

A Review on Various Pharmacological Actions of Silybum Marianum (Milk Thistle)

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ABSTRACT

Milk thistle extracts have been used as medicinal herbs in the treatment of liver cirrhosis, chronic hepatitis (liver inflammation), and gallbladder disorders. Treatment claims also include lowering cholesterol levels; reducing insulin resistance; reducing the growth of cancer cells in breast, cervical, and prostate gland cancers; and antiviral activity. Other reported uses of milk thistle in folk medicine include as a treatment for malarial fever, bronchitis, gallstones, a milk production stimulant for nursing mothers. The roots soaked in water overnight are used in food, and the despoiled leaves are added to salads. Roasted milk thistle fruit has been used as a coffee substitute. Milk thistle extract was nominated for study by the National Institute of Environmental Health Sciences because it is one of the most widely used herbs in the United States.

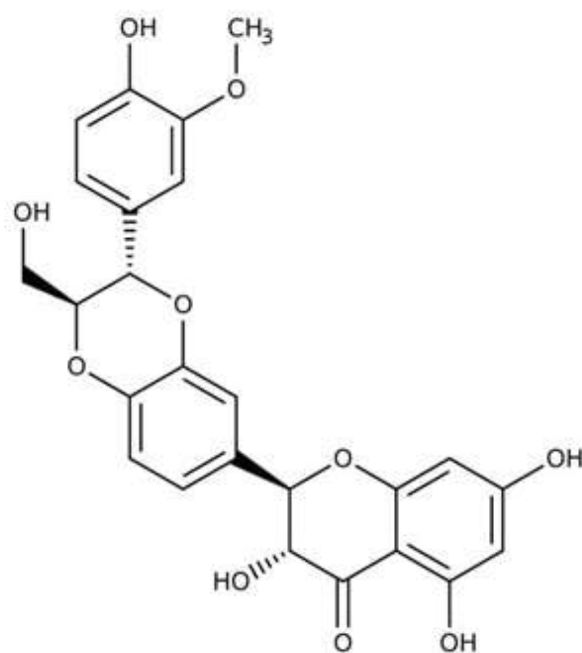
I. INTRODUCTION

Silybum marianum is an annual or biennial thistle-like plant. The seeds yield 1.5–3% of flavonolignans, considerably termed as silymarin. This mixture holds primarily silybin, together with silychristin, silydianin, and little sum from claiming isosilybin. Both, silybin as well as isosilybin are equimolar mixtures which are of two trans diastereoisomers. *Silybum marianum* may be broadly utilized within accepted European medicine. The seeds constantly are utilized to treat hepatic as well as other disorders. Silymarin has been indicated to conserve animal livers against the harming impacts of carbon tetrachloride, thioacetamide, medications for example paracetamol, and the toxins α -amanitin and phalloin discovered in the death cap fungus (*Amanita phalloides*). Silymarin might be utilized within huge numbers, for instance, in liver

infection and injury. However, even now it stays subsist to standard medication. It could offer specific profit in the medication of poisoning, towards the death cap fungus. These agent show up on two fundamental modes of action. They follow up on that cell membrane of hepatocytes hindering absorption from claiming toxins. What's more secondly, due to their phenolic nature; they act as antioxidants as well as scavenger's free radicals which are harmful to liver. The silymarin start with liver detoxification to remove exotic chemicals. Subsidiaries about silybin with enhanced water-solubility or bioavailability have also been developed, e.g. The bis-hemisuccinate and phosphate dylcholine intricate (1).

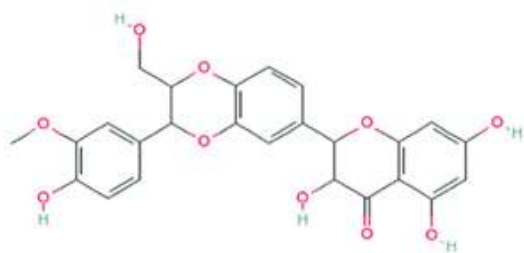
HISTORY

Milk thistle has been utilized since the time of antiquated doctors and botanists to treat an extend of liver and gallbladder clutters, counting hepatitis, cirrhosis, and jaundice, and to protect the liver against harming from chemical and natural poisons, counting wind nibbles, insect stings, mushroom harming, and alcohol. Milk thistle's history starts with its title. The scientific title for milk thistle is *Silybum marianum*: "Silybum" is the title that Dioscorides gave to consumable thistles and "marianum" comes from the legend that the white veins running through the plant's leaves were caused by a drop of the virgin mary's milk. As trying to find a place to nurture the newborn baby, Jesus when intending Egypt, Mary could only find shield in a bower shaped by the prickly leaves of the milk thistle. From this story was born the folk belief that the plant was great for nursing mother (2-6).

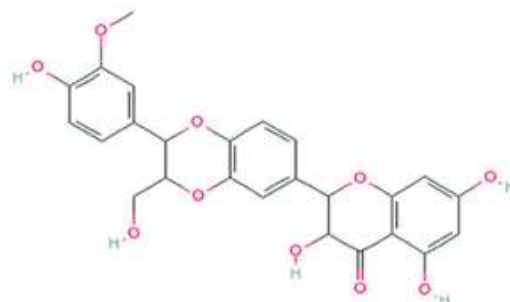


Silymarin

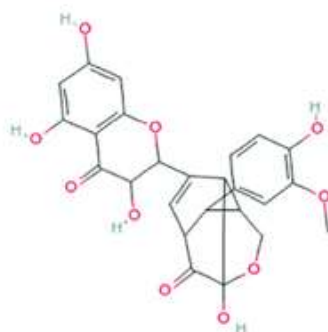
STRUCTURE OF SILYMARIN



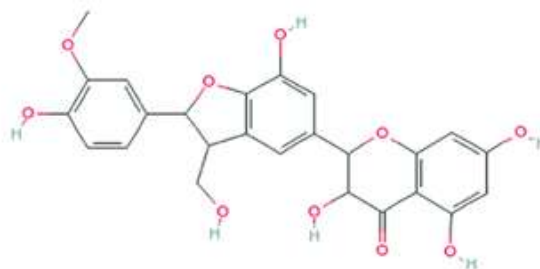
A Silybin



B Isosilybin



C Silydianin



D Silychristin

Chemical structure of the silibin diastereoisomers, silibinin A and silibinin B (C₂₅H₂₁O).

PLANT PROFILE

Kingdom : Plantae
Clade : Tracheophytes
Clade : Angiosperms
Clade : Eudicots
Clade : Asterides
Order : Asterales
Family: Asteraceae
Genus: Silybum
Species: S.marianum



SILYBUM MARIANUM

Plant material as the search for milder and “greener” solvents intensifies. The use of hot water as an extraction solvent for milk thistle at temperatures above 100°C was explored. The maximum extraction yield of each of the silymarin compounds and taxifolin did not increase with temperature. Hot water is attracting attention as an extraction solvent in the recovery of compounds from e, most likely because significant compound degradation occurred. However, the time required for the yields of the compounds to reach their maxima was reduced from 200 to 55 min when the extraction temperature was increased from 100 to 140°C. Severe degradation of unprotected (plant matrix not present) silymarin compounds was observed and first-order degradation kinetics were obtained at 140°C. Silymarin is frequently used as helpful treatment in foodstuff toxic owing to fungus. Root: Root is eaten boiled as a potherb. Herb: Herb is used for intermittent fevers, dropsy & uterine troubles(6). Application in cancer. Leaves: Leaves are sudorific and aperient. Juvenile leaves dish up as salad and blossoming skulls are inspired by diabetics. Seeds: Seeds are pungent, demulcent and antispasmodic. They are used for the treatment of jaundice and calculi of liver and gall-bladder and are useful in controlling hemorrhages. (7)

PHARMACOKINETICS

Not soluble in water of Silymarin, making tea preparations ineffective; therefore it is usually administered orally in

encapsulated form. Since incorporation of silymarin from the GIT is only temperate (23-47%), it is best administered as a standardized extract of 70-80 percent silymarin. In animals and humans, peak plasma levels are reached in four to six hours after an oral dose. Silymarin is excreted primarily via the bile but some clearance is also achieved via the kidneys. The clearance half-life of silymarin is six to eight hours.(8,9)

DOSAGE/TOXICITY

Silybummarianum is typically given as a homogeneous extract (70-80% Silybummarianum) in encapsulated form, 100-300mg 3 times every day being the characteristic adult dose. Both animal and human studies have shown silymarin to be non-toxic. At high doses (>1500 mg per day) a laxative effect is possible due to increased bile secretion and flow. Mild allergic reactions have also been noted but not were series.(9)

CLINICAL EFFECTS OF SILYMARIN LIVER CIRRHOSIS/ALCOHOL RELATED DISEASE

Fatty liver disease (FLD) is caused by the accumulation of excess fat in the liver, which can lead to serious liver disease for many people. In individuals who consume too much alcohol, alcoholic fatty liver disease (AFLD) is the earliest stage of alcohol-related liver disease. Silymarin

has been investigated in a number of clinical studies in patients with liver cirrhosis and/or alcohol-related liver disease . Six of these clinical trials were conducted in patients affected by liver cirrhosis (mainly alcohol-related) . Four studies examined the impact of silymarin on clinical outcomes such as mortality , and two of these trials had survival as the primary clinical endpoint . showing a significant impact on mortality . This was a double-blind, prospective, randomized study that was performed to determine the effect of silymarin (Eurosil 85[®]-derived formulation) on the outcome of patients with cirrhosis . Of the 170 patients with cirrhosis, 87 were treated with silymarin 420 mg/day (alcoholic: 47, non-alcoholic: 40), and 83 received placebo (alcoholic: 45, non-alcoholic: 38) for at least 24 months, with a median observation period of 41 months. In the placebo group, there were 32/39 liver-related deaths, whereas in the silymarin group 16/28 patient deaths were related to liver disease. In this study, the 4-year survival rate was significantly higher in silymarin recipients than placebo recipients.(10-20)

EFFECTS OF SILYMARIN ON LIVER CELLS

The roots and aerial parts of the milk thistle plant have a bitter and appetizing (motive and savoury) taste and are used in traditional medicine to treat patients with spleen or liver disorders as well as patients with chronic constipation. The use of silymarin in traditional European medicine in the treatment of some liver diseases and complications dates back many years.

Scientific studies in the field of nonalcoholic fatty liver have proven the effectiveness of silymarin treatment to prevent vascular formation in cancerous tissue. Toxicology studies in rodents have shown that silymarin has no toxic effects and is considered a safe drug in the treatment of liver disorders.

The flavonolignan of silandrin, silybinum, silihermin, and myristic acid, palmitic, and acetic acids may have hepatic protective properties . Silymarin is obtained as a flavonoid compound from the purified seed extract of the medicinal plant *Silybum marianum* . In a dose dependent pattern, silymarin exerted antioxidant and anti apoptosis effects Silymarinphytosomes in milk MTS can reduce free radicals caused by fungal toxins and increase cellular activity for protein synthesis by affecting cell nucleus activity and liver cell microsomes.

In addition to stabilizing the membrane by removing free radicals and increasing the activity of the enzyme superoxide dismutase, those phytosomes play this protective role . It also protects the cell against any acute or chronic destructive damage, regardless of the causes of liver cell disorders . Silymarin (especially silybin or silibinin) is known to be a very strong antioxidant and free radical scavenger . Its side effects are rare but may include gastrointestinal symptoms (nausea, vomiting, and diarrhoea) and skin allergies .

Silymarin and other compounds in the extract inhibit bacterial beta glucuronidase inhibitors in the gut and thus prevent the reabsorption of toxins from the gut . Silibinin in the category of liver cells (HepG and Hep3B) has a very strong toxic effect that caused cell apoptosis and has been shown to inhibit growth and increase cell death .

Consumption of silymarin has been used in the treatment of liver diseases, including alcoholic liver disease , chronic viral and toxic hepatitis, abdominal fat due to chemicals, and alcohol and bile duct inflammation. Therapeutic effects have been shown to be due to silymarin's properties including: antioxidant, antilipid peroxidase, antifibrotic, anti inflammatory, immune regulating, liver cell regenerating, calcium lowering, and iron trapping.

Silymarin protects liver cells from damage due to viruses, chemicals, and natural toxins such as fungal toxins. There are various reports of improved liver function following prescription (administration) of silymarin . Consumption of 120 mg of silymarin twice daily for two months significantly reduced aspartate transaminase (AST) and alanine transaminase (ALT) in the blood serum of liver patients . Also, it can prevent the peroxidation processes involved in liver lesions caused by carbon tetrachloride, ethanol, paracetamol, and other substances that are toxic to the liver .

silymarin effectively increases the dissolution of carbon tetrachloride, which is involved in the formation of liver fibrosis. This is by various mechanisms such as stimulation of DNA polymerase, stabilization of cell membranes, inhibition of free radicals, and increased cellular glutathione concentration. The latter indicates the protective effect on the liver against damage by inhibiting the gene and subsequently reducing the production of pre inflammatory cytokines . Silymarin is used to treat various liver disorders such as fatty liver, hepatitis, jaundice, alcohol

abuse, ischemia, drug and environmental poisoning, and even liver fibrosis .

Due to its antioxidant properties, silymarin is very effective in inhibiting lipid peroxidation, especially in liver cells, thereby reducing metabolic disorders . Regardless of the causative agents in liver cells, it protects cells against any acute or chronic destructive damage. Silymarin affects the stability of the liver membrane and prevents the binding of many toxins and drugs to this membrane. Its protective role is through elimination of free radicals and increased activity of the enzyme superoxide dismutase .

Silymarin reduces LDL and lowers cholesterol synthesis in liver cells, prevents negative effects of high cholesterol and increases the production of ribosomes , due to the stimulation of RNA polymerase I activity in the nucleus of liver cells. This is followed by more active protein synthesis in the liver and increased liver rejuvenation capacity induced by Silymarin. Silymarin stimulates DNA polymerase, stabilizes cell membranes, inhibits free radicals, and increases cell glutathione concentrations, with a protective effect on the liver . Prescribing it improves the liver and kidney cleansing index and reduces the accumulation of lipids in the liver .

Evidence suggests that silymarin and silybin affect the liver in four ways: (1) as an antioxidant, neutralizing free radicals and regulating the cell's internal glutathione, (2) as a cell membrane stabilizer and permeability regulator in liver cells to prevent the entry of toxic agents into liver cells, (3) as a stimulant of ribosomal RNA synthesis and hepatic cell renewal, and (4) as an inhibitor of the deformation of star shaped hepatocytes into myofibroblasts, a process that is responsible for the deposition of collagen fibres which lead to liver cirrhosis (alcoholic liver disease). Silymarin neutralizes several toxic agents such as Amanita phalloides, ethanol, and acetaminophen on the liver. It also inhibits the absorption of amanitin (amantine and faludin), two peptides in poisonous fungi which are very potent liver cell destroyers. The toxic agent of Amanita fungus inhibits TNF α in hepatocytes, which exacerbates fat peroxidation. Silymarin has a hepatic protective effect against these toxins Even if silymarin is prescribed 10 min after exposure to amanita poison, it completely prevents poisoning, and if given within 24 h after exposure to the poison, it significantly prevents liver death and injury . In addition to the above, silymarin can prevent the absorption of toxic substances into hepatocytes by occupying connective sites and

inhibition of many transfer proteins in the membrane . The return of bilirubin to its normal values following liver damage from cell phone waves can be due to reduced intracellular enzyme leakage due to cell membrane protection or regeneration of damaged liver cells .

Liver parenchyma cells are responsible for the synthesis of plasma proteins, which include blood factors such as white blood cells and globulins. Thus, by stimulating protein synthesis, silymarin can accelerate the process of restoration and renewal of damaged tissues, such as liver tissue . In laboratory research, silymarin is a potent inhibitor of cAMP phosphodiesterase .

Briefly, silymarin exerts its effects on liver cells in three ways: (1) It binds to the membrane receptors of liver cells that are responsible for the absorption of toxins and by changing their phospholipid compounds, they prevent the absorption of toxins by the cell. (2) Because it is a powerful antioxidant (which has many times the antioxidant properties of vitamin E), it inhibits metabolic disorders by inhibiting lipid peroxidation, especially in liver cells. (3) By stimulating protein synthesis, it regenerates liver cells .(21-29)

IDENTIFICATION AND MORPHOLOGICAL CHARACTERS OF THE PLANT

Milk thistle is a tall, biennial herb with a height of five to ten feet, hard, green, shiny leaves with spiny edges and white streaks along the veins. The solitary floral heads are reddish-purple and the bracts end in sharp spines (Figure 2). The small hard fruit in the flowers, technically known as achenes, looks like seeds and is part of a medicinally used plant (Figure 3). Milk Thistle is grown in South and Western Europe, South America and North America in eastern USA and California. Dried seeds contain 1-4% flavonoids of Silymarin . Silymarin is a mixture of three or more flavonolignans, including silybin (silibinin), silidianin and silychristine. These are the main active ingredient in milk thistle and can also be found in related species like artichokes. dehydrosilybin, deoxysilycistin, deoxysilydianin, silandrin, silybinome, silyhermin and neosilyhermin are other flavonolignans identified in *S. marianum*. Moreover, milk thistle contains apigenin; silybonol; myristic, oleic, palmitic and stearic acids.(30)

CHEMICAL CONSTITUENTS

Silymarin accounts for 1.5–3 percent of the dry weight of the fruit and is an isomeric mixture of unique flavonoid-flavonolignan complexes.

Silymarin, isosilybin, silychristin, isosilychristin, silydianin (Figure 4) and silimonin are the main representatives of this group (31-36). The chemical composition of milk thistle fruit in addition to flavonolignans also include other flavonoids (such as taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodictiol, and chrysoeriol), 5,7-dihydroxy chromone, dehydroconiferyl alcohol, fixed oil (60% linoleic acid; 30%, oleic acid; 9% palmitic acid), tocopherol, sterols (cholesterol, campesterol, stigmasterol, and sitosterol), sugars (arabinose, rhamnose, xylose, and glucose), and proteins. The highest concentration of silybin, which comprises approximately 50-70 percent of the extract, is the main bioactive component of the extract, which has been confirmed in several studies. The concentrations of silybin typically found in common pharmaceuticals with a silymarin range of 20-40 percent. In addition to the hepatoprotective action, silybin has strong antioxidant properties and modulates a variety of cell signaling pathways, reducing pro-inflammatory mediation. Silybin is also studied as an anti-cancer and chemotherapy agent. Research has shown that silybin can inhibit serine proteases associated with the blood coagulation process, and also reduce the response of blood platelets to physiological agonists (37-43).

SILYBIN STRUCTURE AND CHEMISTRY

In 1968, Pelter and Hansel first established the chemical structure of silybin by careful examination of ¹H-NMR (100 MHz, DMSO-d₆) and MS spectra. However, the absolute configuration of silybin in positions C-2 and C-3 was found by the same researchers using a degrading method in 1975 (44). Silybin, also referred to as flavobin, silybin, silymarin I, silybin and silybin, has a C₂₅H₂₂O₁₀ molecular formula and a molecular weight of 482.441, CAS No. 22888-70-6 (data obtained from the pubchem website). The structure of silybins consists of two main units. The first is based on a taxifolin, which is a flavonol group in flavonoids. The second is a phenylpropanoid unit, which is coniferil alcohol in this case. These two units are connected to a single structure by an oxeran ring (Figure 5) (44-49). Silybin has weak acidic properties in neutral

aqueous solutions, with pK_a of 6.63 for 5-OH group, 7.7-7.95 for 7-OH group and 11.0 for 20-OH group. In the structure of silybin, we can identify five hydroxyl groups, which are the main goals of the derivation process. Three hydroxyl groups (5-OH, 7-OH and 20-OH) have a phenolic character. The 5-OH group has a very strong hydrogen bonding to the adjacent oxo group in conjunction with the aromatic ring and acts as a free electron pair donor to the 5-OH group. The 7-OH and 20-OH have similar properties, although the C-7 OH group is more reactive than the 20-OH group because of its lower steric barrier and the presence of a hydrogen bond. The C-23 OH group has properties that lead to carboxylic esterification or oxidation. OH group can easily be oxidized to a ketone (even with atmospheric oxygen) that produces 2,3-dehydrosilybin. Silybin is poorly soluble in polar protic solvents (EtOH and MeOH) and insoluble in non-polar solvents (chloroform and petroleum ether), but highly soluble in polar aprotic solvents like DMSO, acetone, DMF and THF. Silybin is found in nature as two trans diastereoisomers: A and B. These two diastereoisomers are differentiated with respect to reference positions C-10 and C-11 in the 1,4-benzodioxane ring (50-52). Silybin A and silybin B both have ¹H and ¹³C NMR spectra, which are very similar (without any characteristic signals), and impede the detailed identification of individual isomers. The most popular method for separating these two diastereoisomers is high-performance liquid chromatography (HPLC), which can distinguish the molecules by analyzing the retention time.

II. CONCLUSION

Silybum marianum is one of the most important medicinal plants grown in the world. This article reviews the history, morphology, chemical constituents, pharmacokinetics, dosage, toxicity, effects on liver cells. The plant has been extensively used as a medicinal and legendary plant for a long period of time. Silybum marianum has attracted substantial attention due to its outstanding benefits. Pharmacological investigation on flavonolignans have been carried out in vitro and also urbanized in vivo in animal models and human experiments. Though several pharmacological mechanisms.

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