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Silymarin: An Overview With Its Phytopharmacology Concept

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ABSTRACT

Silybum marianum (Milk thistle), a part of the Asteraceae family, is a tall herb with huge prickly white- veined green leaves as well as a reddish-purple flower that split ends in sharp spines. Many of the phytoconstituents were shown such as silybin A, silybin B, isosilybin A, isosilybin B, silychristin, silydianin, kaempferol, taxifolin and quercetin. The sylimarin microscopic characteristic with its morphological characteristic were also known. The plant is entirely used as anti-diabetic, hepatoprotective, hypocholesterolaemic, anti-hypertensive, , anti-cancer, and as an anti-oxidant.. The plant is also serves as a galactagogue and used in the treatment of uterine disorders. These plant showing the synergistic effect with glyrrihizin and cancer drug. This review paper focuses mainly on phytochemistry and pharmacological activities as well as dosage regimen and its pharmacokinetics of the well-known plant milk thistle.

Keywords: Silybum marianum , Hepatoprotective , SILIPHOS®, Legalon® ,Anti-diabetic.

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INTRODUCTION

Milk thistle (Silybum marianum (L.) Gaetrn) has been introduced from the time when ancient to treat a variety of liver and gallbladder disorders (hepatitis, cirrhosis and jaundice) and to look after liver damage due to alcoholism, other drugs, and chemical pollutants.[1] It is also known as a general medicinal herb from near the beginning 4 th century B.C. and first introduced by Theophrastus . Extract from the seeds of the milk thistle is used traditionally as a herbal remedy in favour of hepatotoxicity and acute and chronic liver diseases. Silymarin effects have also been identified in various disease of different organs such as prostate, lungs, CNS, kidneys, pancreas, and skin. [2] The major component of this plant is silymarin – a standardized extract obtained from the seeds of S. marianum consist of approximately 70% to 80% of the silymarin flavanolignans (silymarin complex) and about 20% to 30% of a chemically undefined fraction, along with mostly polymeric and oxidized polyphenolic compounds (polyphenolic fraction – PP). [3] The active constituents of milk thistle seed are three flavonolignans viz. silibinin, silychristin, and silidianin together known as silymarin extracted from milk thistle seeds, existing commercially as standardized extract. Milk thistle seed extract (silymarin) and its constituents (mainly silibinin) play role as antioxidant and hepatoprotective ; effective in treating toxin poisoning, hepatitis, cirrhosis, fibrosis of liver; stimulate liver rejuvenation.[4] Mechanism of sylimarin action include :stabilization of hepatocytes by decreasing of hepatotoxin binding to receptor sites on hepatocyte membranes ; decline of glutathione oxidation to raise glutathione levels in the liver and intestines; antioxidant activity; stimulation of ribosomal RNA polymerase and following protein synthesis which turn to enhanced hepatocyte regeneration.[5]

Plant Profile [2, 3, 7]

Synonyms

Carduus marianus L., *Carthamus maculatum* Lam., *Cirsium maculatum* Scop., *Mariana mariana* (L) Hill., *Silybum maculatum* Moench. Asteraceae are also known as Compositae.

Taxonomical Classification[1,2,9]

Table: 1 Taxonomical Classification of SM

Domain	**Eukaryota**
Kingdom	Plantae
Subkingdom	Viridaeplantae
Phylum	Tracheophyta
Subphylum	Euphyllophytina
Infraphylum	Radiatopses
Class	Magnoliopsida
Subclass	Asteridae

Superorder	Asteranae
Order	Asterales
Family	Asteraceae
Genus	Sylibum
Species	Marianum
Botanical name	Silybum marianum

Vernacular Names [10,11,12]

Botanical name Silybum marianum (L.) Gaertn (Syn. Carduus marianum L.) Silybum is the name Dioscorides gave to edible thistle and marianum comes from the legend that the white veins running through the plant leaves were caused by a drop of the Virgin Mary's milk. Pharmacopeia name: Cardui mariae fructus[1]

Table: 2 Vernacular Names of SM

Dutch	Mariendistel, Vrouwendistel
English	Holy thistle, Lady's thistle, Milk thistle
French	Artichautsauvage, Chardon marie
German	Feedistel, Mariendistel, Silberdistel
Greek	Silybon
Italian	Cardodel latte, Cardomariano
Malta	Blessed thistle
Romanian	Armurariu
Russian	Ostropestro
Spanish	Cardolechal, Cardolechero
Swedish	Sempertin

Morphology Characteristic

- Milk thistle (*Silybum marianum*) is a thorny plant representing decorative leaves with a white pattern of veins and purple flower heads in fig no: 3.
- An annual to biennial herb, up to 2m high
- Has dark shiny green and white-veined leaves with spiny edges.
- STEM: 20-150 cm high, rarely shorter, glabrous or slightly downy, erect and branched in the upper part.
- LEAVES: alternate, large, white veined, glabrous with strongly spiny margins as in fig.no:1
- INFLORESCENCES: Large and round capitula, solitary at the apex of the stem or its branches, surrounded by thorny bracts.
- FLORETS: Hermaphrodite, tubular in shape with a red-purple corolla.
- SEEDS: Hard-skinned achenes , 6–8 mm long, shiny, generally brownish in colour and with a white pappus at the apex as shown in fig 2 .

- POLLEN GRAINS: In milk thistle is prolate in equatorial view and semi angular in polar view.

Geographical Distribution Local[9]

Regional: All North African countries.

Global: Silybum marianum is native to Central and Southern Europe, Southern Russia, Asia mino, North and South America and South Australia. The plant originates from mountains of the Mediterranean region, where it forms scrub on a rocky base. Silybum marianum also found in Nile region, including the Delta, the Valley, the Faiyum, Oases, Western Mediterranean Coastal Region, and the Isthmic desert, i.e. El-Tih and the region North of Wadi Tumilat.

Figure 1: Flower

Figure 2: Seed

Figure 3: Leaf

The plant grows wild in Egypt on canal banks and in wet ground regions in the Nile Valley. The soil supporting this plant is fine-textured and moist. It occurs in two types, the most abundant has purple flowers while the least abundant has white flowers (v. albiflora). It is indigenous to Europe.

Botanic Characteristics—

Microscopic[28]

The fruit wall epidermis comprise of roughly colorless palisade cells in order at right angles to the surface. They have greatly thick outer walls, into which the lumen extended for some distance in the structure of a slit. When viewed from above under high magnification, the cells show only a slit-shaped lumen as shown in fig 4. They have thick ridges that appear as nodular thickenings of the cell wall. The sub-epidermal layer of the fruit wall is made up of unlignified thin-walled parenchymal cells and consist of a pigment layer. Colorless cells and groups of cells alternating with pigment cells, the later altering in number; this rise up the fruit wall its spotted appearance. Subsequently comes the fruit wall tissue, as regards 8cell layers thick, with spotted parenchymal cells extended in the longitudinal axis of the fruit. The cells of the intimate layer of the fruit wall may be distorted; they contain large cigar shaped or monoclinic calcium oxalate prisms. The seed

coat epidermis is produced from large yellow palisade cells. The cells have a narrow lumen, fairly expanded at each end of the cell, and the cell walls illustrate conspicuous lamination. The sub-epidermal cells of the seed coat comprise of peculiar mottled cells; their lignified cell membranes have major, close-set ridges or thickenings ("net cells"). Further is a single layer of cells having tough, fairly swollen walls and lipophilic filling (endosperm residue).The embryo comprise of thin-walled cells which, in accumulation to small glands, enclose clumps of crystals and fat droplets.

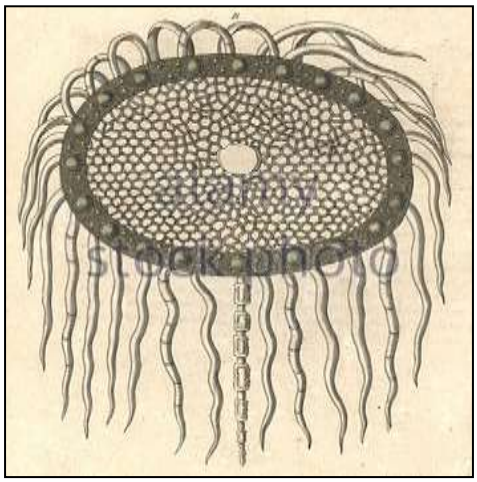

Figure 4: Microscopic structure of *Silybum marianum*

Chemistry of Flavonolignans[13]

The major components of silymarin are silybin A, silybin B, isosilybin A, isosilybin B, silychristin A, silychristin B and silydianin. The first six compounds represent as equimolar mixtures as trans diastereoisomers. These diastereomers have very like 1H and 13C NMR spectra and have no distinctive signals for simplistic identification of the individual isomers.[52] Several other chemically associated compounds have been found in the fruits including dehydrosilybin, desoxysilychristin, desoxysilydianin, silandrin, silybinome, silyhermin and neosilymermin. The ordinary trait of these compounds is a flavonolignan skeleton (C25H22O10, mol wt 482). Principally, flavonolignan nucleus consists of the dihydroflavanol taxifolin correlated to coniferyl alcohol moiety through an oxeran ring. The oxeran ring is dependable for the biological activity of silymarin, and opening of this ring results in loss of activity. Only silybins and isosilybins contain the 1, 4- dioxane ring system in their structure. Silybin and isosilybin have the similar trans conformation of C-2, C-3 and C-7', C-8'. Silybin is considered the major and principle component in silymarin. The chemical structure of silybin has been identified in 1975 using a degradative method. The first trials to synthesize silybin suffered from the problem of giving a product which is a mixture of regioisomers, silybin and isosilybin (57:43). Regioselective synthesis of diastereomeric silybin in

63% overall yield was produced by synthesizing a key intermediate which was coupled with 2,4,6-trimethoxyacetophenone to form a chalcone intermediate. Epoxidation, deprotection and acidic cyclization were followed.[12] Silymarin consist of structural flavonolignan isomers: silybin (silibinin) (50 - 60%), isosilibinin (5%), silicristin (20%), silidianin (10%) and other components such as taxifolin (5%) [40]. Other constituents include apigenin, silybonol, dehydrosilybin, deoxysilycistin, deoxysilydianin, silandrin, silybinome, silyhermin, and neosilyhermin as shown in fig. No 5. It has been reported that milk thistle fruits have a relatively high amount of oil (20–31%) that contains fatty acids such as linoleic acid, oleic acid, linolenic acid, palmitic acid, stearic acid. Silybin is the major biologically active constituent of milk thistle and responsible for its pharmacological activity. It has been used for centuries to self- treat liver disorders.

Table: 3 Component of Sylimarin

Sr. No	Name of Compound
1	4,7-Epoxy-3,8-bilign-7-ene-3,4,5,9,9- pentol
2	1,8,15-Hepta decatriene-11,13-diyne
4	2,9,16-Heptadecatriene-4,6diyn-8-ol
5	Isosilybin
6	Isosilychristin
7	Neosilyhermin A
8	Neosilyhermin B
9	Kaempferol3,7diglycoside
10	Silandrin
11	Silychristin
12	Silybin
13	2,3-Dehydrosilybin
14	2,3-dehydrosilychristin
15	Silymonin
16	Silydianin
17	Silyhermin
18	2-(1-Undecen-3,5,7,9-tetraynyl) oxirane
19	12-Tridecene4,6,8,10-tetraynal
20	4,5-Dihydroxy flavon 7- 0[rhamnopyranosyl-(12)-D- galacturonopyranoside

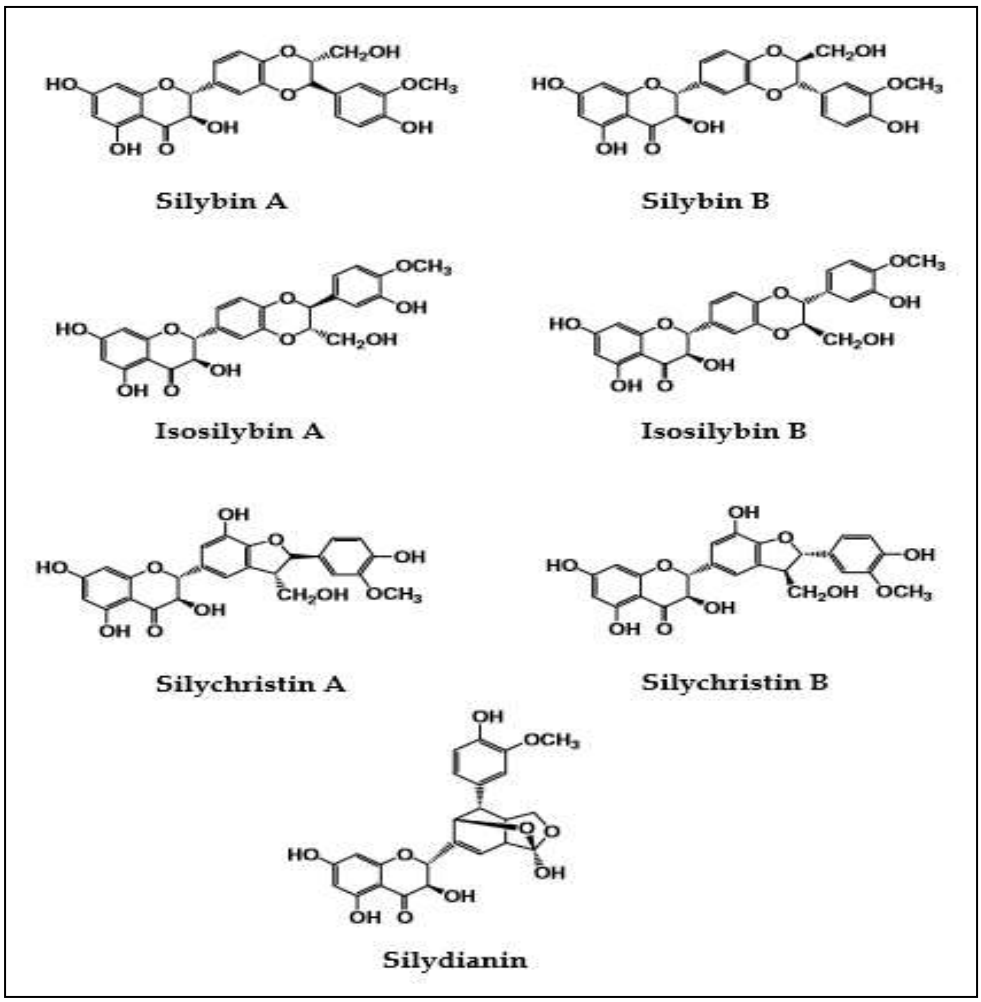

Figure: 5 Structure of SM Component

Mechanism of Action[39]

- Free radical scavenging
- Inhibition of lipid peroxidation
- Suppression of NF-jB translocation and binding Suppression of TNFa, TNF receptor 1, and TNF receptor 1 – associated apoptosis-ligand expression
- Decreased IL-4 expression Inhibition of 5-lipooxygenase pathway and leukotriene formation in Kupffer cells
- Inhibition of nitric-oxide synthase expression secondary to LPS stimulation Reduced monocyte chemo attractant protein 1 with IL-1b stimulation
- Reduced IL-1b and prostaglandin E2 in LPS sepsis
- Inhibition of selection adhesion molecule expression Reduction in stellate cell DNA synthesis, proliferation, and migration Reduction in hepatic collagen, procollagen III, procollagen a1, and profibrogenic mRNA expression

- Up-regulation of bile salt export pump and choleresis
- Competitive inhibition of hepatocyte-specific OATP2 transporters

Following figure no: 6 show the mechanism action with its brief

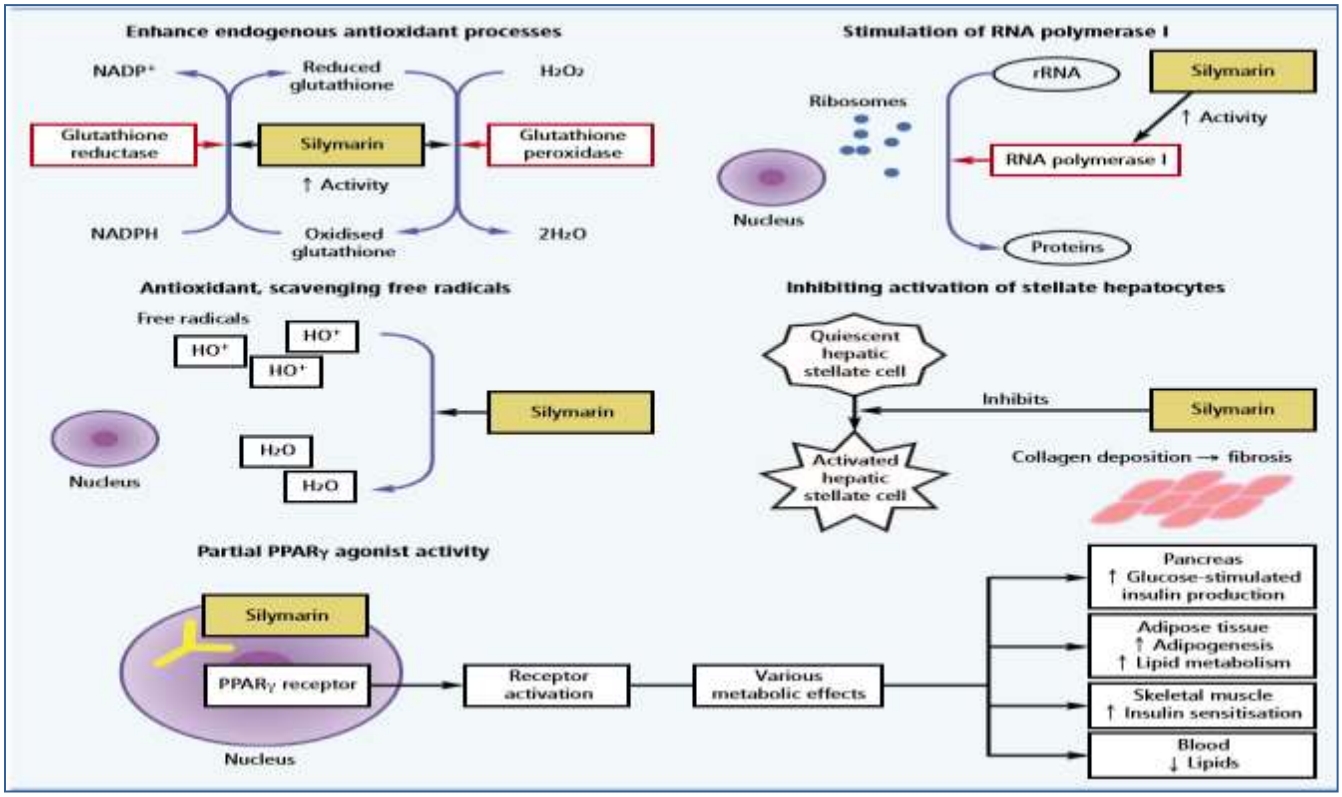

Figure 6 Mechanism action of silymarin

PHARMACOLOGICAL ACTIVITY

Silymarin is the pharmacological active constituent of milk thistle fruits. Milk thistle is known for multiple medicinal activity , due to its various physiological response. Research has established that silymarin extracted from milk thistle fruits can care for healthy liver cells from deterioration, help in purifying and detoxification, as well as maintenance of regeneration from damaged cells. A variety of components of milk thistle (silymarin, silybin, etc.) have many mechanisms of action that may be hepato- protective, including anti-inflammatory activity, antioxidant activity, toxin blockade, enhanced protein synthesis and anti-fibrotic activity.

Antioxidant Properties [13,14,51]

The water-soluble dehydrosuccinate sodium salt of silibinin is a potent inhibitor of the oxidation of linoleic acid-water emulsion catalyzed by Fe2+ salts. It also inhibit in a concentration-gradient approach the microsomal peroxidation formed by NADPH- Fe2+ -ADP, a recognized experimental system for the arrangement of hydroxy radicals. In studies performed in rat hepatic microsomes, it has been confirmed that lipid peroxidation produced by Fe(III)/ascorbate is reduced

by silibinin dihemisuccinate; the reduction is concentration-dependent. It has been revealed that silymarin is as active as quercetin and dihydroquercetin, and further active than quercitrin, in terms of antiperoxidant activity, self-governing of the experimental model used to produce peroxidation. It has in recent times been reported that in rat hepatocytes treated with tert-butyl hydroperoxide (TBH), silymarin inhibit the loss of lactate dehydrogenase (LDH), raise oxygen consumption, decrease the formation of lipid peroxides, and increases the synthesis of urea in the perfusion medium. Furthermore, silymarin is capable of antagonise the increase in Ca2+ formed by TBH, reducing ion levels down to below 300 nmol/L. The protecting effect of silymarin is mediated by the inhibition of lipid peroxidation, and the modulation of hepatocyte Ca2+ content which play a crucial role.[17] Free radicals, including the superoxide radical, hydroxyl radical, hydrogen peroxide and lipid peroxide radicals have been concerned in liver diseases. These reactive oxygen species (ROS) are produced in the body as a result of biochemical processes in the body, and as a result of increased exposure to xenobiotics . The mechanism of free radical damage include ROS- induced peroxidation of polyunsaturated fatty acid in the cell membrane bilayer, which leads a chain reaction of lipid peroxidation, therefore damaging the cellular membrane and lead to further oxidation of membrane lipids and proteins. Silymarin is possibly capable of antagonize the reduction of the 2 main detoxifying mechanisms – GSH and superoxide dismutase (SOD), by depleting the free radical load, growing GSH levels and help in SOD activity. Consequently, the cell contents, along with DNA, RNA and other cellular components, are damaged. The cytoprotective property of silymarin are primarily relevant to its antioxidant and free radical scavenging properties. Silymarin can also intermingle directly with cell membrane components to prevent any abnormalities in the content of lipid fraction lead to maintain normal fluidity. Silymarin prevent cells from ROS damages by rising up endogenous antioxidant enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD). Furthermore, it also inhibits the activation of NF-κB.[30] In Myoglobinuric hepatic failure which is modulated by co-administrating vitamin C along with sylimarin.[53]

Mushroom Poisoning[13,15,24]

The mainly notable use of silymarin is in the treatment of Amanita mushroom poisoning. Amanita mushrooms have two extremely powerful hepatotoxins, amanitin and phalloidin. Variety of liver damage (and death) was protect if silymarin was administered within 24 hours. The daily dosage of silibinin was $\leq$ 20 mg/kg day in 53.2% of the reports and up to 50 mg/kg day in 31.8% of the reports. Treatment period was 4–5 days in most cases. Silibinin or silymarin, ultimately combined with N-acetylcysteine, tend to represent the therapeutic support in the therapy of the intoxications

with Amanita phalloides. The drug Legalon Sil® was provided by Madaus Pharma (Brussels, Belgium; division of Madaus AG, Cologne, Germany). The FDA approved permission to use MT after in view of that all patients were going to die of liver failure. Only 1 of the 6 patients died, and all of the remaining have had a full recovery after treatment (http://www.herbalgram.org:80/ default.asp? c= 8284ThistleMushroom).[16] In recent times, the position of tumour necrosis factor-α (TNFα) in hepatic injury formed by α-amanitin has been investigated in primary cultures of rat hepatocytes. At a concentration of 0.1 µmol/L , the toxin inhibits RNA and protein synthesis within 12 hours, but cytotoxicity appears only much later (36 hours). TNFα is not essential for the improvement of cytotoxicity, but exacerbates it and noticeably increases lipid peroxidation. The accumulation of silibinin at a concentration of 25µmol/L to the culture medium prevented the effects of TNFα (50µg/L)[17]

Alcoholic Liver Diseases[13]

Silymarin considerably maintain the superoxide dismutase activity of erythrocytes and lymphocytes, the serum level of free-SH groups and the action of glutathione peroxidase. Research on In Vitro and In Vivo animal models revealed that silymarin has capability to keep liver cells from toxins. In alcoholic liver diseases (ALD), silymarin was originate to apply hepatoprotective effects by achieving the tumor necrosis factor (TNF) formation along with reducing the serum alanine aminotransferase (ALT) activity, depleting lipid peroxidation , and rising up the intracellular reduced glutathione content in mouse model of ALD. A double-blind study done on patients suffered from chronic alcoholic liver disease. The effect demonstrated that serum bilirubin, aminotransferase values and gamma glutamil transferase (GGT) activity were normalized in the silymarin group. Long-term survival in patients with alcoholic hepatitis who discontinue alcohol is drastically better than in those who continue to drink, though it ruins considerably below that of an age-matched population. 3-year survival approaches 90% in abstainers, whereas it is <70% in active drinkers.

Anti-Cancer Activity[25,50]

Carcinogenesis is a several step process that is activated by changed expression of transcriptional factors and proteins implicated in proliferation, cell cycle parameter, differentiation, apoptosis, angiogenesis, invasion and metastasis. Silymarin and silybin alter imbalance involving cell survival and apoptosis throughout interference with the expressions of cell cycle regulators and proteins implicated in apoptosis. Anti-cancer activity of silymarin has been demonstrated in human breast cancer, skin cancer, androgen-dependent and -independent prostate cancer, cervical cancer, colon cancer, ovarian cancer, hepatocellular carcinoma, bladder cancer, and lung cancer cells.

Mechanism of cytoprotective activity of silybin related to antioxidative and radical- scavenging effects with the specific receptor interaction and modulation of a multiplicity of cell-signaling pathways e.g. NF- kappa B, suppression of EGFR- MAPK/ERK1/2 signaling and IGF-receptor signalling . Treatment with silymarin considerably decrease the production of MDA-DNA adducts and hepatocellular carcinoma serum markers such as alpha-fetoprotein, carcinoembryonic antigen, aminotransferase, alkaline phosphatase, lactate dehydrogenase, gammaglutamyltransferase and 5´-nucleotidase . silymarin inhibits β-catenin increase, which will suppress the proliferation of hepatocellular carcinoma HepG2 cells. β-catenin is a vital factor in cell adhesion complex. It stimulates T-cell transcription factor and plays an vital role in regulation of oncogenic progression, with anti-apoptotic effects in a variety of cancers. Silybum marianum inhibition of two cell lines SK-BR-3 and BT-474 growth at unlike concentrations, and rise up cell death in both cell lines. Silymarin can be combined with other anti-neoplastic agents to obtain better results.[55]

- Inhibits proinflammatory pathways
- Modulates cox-2 expression
- Inhibits lox expression
- inhibits inflammatory cytokine expression
- Inhibits both tnf signaling and tnf expression
- Inhibits activation of inflammatory nf-κb activation
- Suppresses proliferation of tumor cells
- Modulates protein kinase c
- Suppresses cellular proliferation by modulating protein kinases.
- Induces cell cycle arrest
- Induces cell cycle cyclin-dependent kinase inhibitor
- Inhibits the egfr pathway
- Up-regulates insulin-like growth factor-binding protein 3 expression
- Down-regulates cell survival proteins
- Suppresses the expression of the inos gene
- Silymarin inhibits telomerase activity
- Silymarin inhibits rb phosphorylation and increases rb- e2f complex formation
- Binds to estrogen receptors
- Inhibits function of the androgen receptor
- Down-regulates p-glycoprotein

- Silymarin is a chemo sensitizer
- Alters the expression of tgf
- Inhibits the secretion of prostate-specific antigen (psa)
- Inhibits the expression of cell surface adhesion

Anti-Diabetic Activity[18,33]

The characteristic of silymarin in depleting fasting glycaemia and insulin level have helping its use as an antihyperglycaemic compound. The potent hypoglycaemic and antihyperglycaemic actions of an aqueous extract of milk thistle have also been demonstrated in experimental animal models of diabetes. The clinical trial examined type 2 diabetic patients (n = 51) using a 200 mg silymarin tablet three times a day earlier than meals day and the control group (26 patients) received a placebo tablet three times a day before meals for 4 months. The results predict a significant reduction in HbA1c, FBS, total cholesterol, LDL, triglyceride SGOT and SGPT levels in silymarin treated patients compared among placebo also with values at the start of the study in each group . In an additional RCT study, given silymarin tablet in 54 type 2 diabetic patients lead to reduction in blood glucose and HbA1c as well as decreasing triglyceride and SGOT and SGPT. These studies, propose a probable effect of S. marianum in glycemic control, though, more huge clinical trial examination is required.[18] The study was conducted on cirrhotic patients with diabetes mellitus admitted to Medical Trust Hospital, Cochin, Kerala, during the period from July 2009 to December 2009. Patients of both gender, aged between 20 and 70 years, were incorporated in this study. The study was perform later obtaining grant from Institutional Ethical Committee. Manonmani Alvin Jose et al selected 10 patients with silymarin + insulin therapy and another 10 patients with insulin + (L-ornithine + L-aspartate). The efficiency was examined by monitoring the random sugar levels, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), serum albumin before treatment, and after 3 and 5 months of treatment. The decrease in random blood glucose, SGOT and SGPT level formed by silymarin was reliable. The hypoglycemic effect of silymarin may be because of its antioxidant activity by reducing insulin resistance.[19] Sylimarin helps in the diabetic wound healing activity.[31] The Michaela Petrie et al perform a study which included 59 patients with diabetes, previously maintained on 10mg/day glibenclamide and diet, randomized into three groups: the first two groups were treated with either 200mg/day silymarin or placebo added to glibenclamide, and the third group continual glibenclamide alone for 120 days. Compared with placebo, silymarin treatment significantly enhanced both fasting and postprandial plasma glucose

measurements, in addition to considerably falling HbA 1c levels by 16% after 120 days [38]. Silymarin extract could safely be used simultaneously with metformin to increase the antioxidant potency and better renoprotection. Therefore, combination of metformin, silymarin and renin-angiotensin system (RAS) inhibitors or angiotensin receptor blockers may have kidney protective property beyond controlling the blood sugar of metformin, to protect or slowing the diabetic nephropathy.[43]

Hepatoprotective Activity [13,22]

Silymarin is most investigated plant extracts with recognized mechanisms of action for oral treatment of toxic liver damage. Silymarin is used in treatment in acute and chronic liver diseases. Silymarin helps the liver cells by multifactor action which consist of binding to cell membrane to suppress toxin penetration into the hepatic cells, enhancing superoxide dismutase activity , enhancing glutathione tissue level , inhibition of lipid peroxidation and increasing hepatocyte protein synthesis [20,54]. The hepatoprotective activity of silymarin can be demonstrated based on antioxidant properties due to the phenolic nature of flavonolignans. It also play a major role through stimulating liver cells regeneration and cell membrane stabilization to permit hepatotoxic agents from entering hepatocytes .In recent times it has been proved that flavonolignans inhibit leucotriene production; this inhibition explains their anti-inflammatory and antifibrotic activity. Silymarin has been used for centuries as a hepatoprotectant. This effects have been recognized to direct and/or indirect anti-oxidant capacity of silymarin, such as being scavenger of reactive oxygen species, scavenger of phenylglyoxylic ketyl radicals, chain breaking antioxidant. Silymarin is an active principle that having hepatoprotector and regenerative action; its mechanism of action derives from its capacity to counter arrest the action of FR, which are produce because of the action of toxins that injure the cell membranes (lipid peroxidation), competitive inhibition by external cell membrane alteration of hepatocytes; it produce a complex that impedes the entry of toxins into the interior of liver cells and, on the other hand, metabolically stimulates hepatic cells, in addition to activating RNA biosythesis of the ribosomes, stimulating protein formation.[20] It can be concluded that doxorubicin applied in a dose of 1.66 mg/kg every second day for 12 days, lead to a significant decrease in body weight of treated animals and that silymarin prevents this body weight reduction in rats treated with doxorubicin. Treatment with silymarin prevents rise in AST and CK serum activity and myocardial excitability of rats caused by doxorubicin. It also significantly deplete doxorubicin-prooxidative activity and reduction in histological alteration in liver and heart tissue of animals treated with doxorubicin. Altogether, the data predict that silymarin ameliorated doxorubicin-induced cardiotoxicity and protected against doxorubicin-

induced hepatotoxicity in male Wistar rats.[21] The milk thistle native seed oil to enhance the antioxidant defense system and thus provide protection against CCl4 -induced hepatotoxicity in mice.[26] Milk thistle extract is a introduce as hepatoprotectant with low bioavailability (20-50%). The objective of the present study is to prepare and characterize silymarin phytosomes and to test the hepatoprotective effect of the phytosomes in CCl4 induced liver injury in rats compared to milk thistle extract. Phytosomes were prepared using lecithin from soybeans and from egg yolk.[27] It was found that decrease absorption into the bloodstream by the generation of the drug transporting P- glycoprotein (P-gp), mainly at the level of the intestine. P-gp is a molecule that acts as a drug efflux pump at epithelial cells, particularly the intestinal wall. In other words, generation of P-gp results in less absorption of any drug that is subject to its effects. So the probably explanation of the findings is a decrease uptake due to P- gp induction, rather than elevating clearance resulting from the induction of hepatic phase I cytochrome P450 enzymes such as CYP3A4.[57,] It has been found that the combination of drugs at higher doses, that is, Sylimarin (200mg/kg) and Glycyrrhizin (50mg/kg), may have synergistic activity and confirm the best hepatoprotective effects. The time-dependent studies predict that the healing process for serum enzymes induced by SLN and GLN is directly related to the time course of treatment and that the herbs achieve an almost complete healing after six weeks of constant administration.[59]

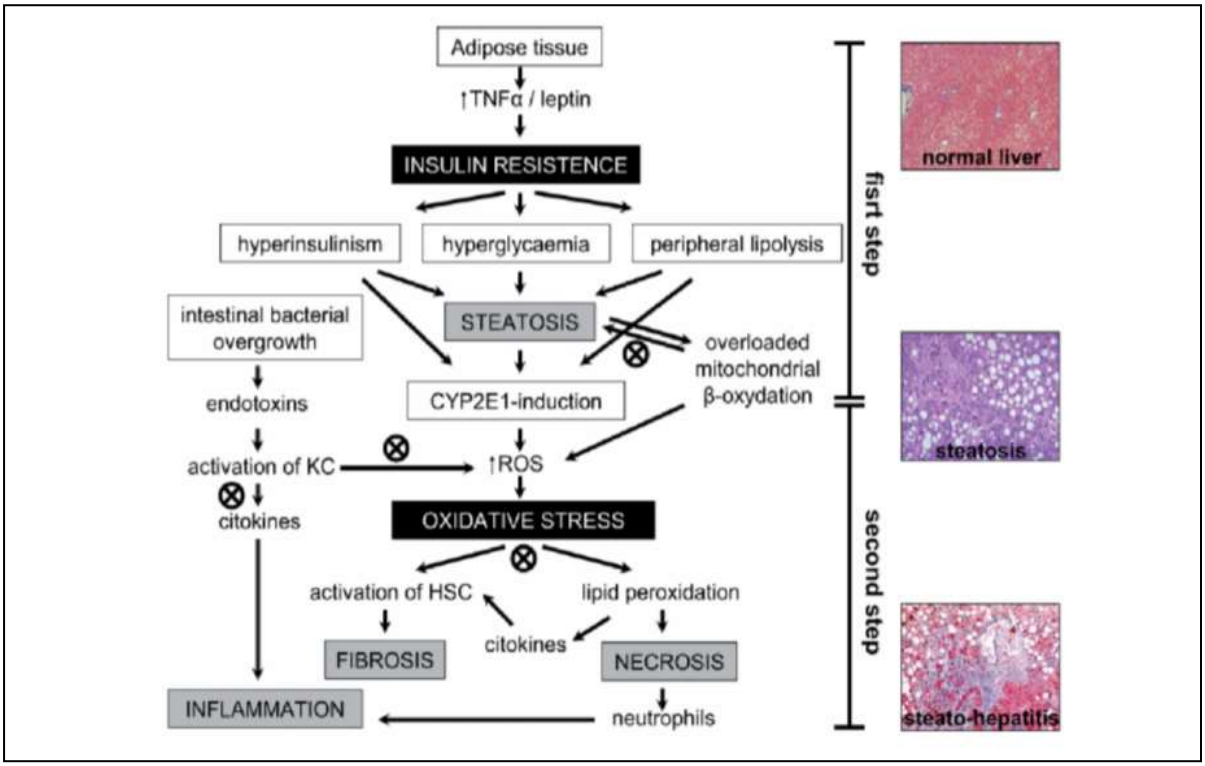

Figure 7 : Pathogenic Mechanism In The Histological Progression Of NAFD And The Site Of Action (Cross Circle)(Cypet Cytochrome P450 2Et, ROS,HSC,Kupffer Cell)

Hypocholesterolaemic Activity[49]

Investigation the control of silymarin and its polyphenolic portion on rats fed with a high-cholesterol diet revealed that silymarin decrease cholesterol levels in the liver and plasma of rats. The hypocholesterolaemic activity of silymarin based on experimental evidence representing that silybin inhibits HMG-CoA reductase activity in vitro; and silymarin enhanced the binding of low density lipoproteins (LDL) to rat hepatyocytes, reduced the liver cholesterol substance in rabbits fed with a high-cholesterol diet, reduction in the plasma-cholesterol and LDL- cholesterol levels in hyperlipaemic rats. The effect of silymarin and polyphenolic fraction (PF) of silymarin on cholesterol absorption in rats fed on high cholesterol diet (HCD) was studied. Silymarin and PF significantly decrease cholesterol absorption in rats fed on HCD and lead to significant reduction in content of cholesterol and triacylglycerol (TAG) in the liver. These results predict that the inhibition of cholesterol absorption caused by silymarin and its polyphenolic fraction could be a mechanism contributing to the positive changes in plasma cholesterol lipoprotein profile and in lipid content in liver. Silymarin in spite of of its form, significantly rise up levels of protective HDL particles, extensively decrease levels of total plasma triglycerides and cholesterol. The positive effect of silymarin on HDL cholesterol level is explained for the first time in rats suffering from the metabolic syndrome associated with chronic severe hypertriglyceridemia. positive effect of silymarin on total plasma cholesterol is partly effective by higher elimination of the cholesterol mediated by CYP7A1, enzyme with considerably enhancing protein expression in rats fed by all forms of silymarin and ABCG5 and ABCG8 transporters, essential transporters for the cholesterol efflux from the hepatocytes into the bile. The reduced plasma level of triglycerides could by caused by increased triglycerides metabolism through CYP4A. Silymarin in the variety of phytosome and micronized silymarin are more efficient forms of silymarin than standardized silymarin extract, possibly because of their good bioavailability.[23] Lipid analyses noticed that treatment of HCD-fed rabbits with 200 mg of both silymarins from cultivated and wild plants daily for two months lead a significant decrease in their serum total cholesterol, LDL-C and TAG levels, as compared to those of rabbits in positive control group. Anti-hypercholesterolemic activity of silymarins from cultivated and wild plants at the dose of 200 mg/kg/day was related with a significant rise in HDL-C levels, an effect considered to be benefit to treatment of atherosclerosis.[35]

Galactogogue Activity[29]

Silymarin treatment helps the cow body functions, liver included. The animal eats repeatedly, does not drop weight, has a better liver functionality and a minor pathology incidence. As a effect, the

animals produce more daily milk in comparison with untreated cows. While humans undergo a total different situation, an alternative explanation has to be found. Initially from some experimental results presenting the role of weak estrogens played by flavanolignans in tumour mice models. It can be believed that Silymarin, by decreasing the estrogenic value, promotes, or at least enhancing , lactation. Few other, still unreveal, results show that administration of the product in rats describes a clear rise in prolactin production and secretion. The same examination in humans could predict a possible definitive answer in some how and why Silymarin oral administration in healthy lactating women increases daily milk quantity without affecting its chemical composition.

Skin Prevention

Silymarin on topical treatment inhibit 7, 12-dimethylbenz(a) anthracene initiation and numerous tumor promoters, as of 12-O-tetradecanoylphorbol-13-acetate, mezerein, benzoyal peroxide and okadaic acid, lead to skin carcinogenesis in mouse models. Likewise, silymarin also inhibit UVB-induced skin carcinogenesis. Several in vivo mechanistic studies noticed that silymarin having antioxidant, anti-inflammatory and immunomodulatory characteristic which may induced the prevention of skin cancer in in-vivo animal models as well as the probable mechanism of action is shown in fig. No:7. The existing experimental knowledge suggests that silymarin is a showing potential chemo-preventive and pharmacologically harmless agent which can be exploited or tested beside skin cancer in human system. In addition, silymarin may also use as a supplement sunscreen protection and give additional anti-photocarcinogenic protection. Silymarin raise cell viability and clonogenic cell survivability. Silymarin play role as a potent radiation contradict measure agent and has ability for use during nuclear/radiological emergencies following trials and validation in higher mammalian model systems.[60] Sylimarin gives strong protection against skin cancer induced by UVB in nude mouce, and administratin of sylimarin frequently decrease the formation of tumour and interruption in the incubation phase. Silymarin concurrently inhibited apoptosis of HaCaT cells induced by a high dose of UVB irradiation.[61]

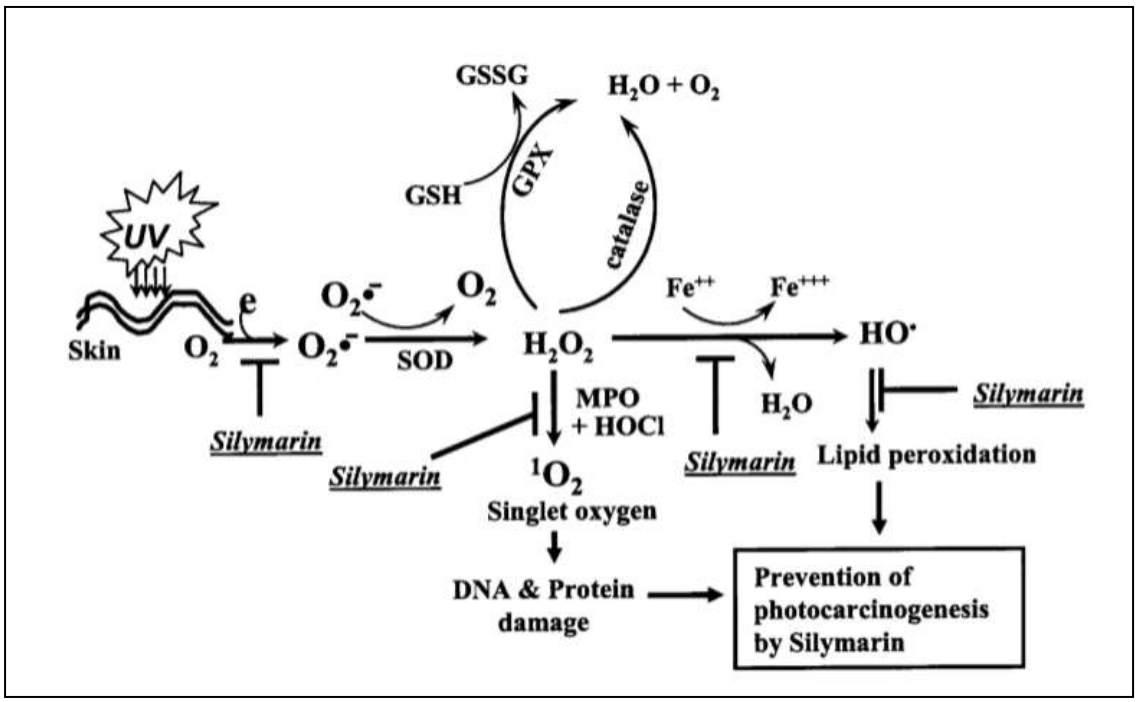

Figure 7 Mechanism of Skin Prevention by Silymarin

Viral Hepatitis[37]

All 5 known types of viral hepatitis (A to G) cannot be differentiate consistently by clinical features or regular laboratory tests. The exact aetiology of viral hepatitis is resolute by serological testing. Chronic hepatitis does not take place after hepatitis A or E. It noticed in 1–5% of cases of acute hepatitis B virus (HBV) disease and 85% of cases of acute hepatitis C virus (HCV) disease. Now days, a new silibinin complex (IdB1016 240 mg of silibinin 2 × daily) was studied in a immediate placebo-controlled pilot study on 20 patients with chronic active hepatitis, found reduction of the AST concentrations but no reliable differences in the other liver function tests. HCV proteins activate STAT-3 via oxidative stress and Ca21 signalling, also lipid peroxidation products and antioxidant gene expression. Oxidative stress may give to fibrosis and carcinogenesis in chronic HCV and damage interferon- α signaling. Thus, it was exploited whether the antioxidative properties of silibinin may progress the response to peginter- feron/ribavirin (PegIFN/RBV) in chronic hepatitis C. Unpredictably, effective antiviral properties of intravenous (IV) silibinin (as silibinin hemisuccinate, Legalon SIL; Madaus/Rottapharm, Modena, Italy) against the hepatitis C virus (HCV) in patients with chronic α-hepatitis C were documented.[45] The antiviral properties of silibinin were also examined in vitro via a standardized silymarin formulation (MK-001) in the HCV replicon system. As well, MK-001shown anti-inflammatory activity via inhibition of nuclear factor kappa B–induced transcription in human liver cell cultures

and inhibition of inflammatory cytokine stimulation in human peripheral blood mononuclear cells. Legalon SIL As well as silibinin inhibit in vitro NS5B polymerase activity[41]

Antifibrotic Activity [13, 51]

In the early phase the proliferation of hepatic parenchymal cells is progress. Hepatic stellate cells (HSC) is converted into myofibroblast is taken as the central event in fibrogenesis. Silymarin inhibits NF-kB and also delay HSC activation. It may also inhibits protein kinases and other kinases which take part in signal transduction and may interefere with the intracellular signalling pathways. The indication for anti-fibrotic action arise largely from animal studies.[42] The effective parameters for the efficacy of silymarin (alkaline phosphatase, aspartate transaminase, albumin, bili-rubin, and the Mayo risk score) were, good and alternate way of disease recovery and unpredictable of fibrosis , particularly in patients receiving UDCA. As progression of fibrosis finally determines the prediction of PBC, fibrosis associated parameters must be monitored, along with chronological histology, amino terminal procollagen type III peptide, collagen IV, hyaluronic acid, and others.[44]

Psoriasis Treatment[46]

A multifactorial etiological study of liver disease in patients with psoriasis consist of changes because of alcohol use, nutritional factors, anti-psoriatic medications and a through effect of the psoriasis itself. Unusually rise levels of cAMP and leukotrienes have been noticed in psoriatic patients and normalization of these levels may recover the condition. The significance of silymarin in the treatment of psoriasis may be caused by its ability to improve endotoxin deletion by the liver, inhibit cAMP phosphodiesterase and inhibit leukotriene synthesis. Pathan Azhar Khan et al prepare a gel for the psoriasis treatment.[47]

Dosage and Administration

In the clinical trials as seen, the everyday oral dose of silymarin used ranged from 280 to 800mg. This is corresponding to 400 to 1140 mg of standardised extract containing 70% -80% silymarin.[62] The required dosage for active disease is 140 mg of silymarin (200mg of extract) three times daily. If the preparation silipide (silymarin-phosphatidylcholine) is used,100mg three times daily is the suitable dosage. At higher dosages (>1500 mg/day) silymarin may have a laxative effect because of an increase in secretion and bile flow. Fair allergic reactions have also been reported.

Typical adult dosages: [57]

- Dry seeds – 12-15 g daily in divided doses10
- 1:1 Liquid extracts, 1:1 Glycetract - 30-60 mL per week4

- Flordis Legalon® (MZ 80) (Silybum marianum equivalent to 14.7 dry seed) (Maintenance: 1 capsule 2 times a day)[58]
- Tablets/capsules (equivalent to 14.7 g dry seed) - 1 tablet/capsule 2-3 times per day
- MediHerb Silymarin[56]
- Metagenics Silymarin Intensive Care
- Thompson's Milk Thistle (107 mg standardised extract, 84% flavonolignans 7,500 mg)

Pharmacokinetics[34]

Sylimarin is poorly water soluble and is frequently administered in an encapsulated form. Oral absorbed of silymarin is poor i.e 23-47% which lead to low bioavailability of the compound. Peak plasma concentration is achieved in 6-8 hr. It is administered as a standard extract (70-80% silymarin).After oral administration the improvement in bile juice ranges from 2-3%.silybin and the other components of silymarin are are rapidly metabolised and conjugated with sulphate and glucuronic acid in the liver and excreated via the bile. The poor aqueous solubility and bioavalability of sylimarin rise up to the advance formulations with better parameter eg ; silipide (siliphos), a complex of silymarin and phopatidycholine that is 10 times more bioavailable than silymarin.[32] Silybin-PC complexed (SILIPHOS®) as a phytosome provides considerable liver protection and improved bioavailability over conventional silymarin when administered orally. Phytosomal silybin is more rapidly absorbed than silymarin, possibly more so when taken in soft-gels. It is also absorbed at least four times further completely than silymarin, reaching the liver quickly and found in the bile within a few hours. As silymarin must be taken at doses of approximately 420 mg daily to achieve benefit, phytosomal silybin (Siliphos) can produce benefit at intakes as low as 120 mg daily, but can be safely administered at doses of 240-360 mg daily.[36] Because of poor solubility of silymarin it is formulated as of encapsulated form , sugar coated tablets, self-microemulsifying drug delivery system (SMEDDS) or beta cyclodextrin inclusion complex etc.[51]

CONCLUSION

Milk thistle is one of the most considerable medicinal plants grown-up in the world. Pharmacological active principle of the fruit of this plant is known as Silymarin. The seeds consist of the large amount of silymarin, but the entire plant is medicinally useful. Although the world requirement of silymarin, there is a need of research labours on the domestication and cultivation of this plant especially in Iran. A very few number of varieties of milk thistle have been introduced. The solubility and bioavailability of silymarin now days enhanced with the help of

variety of pharmaceutical techniques. In most of cases, nanotechnology-based formulation techniques were establish to be the most effective for this reason. Silymarin and silybin applicable so far mostly as hepatoprotectants were shown to have other remarkable activities as e.g., anticancer and cancer protective. These activities were demonstrated in a large variety of illnesses of different organs as e.g., prostate, lungs, CNS, kidneys, pancreas and others. As well the cytoprotective activity of silybin mediated by its antioxidative and radical-scavenging properties also new activities based on the specific receptor interaction were discovered – e.g., inhibition and modulation of drug transporters, P-glycoproteins, estrogenic receptors, nuclear receptors and some others. Recent derivatives of silybin lead to new window to its therapeutic applications.

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