tolerance to oxidative stress. The flavanolignans displayed concentration-dependent cytoprotection against the toxic effects of both allyl alcohol and carbon tetrachloride models, but with toxicity models with paracetamol and/or galactosamine, no significant toxicity was observed. This was attributed to the effect of silybum substances to stabilise the cell membrane against glucosamine toxicity in addition to their antioxidant potential. Silydianin and silychristin gave the best hepatoprotectivity, silymarin is moderate in its activity, while silybin and isosilybin were less effective [69]. The functional integrity of the cell membrane was maintained by silybum substances, as proved by lowering liver enzymes, aminotransferases and alkaline phosphatase due to fewer enzymes leaking as a result of stabilisation of the cell membrane [71]. As a result of stimulation of DNA synthesis, silymarin (especially silibinin) inhibits phase I detoxification pathways, stimulates phase II detoxification pathways, and accelerates liver cell regeneration. The mechanisms of silymarin chemoprotection is due to the effect of silibinin to stabilise cell membranes, thus preventing toxic chemicals from entering the cell, antioxidant and chemoprotectant activity, silymarin challenged with higher levels of glutathione in liver cells, decreased oxidative stress (measured by malondialdehyde concentrations), and fewer elevations in liver enzyme tests [72, 73].

e- Silymarin Antiproliferative activity: silymarin serves key functions that impede cancer progression, such as regulating cell cycle, stimulating apoptosis, and inhibiting cancer cell growth, angiogenesis, invasion, and metastasis [74]. The flavanolignans of *S. marianum* have shown efficacy in arresting the proliferation of colorectal carcinoma, human prostate carcinoma and ovarian cancer [75], rodent skin cancer [76], adenocarcinoma, estrogen-dependent and independent breast carcinoma, , ecto- cervical carcinoma, small and non-small cell lung carcinoma, UV radiation induced nonmelanoma skin carcinogenesis [77, 78], and antiproliferative effects on human melanoma cells. [79].

e.1: Colorectal carcimmmnoma: In an in vivo experiment, silibinin significantly reduced cancer cell viability in a concentration-dependent manner ($p < 0.001$) and remarkably induced SW480 cell death in addition to decreasing the colony formation rate and it does not affect the survival rate of surviving cells. Silymarin increased the cell population at G0 phase, indicating the onset of apoptosis as concluded from increased apoptotic cell number, and significantly lower number of cells in the G1, S, and G2/M phases, that is to say, it provokes cell cycle arrest. In addition, silymarin could inhibit angiogenesis and metastasis and increase P53 and BAX while decreasing BCL2 expression [80].

e.2: Human Prostate Carcinoma: silymarin is shown to inhibit growth, cell cycle arrest, and apoptosis induction of prostate carcinoma. This effect was shown by antiproliferative activities of silybinin (pure substance) and silymarin (mixed flavolignans) in human prostate carcinoma [81]. The cytoprotective activity of silymarin and silibinin is a function of their antioxidative and radical-scavenging activity. On the molecular level, NF-κ B inhibition of EGFR-MAPK/ERK1/2 signalling, activity upon Rb and E2F proteins, and IGF-receptor s1 signaling was disclosed. Silibinin and silymarin cause down-regulation of survival in

prostate carcinoma, inhibition of Akt and NF-kb 13signaling, inhibition of matrix metalloproteinase-2 (MMP-2) secretion and inhibition of extracellular signal-regulated kinase (ERK1/2) activation in prostate cells carcinoma, and reduces invasion and migration of human endothelial cells. In addition, Proapoptotic and anti-angiogenic activities of silybin are other important findings that give opportunity to silymarin prostate cancer application. [130].

e.3: Ovarian cell carcinoma: silymarin suppresses the proliferation of ovarian cells A2780 s and PA-1 as indicated by MTT assay in a concentration- and time-dependent manner through cell cycle arrest in the G1 phase and apoptotic occurrence. In vitro treatment of A2780s and PA-1 cells with silymarin blocked cell cycle progression at the G1/S phase, resulting in a significant increase in the G1 phase and a concomitant decrease of the S and G2 phase. Silymarin was found to upregulate tumour-suppressor protein P53, P21 and P27 and downregulate CKD2 protein expression [128]. In PCOS silymarin increases the number of primordial and preantral follicles and corpus luteum, and significantly decreases the number and size of cysts, and doubling the silymarin dose (200 mg/kg BW), almost no cysts were found, and corpus luteum showed ovulation. On a hormonal level, silymarin caused a significant decrease in the levels of estradiol, testosterone, LH and a significant increase in the levels of progesterone and FSH [56].

e.4: Breast carcinoma: In a dose-dependent manner, silymarin affects the viability of MDA- Mp-231 and MCF-7 cancer cells. At 200 μg/ml silymarin, 51.5% and 26.1% of both cell lines were viable, respectively. Moreover, the proliferation of both breast cancer cells was inhibited in a concentration-dependent manner; 12.1% (200 μg/mL) for MDA-MB-231 and 21.6% (100 μg/mL) for MCF-7 cells. The induced decrease in MDA-MB-231 and MCF-7 cell viability was closely associated with induced apoptosis by modulating the expression of apoptosis-related proteins and related to MAPK signalling pathway modulation [82].

e.5: Salivary gland carcinoma: silymarin inhibits MC3 and HN22 cell growth as shown by an increased number of apoptotic cells. This is achieved by probable induction of caspase- and mitochondria-mediated apoptosis, moreover, through Bim translocation from the cytoplasm to mitochondria [83].

e.6: Lung carcinoma: Agarwal group was the first to report that μmols of silibinin could significantly inhibit growth, cell cycle arrest, and apoptotic cell death of lung carcinoma. This was done using established cell models of small cell (SCLC) and non-small cell (NSCLC) lung carcinoma. The results warranted further studies to establish the efficacy and mechanism(s) of action of silibinin as a non-toxic therapeutic agent in additional lung tumour models.

Chronic oral consumption of silibinin significantly lowered lung tumour multiplicity, prevented lung tumours from growing beyond a small size (in a dose-dependent fashion), and blunted tumour angiogenesis. Mechanistically, the activity of silibinin was initially attributed to the reduced lung tumour expression of the angiogenic factor vascular endothelial growth factor (VEGF), mediated by the suppression of VEGF regulators such as cyclooxygenase-2 (COX2) and inducible nitric oxide synthase (iNOS). Silibinin appeared to target multiple cytokine (IFNγ, IL-1β, and TNF-α)-induced signalling pathways, such as the Signal transducer and activator of transcription 3 (STAT3), to ultimately lower COX2 and iNOS expression in lung cancer cells. Significantly, silybin inhibited cell proliferation by inducing cell cycle arrest and modulating multiple cell cycle regulators, including cyclin-dependent kinases and their corresponding cyclins. In later studies, silibinin exerted cytostatic, cytotoxic, and apoptotic effects in various NSCLC cell models. Importantly, silibinin could restore drug sensitivity to NSCLC cells with acquired resistance to EGFR- and ALK-TKIs in vitro and in vivo [135]. Silibinin can target lung cancer metastatic traits by inhibiting EMT per se. Silibinin efficiently suppresses the ability of brain metastatic NSCLC cells to co-opt a pro-metastatic program driven by STAT3 in a subpopulation of reactive astrocytes surrounding metastatic lesions. In particular, STAT3 participates in the initiation, development, and therapeutic resistance of lung cancer via promotion of proliferation, survival, inflammation, angiogenesis and metastasis [84].

f- ***Anti-Melasma effect*****:** topical silymarin (0.7% and 1.4%), treatment of melasma, versus the 4% hydroquinone (standard drug)

revealed promising efficacy of silymarin. The severity of melasma, as evaluated by MASI score, was significantly reduced after treatment with silymarin cream in both concentrations, and there was no statistically significant difference in the therapeutic response between the used concentrations [85]. The antioxidant and photoprotective activities of silymarin minimise the hazardous effects of UV radiation, such as oxidative stress, inflammation, oedema, erythema, DNA damage, and immune responses. Moreover, the antioxidant effect and inhibition of L-dopa oxidation activity of tyrosinase by silymarin reduce melanin production. Another mechanism was suggested by Choo and co-authors; silymarin decreases the expression of tyrosinase protein [86] and suppresses ultraviolet radiation A-induced oxidative stress, which can induce skin damage. Thus, the topical application of silymarin can be suggested as a useful strategy for protecting against skin cancer [87].

g- Silymarin and Chronic Hepatitis C: HCV causes about 85% of the chronic hepatitis, and the other four liver viruses either don`t cause hepatitis (HAC and HEC or HBC), or cause about 5% of liver hepatitis. Different studies in cell culture demonstrated that silymarin inhibits HCV by variably blocking viral entry, fusion, RNA and protein synthesis, HCV N5SB, RNA-dependent RNA polymerase activity. The antiviral effect may be due to stimulation of the Jak-Stat pathway and induction of an antiviral response by interferon [88]. In spite of that, clinical trial reports were controversial and not encouraging. Some reports suggested that silymarin affected liver chemistries but had no apparent effect on viral load, so silymarin may have a protective effect in the inflammatory response to HCV but no role as an antiviral agent and may have a beneficial effect on variables due to necroinflammation [89]. However the Virus load follow-up for 3 months showed some response, but not significant antiviral effect was observed by PCR follow-up after 6 months [150]. IV injection of silymarin in peginterferon nonresponder patients blocks HCV polymerase function at a half maximal inhibitory concentration (IC50) between 75 μM and 100 μM, and is able to reduce HCV viral loads from three to four logs within one/four weeks [129]. Silymarin is suggested to block both entry and fusion of HCV, and inhibition of viral replication by intervening directly in the HCV life cycle, but this was not statistically significant. Indeed, it inhibits HCV RNA-dependent RNA polymerase function independently from intracellular interferon (IFN)-induced antiviral pathways [90]. A combination of silymarin with other antiviral drugs, such as ribavirin and the immunoenhancer vitamin D, demonstrated a positive effect of ribavirin on HCV-infected patients. This combination was positively effective even with ribavirin-unresponsive patients [5].

In HBV chronic hepatitis, silymarin/silybin positively normalised the chemistry of the liver (AST, ALT, and serum HBsAg), and the response was noticeable when used in combination with antiviral agents such as lamivudine and interferon. The effect is mainly oriented towards the reduction of virus-related liver damage through the softening of the inflammatory cascade and immune system modulation [91].

h: Antiobesity And Hypocholesterolemic Effects: *S. marianum* and its main constituent silymarin showed some positive antiobesity signs in animal studies; however, they failed to show any positive responses in clinical trials. Silymarin reduces total cholesterol, total glycerides, and low-density lipid and increases high- density lipid. The hypocholesterolemic effect demonstrated by silymarin is attributed to decreased absorption of cholesterol after silymarin [149]. Silymarin treatment positively changes the plasma cholesterol lipoprotein profile, lipid content and liver biochemical [71]. Antihyperlipidemic effect of silymarin is achieved through antioxidant activity, increasing the expression of ABC transporters that are responsible for cholesterol efflux from the hepatocytes into the bile, stimulating the production of hepatic LDL receptors, and hepatoprotection [92, 29]. Additionally, silymarin/silybin inhibits HMG-CoA reductase so reduces cholesterol synthesis, enhances lipolysis through the up-regulation of adipose triglyceride lipase, inhibits gluconeogenesis through the down-regulation of Forkhead box O1, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [93] and increases protein expression of CYP7A1 and CYP4A [94]. The silymarin supplementation may decrease TC; however, the results are not significant and inconsistent. Silymarin had a favourable effect on LDL, but data were heterogeneous; at the same time, it was found to significantly increase HDL concentration [95]. Silybin increases gene and protein expressions of adiponectin that can enhance β-β-oxidation of free fatty acids and reduce de novo free fatty acids production within the hepatocytes, thus preventing lipid accumulation [96]. In an in vitro

study, silybin suppressed terminal differentiation of 3T3L1 cells into adipocytes and reduced lipogenesis in mature adipocytes in a dose-dependent manner. In spite of that, clinical studies revealed a negative effect of a combination of Silybum with some of the herbs reported for body weight control on body weight [97].

Furthermore, inhibition of lipid accumulation is known for silymarin as it is stated that this property happens by downregulating adipogenic factors, such as peroxisome proliferator-activated receptor c (PPARc), CCAAT-enhancer-binding protein a (C/EBPa), and fatty acid-binding protein 4 (FABP4) [98].

i: Silymarin and Diabetes mellitus: Although there is a lack of evidence about the beneficial effects of silymarin on T2DM patients, silymarin supplementation might have beneficial effects in decreasing FBS and HbA1c. Silymarin has proven, in vitro and in vivo, positive impact on some diabetes-related disorders [99, 100]. Type 2 diabetes promotes apoptosis of β-cells of the human pancreas and decreases expression of antiapoptotic protein Bc1-2, leading to decreased insulin. Reduction of glucose level in type 2 diabetes could be attributed to the protective effect of silymarin on the liver cells [101]. In addition, it increases β-cells regeneration and insulin gene expression, leading to increased β-cells number and upregulation of their function and viability [102]. So, increasing insulin levels suggests a beneficial candidate for type 2 diabetes [111]. Powerful antioxidant properties of silymarin with its activity against oxidative stress may induce a positive effect on diabetic metabolic abnormalities [103]. Silymarin stabilizes the cells membrane and elevates cells glutathione [101], increases and normalizes the pancreatic levels of free radical quenching enzymes such as SOD, GPX, and CAT in alloxan-induced diabetic animals [104], inhibits aldose reductase enzyme levels increased in diabetic patients [105], and inhibits insulin secretion in response to glucose stimulation [106]. This effect may inhibit hyperinsulinemia and subsequent insulin resistance; silymarin decreases ADMA, which is related to improvement of insulin resistance by decreasing HOMA-IR and increasing the ITT slope [93].

Interestingly, silymarin inhibited lipoperoxidation, and its hepatoprotective effect, which has a reflex effect on pancreas β-cells, may positively influence lipid and glucose metabolism [101]. On the molecular level, silymarin showed an increase in Nkx61 and insulin gene expression, β-cell neogenesis, and a rise in serum insulin.Nkx61 is recovered in rats administered silymarin after the alloxan, which damages pancreatic insulin-secreting β-cells. The Pdx1 gene and the pancreas duodenum homeobox-1 gene are responsible for regulating insulin promoter activity [102].

j: Hyperprolactinemic (galactogenic) Effect: The Increased Milk Production was previously observed in cows and humans feeding *Silybum* [107]. Milk production is a function of prolactin. Traditionally, *S. marianum* fruits have been used by nursing mothers for stimulating milk production [108]. A study on female rats revealed the positive effect of silymarin on the serum level of prolactin in female rats after a 14-day daily treatment. Moreover, revealed that after a 66-day discontinuation of silymarin treatment, prolactin levels were still significantly elevated [109].

k: Silymarin and cardiovascular problems: Some reports revealed that silymarin ameliorates different cardiovascular problems. In diabetes mellitus-induced cardiac dysfunction recorded by echocardiography analysis, silymarin restores ejection fraction and fractional shortening to normal. It ameliorates myocardial fibrosis in diabetic cardiomyopathy since it decreases cardiac interstitial fibrosis, increases the production and deposition of collagen, and decreases the interstitial fibrosis area in the heart of DM rats by transforming growth factor b1 (TGF-b1) Smad7 signalling pathway, inducing antifibrotic effect, thus attenuates myocardial fibrosis and collagen deposition [110]. The antiatherosclerotic effects of *S. marianum* and/or silymarin may be due to their antioxidant, lipid-lowering, and inhibitory effects on endothelial cell dysfunction. Thus, silymarin produce antihypertensive effect and it protects against high blood pressure complications such as cardiac hypertrophy [29]. The improved biochemistry of the liver due to the Silybum substances, which enhances the improvement of the lipid metabolism, reflects the enhancement of the cardiovascular functions. The hepatoprotective properties of silymarin suppress the production and release of inflammatory mediators by the liver, which significantly contributes to the development and manifestation of cardiovascular diseases [138]. Moreover, silymarin has a positive effect on hyperuricemia, which has an impact on vascular inflammation and

oxidative stress. It increases the levels of lipid-metabolising enzymes in the liver and decreases the cholesterol/phospholipid ratio both in the serum and liver, leading to hypocholesterolaemia. Moreover, silymarin plays an important role in cardiomyopathies, improving molecular and biochemical cardiac parameters and eliminating the toxic effect of some cardiotoxic drugs, viz. anticancer adriamycin, doxorubicin and cisplatin [10, 111].

l: Nephroprotective Activity: The flower extract of *S. marianum* increased the urine volume in rats, which suggested a silybum diuretic effect. It significantly increased the excretion of creatinine, sodium, and potassium. The clearance effect of *S. marianum* extract was higher than that of furosemide and without inducing hypokalemia [112]. Silymarin affects DNA and protein synthesis; it abrogates the increase of creatinine, urea, and cystatin- C, elevated as a result of sepsis and nephroenjury induced by carbon tetrachloride tubular damage and keeps the normal histological architecture of the kidney cells [53]. Administration of silymarin abrogated tubular injury and necrosis induced by colistin, which induces apoptosis in the epithelial cells. At the same time, no interstitial inflammation and medullary congestion were detected [99, 113]. In acetaminophen nephrotoxicated rats, (500 mg/kg v.o.) the nephroprotective effect of silymarin (25mg/kg) was proved as it showed a significant reduction in the triglycerides, total cholesterol, BUN, SCr and AST. In bile duct-ligated rats, biomarkers of liver and kidney functions and urine biomarkers were elevated due to liver-induced cholestasis (colemic nephropathy). Silymarin (10 and 100 mg/kg, oral) significantly alleviated serum biomarkers of hepatic and renal injury in cholestatic animals and significantly mitigated urine biomarkers. On the molecular level, reduction of oxidative stress reported for silymarin was reported to in renal tissue through the recovery of antioxidant enzymes and mitochondrial impairment in the kidney of cholestatic animals, revealed depolarisation of mitochondria and decreased dehydrogenase activity [114].

m: Neuroprotective Activity: Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Huntington's disease, Traumatic brain injury, Stroke, and Cerebral ischemia represent the common neurodegenerative disorders. The neuroprotective effect of silymarin was assessed through the use of a neuronal-derived SH-SY5Y cell line primary culture from rat cortical astrocytes challenged with oxaliplatin. Silymarin was combined with α- tocopherol in an in vitro model; treatment protected the cells against the oxidative stress generation by SOD, MDA, CP, and DNA oxidation [115, 116]. In addition, it proved attenuation of neurodegenerative and oxidative stress diseases by ameliorating the oxidative stress mediators and binding to estrogen receptor β in the CNS [115]. It decreases the MAO activity in vitro [117] and increases MAO-β activity, which is associated with an increase in the production of ROS [118]. On the other hand, the inhibition of MAO-α can protect against cell apoptosis [139] while the inhibition of MAO-β is related to a therapeutic role in the treatment of Parkinson's disease [119]. In this way, the neuroprotective effects of the MAO-β inhibitors [120]. Another suggestion for the neuroprotective effect os silymarin was that it inhibits the synthesis of APP and consequently amyloid-beta (Aβ) neurotoxicity, neuroprotection by inhibition of *tau* protein phosphorylation, improving memory deficit due to suppression of TLR4 pathways and then subsequently diminishes the elevated level of TNF-α. So, silymarin has possible therapeutic effects and essential cytoprotective properties in the CNS because of its capacity to prohibit oxidative stress, pathologic protein aggregation, neuro-inflammation, apoptosis, and estrogenic receptor modulation [121].

n: Anti-amnesia effect: protection against the incidence of neurodegenerative diseases such as Alzheimer's disease, dementia, and amnesia reinstates by inhibiting cholinesterase enzymes (AchE and BChE) the neurotransmitter acetylcholine (Ach) [122]. These disorders are secondary to oxidative stress due to ROS production. SAS was suggested as a natural plant resource for memory enhancement and anti-dementia drugs. The potential of SAS to inhibit the AChE and BChE activities was found to be as active as donepezil, a standard anti-amnestic principle [136].

Silymarin is postulated to penetrate the blood–brain barrier and act on the CNS by suppressing neuroinflammation, attenuating brain damage and ameliorating cognitive deficits in various models of neurologic disorders, such as cerebral ischemia, Alzheimer's disease, and Parkinson's disease [49]. Silymarin decreases 4-aminopyridine-evoked glutamate release in a concen-

tration- dependent manner with an IC50 of about 12 μM, with maximal inhibition at 30 μM. Moreover, silymarin attenuates microglia and astrocyte activations induced by Kainic acid and increases neuronal survival rate (Lu et al., 2020). Silibinin ameliorates the neurological function, such as brain oedema and infarct size, after ischemia. This demonstrates a potential effect of silibinin as a candidate drug in ischemic stroke. Silibinin promotes the activation of the Akt/mTOR signal, which is accompanied by upregulation of HIF-1α, Bcl-2 and downregulation of Bax, NF-kB in ischemic brain tissue.Thus, activating Akt/mTOR signalling may be an attractive method to explain the protective effects of silibinin in the acute stage of ischemic stroke [124].

o. Antifungal activity: Silymarin was tested against amphotericin B to reveal whether it has a potential for antifungal activity. Using *Candida albicans, C. parapsilosis, Aspergillus fumigatus, Trichosporon beigelii, Malassezia furfur,* and *Trichosporon beigelii* fungal cultures proved the antifungal potential of silymarin in the range of 2.5–10.0 μg/mL (1.3–2.5 μg/ mL for amphotericin B). Positive effect of silymarin on the cell membrane suggested its antifungal mechanism; it induces injury to the *C. albicans* plasma membrane at concentrations of 10.0 and 20.0 μg/mL; it induces membrane lesions with a decrease of membrane integrity and an increase in membrane permeability at concentrations of 10.0 μg/mL [124].

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