



# ANTIOXIDANT SYLIMARIN IS THE LEVER BETWEEN LIVER AND HOMEOSTASIS FROM HERBAL SOURCE

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**Abstract:** Silymarin is a natural compound derived from the species *Silybum marianum*, which is commonly known as Milk thistle. This plant contains at least seven flavoligands and the flavonoid taxifolin. The hepatoprotective and antioxidant activity of silymarin is caused by its ability to inhibit the free radicals that are produced from the metabolism of toxic substances such as ethanol, acetaminophen, and carbon tetrachloride. The generation of free radicals is known to damage cellular membranes and cause lipoperoxidation. Silymarin enhances hepatic glutathione and may contribute to the antioxidant defense of the liver. It has also been shown that silymarin increases protein synthesis in hepatocytes by stimulating RNA polymerase I activity. A previous study on humans reported that silymarin treatment caused a slight increase in the survival of patients with cirrhotic alcoholism compared with untreated controls.

**Keywords:** *Silybum marianum*, Hepatoprotector, Lipoperoxidation, Silymarin

**Introduction:** Silymarin, an extract from milk thistle seeds, has been used for centuries to treat hepatic conditions. Preclinical data indicate that silymarin can reduce oxidative stress and consequent cytotoxicity, thereby protecting intact liver cells or cells not yet irreversibly damaged. Formula  $C_{25}H_{22}O_{10}$ , Molar mass:  $482.441\text{g}\cdot\text{mol}^{-1}$ .

IUPAC: (2R,3R)-3,5,7-trihydroxy-2-[(2R\*,3R\*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl]chroman-4-one; [CAS: 1265089-69-7]. XLogP3-AA: 2.4. Hydrogen Bond Donor Count: 5. Hydrogen Bond Acceptor Count: 10. Rotatable Bond Count: 4. Exact Mass: 482.12129689. Topological Polar Surface Area:  $155\text{ \AA}^2$ . Heavy Atom Count: 35



**Figure-1: Silymarin-A, Official Formulation & Silymarin-B**

*Silybum* (milk thistle) is a genus of two species of thistles in the family Asteraceae. The plants are native to the Mediterranean regions of Europe, North Africa, and the Middle East. One species has been introduced elsewhere, including in North America. The name "milk thistle" derives from a feature of the leaves, which are prominently banded with splashes

of white. Historically, these milky bands were said to be Mother Mary's milk, and this is the origin of another common name, St. Mary's thistle. The most widespread species is *Silybum marianum*. Claims have been made since ancient times that the active flavanoid-lignan (flavanolignan) group of constituents, called silymarin, contained only in the seed shell has liver-protective and regenerative properties, as well as antioxidant effects. Chemical, pharmacological, and safety research started in Germany in the 1950s. Silymarin has besides antifibrotic, immunomodulating, anti-inflammatory effects as well as antioxidant properties by scavenging free radicals and increasing the glutathione concentrations, so that it can be used in hepatitis and hepatic cirrhosis treatment and in mushroom poisoning. Silymarin also protects new liver cells from being destroyed by these same toxins. It reduces inflammation (which is why it is often suggested for people with liver inflammation or hepatitis) and is a strong antioxidant.<sup>[1-5]</sup>

**Description and classification:** Dried thistle flowers at the end of summer: Members of this genus grow as annual or biennial plants. The erect stem is tall, branched and furrowed but not spiny. The large, alternate leaves are waxy-lobed, toothed and thorny, as in other genera of thistle. The lower leaves are sessile (attached to the stem without petiole). The upper leaves have a clasping base. They have large, disc-shaped pink-to-purple, rarely white, solitary flower heads at the end of the stem. The flowers consist of tubular florets. The phyllaries under the flowers occur in many rows, with the outer row with spine-tipped lobes and apical spines. The fruit is a black achene with a white pappus.<sup>[6-10]</sup>



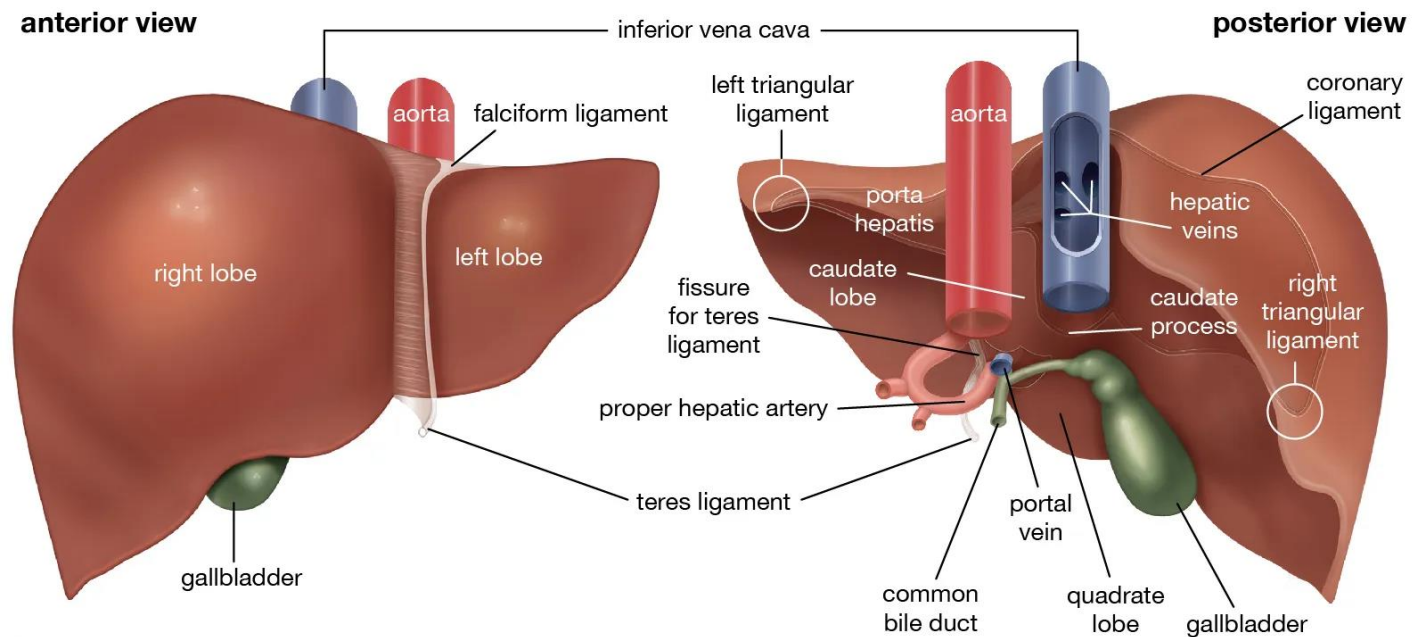
**Figure-2: Milk thistle flower and seeds**

**Species and varieties:** *Silybum eburneum* Coss. & Dur., known as the silver milk thistle, elephant thistle, or ivory thistle - Algeria, Morocco, Tunisia, Spain. *Silybum eburneum* Coss. & Dur. var. *hispanicum*. *Silybum marianum* (L.) Gaertner, the blessed milk thistle, which has a large number of other common names, such as variegated thistle. - widespread across much of Europe, Asia, and North Africa from Norway and the Canary Islands to China and Maluku; naturalized in Australia, New Zealand, and the Americas.<sup>[7-12]</sup>

**Taxonomy:**

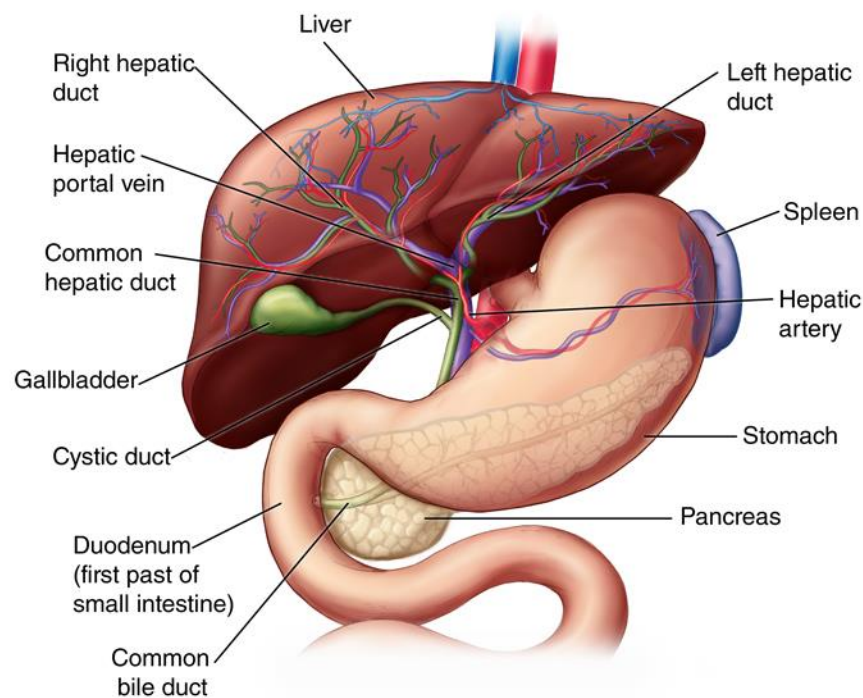
Kingdom: Plantae, Clade: Tracheophytes, Clade: Angiosperms, Clade: Eudicots, Clade: Asterids, Order: Asterales, Family: Asteraceae, Subfamily: Carduoideae, Tribe: Cardueae, Subtribe: Carduinae, Genus: *Silybum*, Adans.

Type species: *Carduus marianus*



**Figure-3: Liver view**

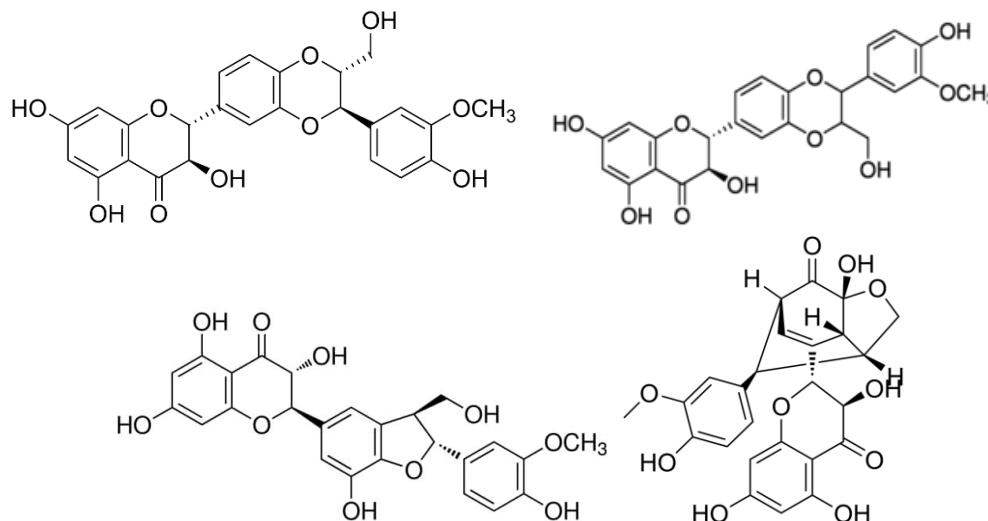
Health benefits: For many centuries extracts of milk thistle have been recognized as "liver tonics." Milk thistle has been reported to have protective effects on the liver and to greatly improve its function. It is typically used to treat liver cirrhosis, chronic hepatitis (liver inflammation), toxin-induced liver damage including the prevention of severe liver damage from *Amanita phalloides* ('death cap' mushroom poisoning), and gallbladder disorders. One study found significant reductions in Hemoglobin A1C levels, fasting blood glucose, insulin, liver enzymes SGOT and SGPT, and LDL Cholesterol of patients with Type II Diabetes after taking silymarin at a dose of 200 mg three times a day. Silymarin supplementation significantly improved some antioxidant markers (TAC and thiol) and decreased liver enzymes in patients with trauma-induced liver injury. The two species hybridize naturally, the hybrid being known as *Silybum × gonzaloii* Cantó, Sánchez Mata & Rivas Mart. (*S. eburneum* var. *hispanicum* x *S. marianum*).<sup>[13]</sup>



**Figure-4: Liver anatomy**

Silibinin (INN), also known as silybin (both from *Silybum*, the generic name of the plant from which it is extracted), is the major active constituent of silymarin, a standardized extract of the milk thistle seeds, containing a mixture of flavonolignans

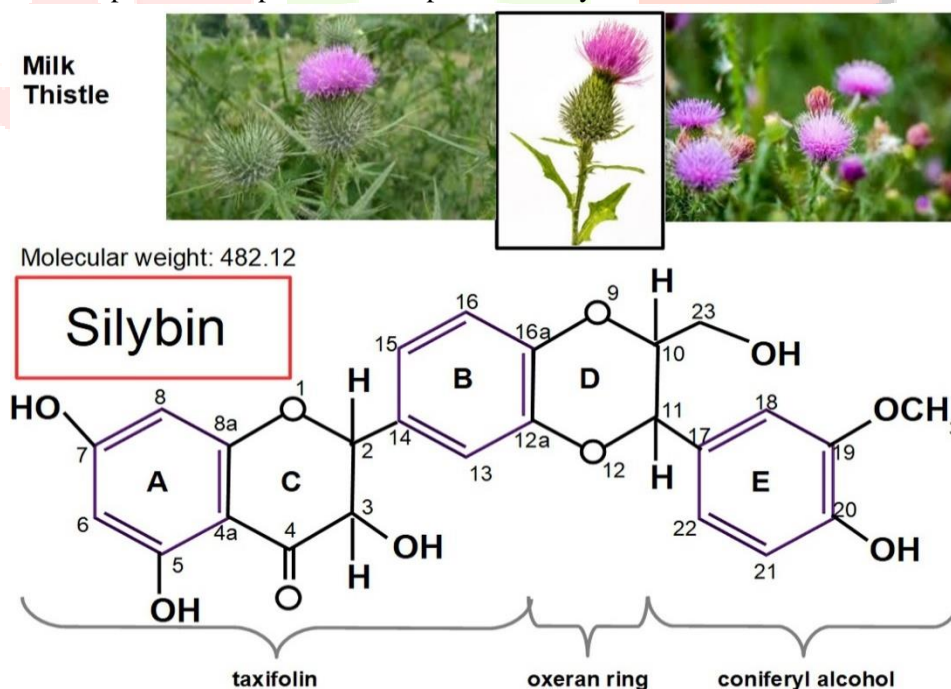
consisting of silibinin, isosilibinin, silychristin, silidianin, and others. Silibinin itself is a mixture of two diastereomers, **silybin A** and **silybin B**, in approximately equimolar ratio. The mixture exhibits a number of pharmacological effects, particularly in the fatty liver, non-alcoholic fatty liver, non-alcoholic steatohepatitis, and there is great clinical evidence for the use of silibinin as a supportive element in alcoholic and Child–Pugh grade 'A' liver cirrhosis. Steatohepatitis is a type of fatty liver disease, characterized by inflammation of the liver with concurrent fat accumulation in liver. Mere deposition of fat in the liver is termed steatosis, and together these constitute fatty liver changes. There are two main types of fatty liver disease: alcohol-related fatty liver disease and non-alcoholic fatty liver disease (NAFLD). Risk factors for NAFLD include diabetes, obesity and metabolic syndrome.<sup>[14,15]</sup>



**Figure-5: Flavonolignans [silibinin, isosilibinin, silychristin, silidianin]**

When inflammation is present it is referred to as alcoholic steatohepatitis and nonalcoholic steatohepatitis (NASH). Steatohepatitis of either cause may progress to cirrhosis, and NASH is now believed to be a frequent cause of unexplained cirrhosis (at least in Western societies). NASH is also associated with lysosomal acid lipase deficiency. The word is from steato-, meaning "fat" and hepatitis, meaning "inflammation of the liver". However, despite its several beneficial effects on the liver, silibinin and all the other compounds found in silymarin, especially silychristin seem to act as potent disruptors of the thyroid system by blocking the MCT8 transporter.<sup>[16]</sup>

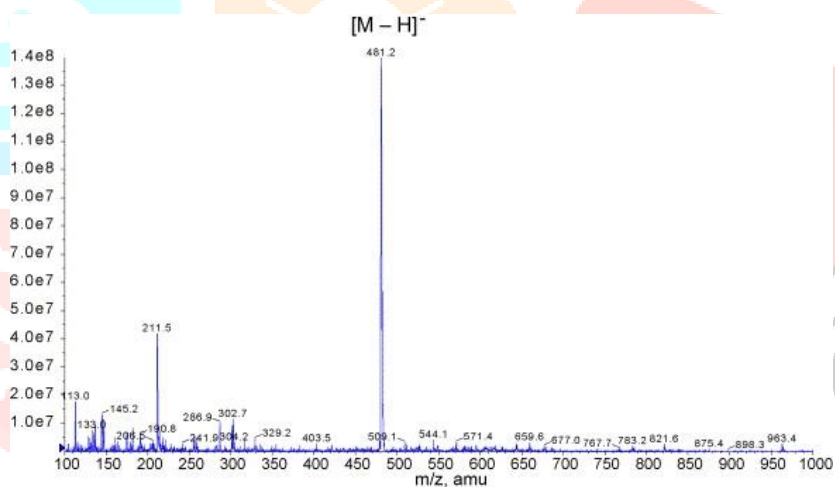
The long term intake of silymarin can lead to some form of thyroid disease and if taken during pregnancy, silymarin can cause the development of the Allan–Herndon–Dudley syndrome. Although this information is not being taken into consideration by all regulatory bodies, several studies now consider silymarin and especially silychristin to be important inhibitors of the MCT8 transporter and a potential disruptor of the thyroid hormone functions.<sup>[17]</sup>

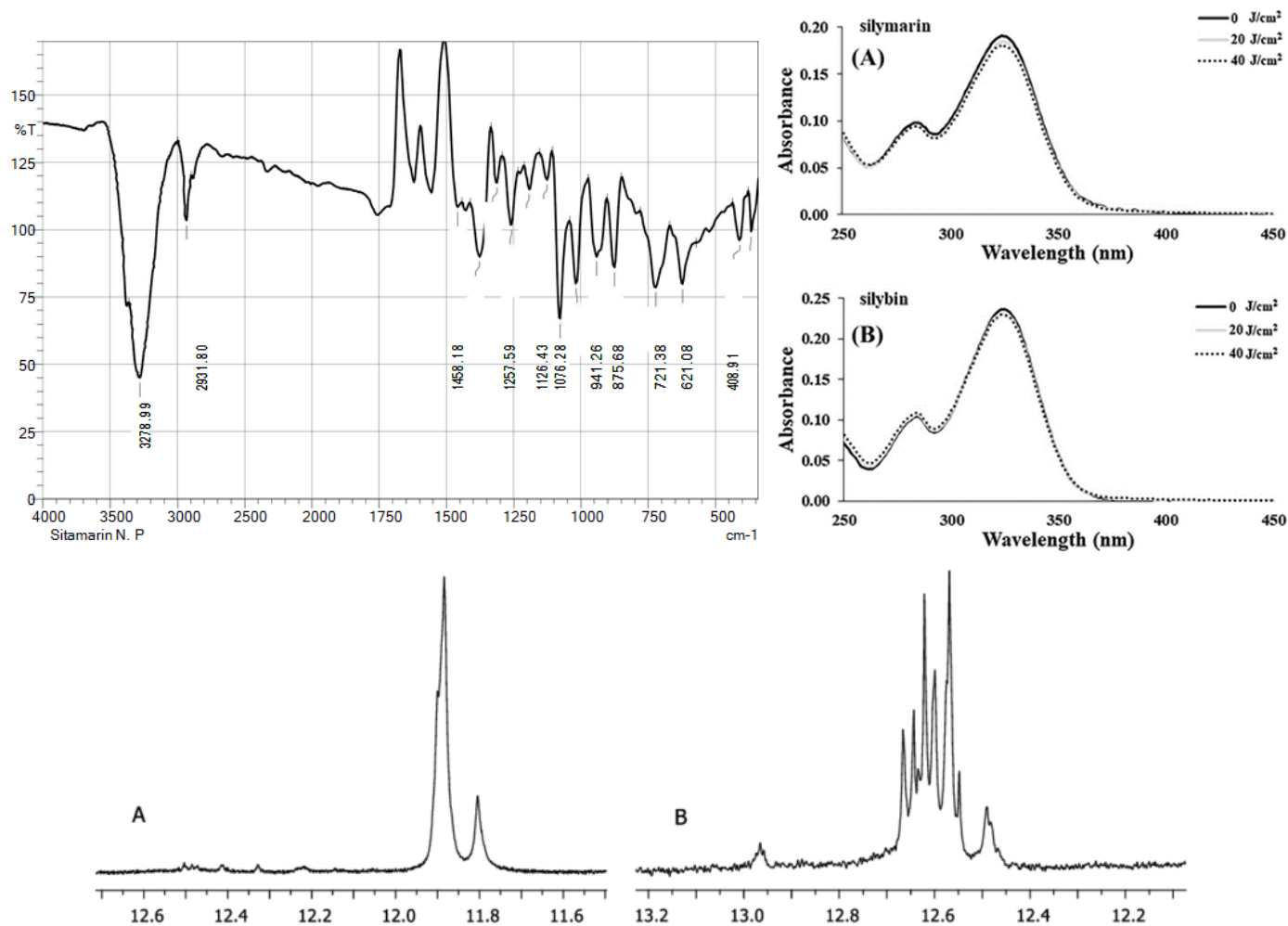


**Figure-6: Silybin flavonoid structure**

**Pharmacology:** Silymarin enhances hepatic glutathione and may contribute to the antioxidant defense of the liver. It has also been shown that silymarin increases protein synthesis in hepatocytes by stimulating RNA polymerase I activity. Poor water solubility and bioavailability of silymarin led to the development of enhanced formulations. Silipide (trade name Siliphos, not to be confused with the water treatment compound of the same name, a glass-like polyphosphate containing sodium, calcium magnesium and silicate, formulated for the treatment of water problems), a complex of silymarin and phosphatidylcholine (lecithin), is about 10 times more bioavailable than silymarin. An earlier study had concluded Siliphos to have 4.6 fold higher bioavailability. It has been also reported that silymarin inclusion complex with  $\beta$ -cyclodextrin is much more soluble than silymarin itself. There have also been prepared glycosides of silybin, which show better water solubility and even stronger hepatoprotective effect.<sup>[18]</sup>

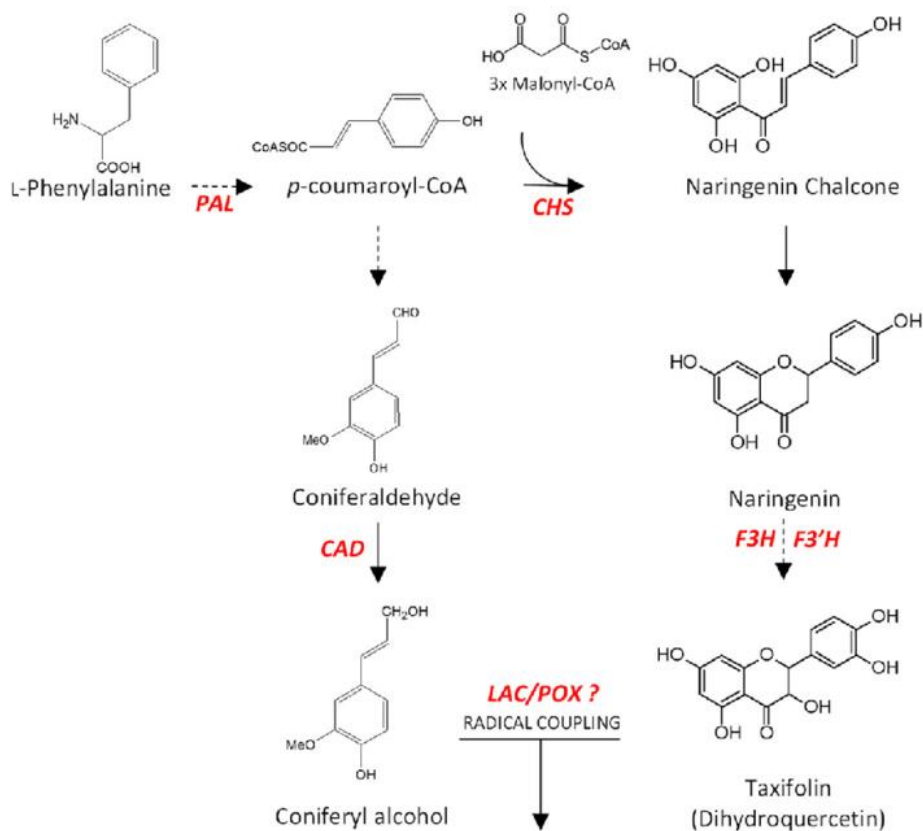
Silymarin, like other flavonoids, has been shown to inhibit P-glycoprotein-mediated cellular efflux. The modulation of P-glycoprotein activity may result in altered absorption and bioavailability of drugs that are P-glycoprotein substrates. It has been reported that silymarin inhibits cytochrome P450 enzymes and an interaction with drugs primarily cleared by P450s cannot be excluded. Silymarin acts as a free radical scavenger and modulates enzymes associated with the development of cellular damage, fibrosis and cirrhosis. These hepatoprotective effects were observed in clinical studies in patients with alcoholic or non-alcoholic fatty liver disease, including patients with cirrhosis. One study found significant reductions in Hemoglobin A1C levels, fasting blood glucose, insulin, liver enzymes SGOT and SGPT, and LDL Cholesterol of patients with Type II Diabetes after taking silymarin at a dose of 200 mg three times a day. In a study of chronic viral hepatitis, silymarin was shown to result in dramatic improvement. Used at a high dose (420 mg) for periods of 3 to 12 months, silymarin resulted in a reversal of liver cell damage (as noted on biopsy), a rise in protein level in the blood, and a lowering of liver enzyme values. If you have breast cancer, uterine cancer, ovarian cancer, endometriosis or uterine fibroids, consider avoiding milk thistle. Milk thistle can cause an allergic reaction, including a severe, potentially life-threatening allergic reaction (anaphylaxis). Recent evidence suggests that silymarin may be just as important for kidney health as for liver. Silymarin concentrates in kidney cells, where it aids in repairing and regeneration by increasing protein and nucleic acid synthesis. The medication is used for the treatment of Chronic Liver Disease and Cirrhosis of the liver. Silymarin is an active concept obtained from milk thistle seed (*Silybum marianum*). It could protect liver cells from chemicals and drugs that are harmful.<sup>[19]</sup>



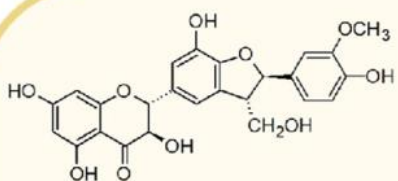


**Figure-7: Spectroscopy of silymarin**

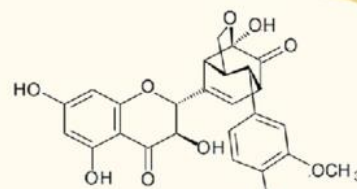
**Toxicity:** Silymarin 70mg medicine very rarely causes side effects. However, some people when using the drug may have the following cases: Digestive disorders: nausea, vomiting, loss of appetite, indigestion, flatulence, bloating, abdominal pain, diarrhea. Headache, dizziness, fatigue. Several studies have documented the potentially dangerous effects of the silymarin mixture on the thyroid system. All of the flavonolignan compounds found in the silymarin mixture seem to block the uptake of thyroid hormones into the cells by selectively blocking the MCT8 trans membrane transporter. The authors of this study noted that especially silychristin, one of the compounds of the silymarin mixture seems to be perhaps the most powerful and selective inhibitor for the MCT8 transporter. Due to the essential role played by the thyroid hormone in human metabolism in general it is believed that the intake of silymarin can lead to disruptions of the thyroid system. Because the thyroid hormones and the MCT8 as well are known to play a critical role during early and fetal development, the administration of silymarin during pregnancy is especially thought to be dangerous, potentially leading to the Allan–Herndon–Dudley syndrome, a brain development disorder that causes both moderate to severe intellectual disability and problems with speech and movement. A phase I clinical trial in humans with prostate cancer designed to study the effects of high dose silibinin found 13 grams daily to be well tolerated in patients with advanced prostate cancer with asymptomatic liver toxicity (hyperbilirubinemia and elevation of alanine aminotransferase) being the most commonly seen adverse event. Silymarin is also devoid of embryotoxic potential in animal models.<sup>[20]</sup>



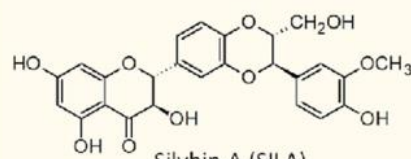
### SILYMARIN



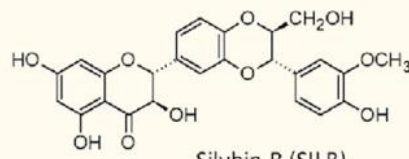
Silychristin (SILC)



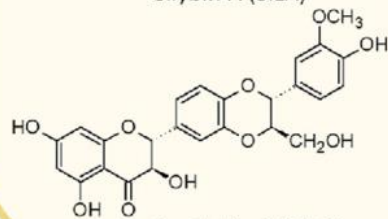
Silydianin (SILD)



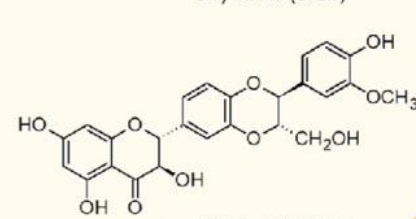
Silybin A (SILA)



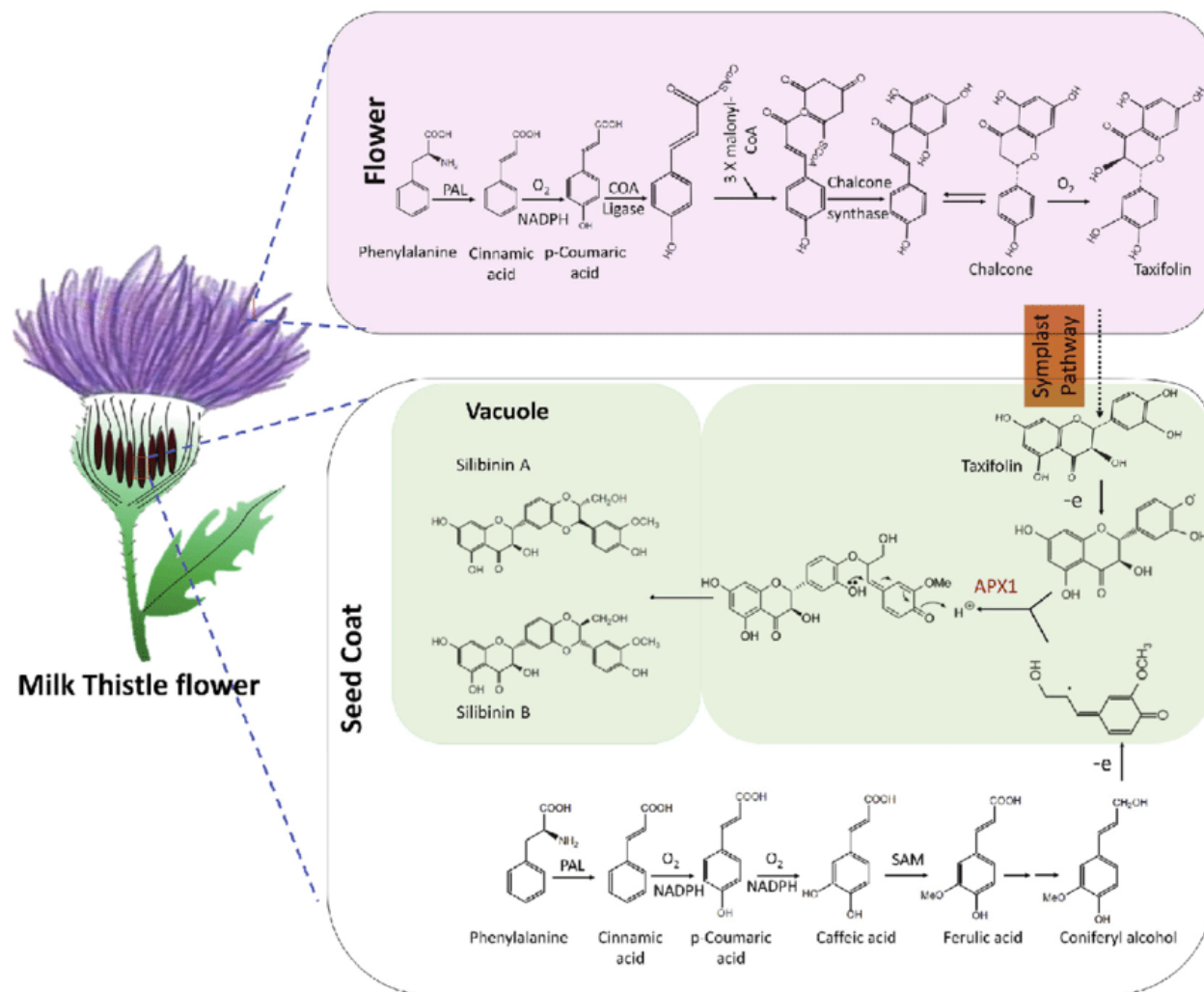
Silybin B (SILB)



Isosilybin A (ISILA)



Isosilybin B (ISILB)



**Figure-8: Silymarin biosynthesis**

**Medical uses:** Plant product flavonoid silymarin, is known for its antioxidant, antiviral and anti-inflammatory properties. In fact, it has traditionally been used to treat liver and gallbladder disease, promote breast milk production, prevent and treat cancer, and even protect the liver from snake bites, alcohol, and other environmental toxins. For approved drug preparations and parenteral applications in the treatment of Amanita mushroom poisoning, the water-soluble silibinin-C-2',3-dihydrogensuccinate disodium salt is used. In 2011, the same compound also received Orphan Medicinal Product Designation for the prevention of recurrent hepatitis C in liver transplant recipients by the European Commission.

**Biotechnology:** Silymarin can be produced in callus and cells suspensions of *Silybum marianum* and substituted pyrazinecarboxamides can be used as abiotic elicitors of flavonolignan production.

**Conclusion:** Silymarin, a flavonolignan from the seeds of 'milk thistle' (*Silybum marianum*), has been widely used from ancient times because of its excellent hepatoprotective action. It is a mixture of mainly three flavonolignans, viz, silybin, silidianin and silychristine, with silybin being the most active. Silymarin has been used medicinally to treat liver disorders, including acute and chronic viral hepatitis, toxin/drug-induced hepatitis and cirrhosis and alcoholic liver diseases. It has also been reported to be effective in certain cancers. Its mechanism of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane; reduction of glutathione oxidation to enhance its level in the liver and intestine; antioxidant activity and stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration. It is orally absorbed but has very poor bioavailability due to its poor water solubility. This review focuses on the mechanism of action, pharmacokinetics, pharmacodynamics, various pharmacological activities and toxicity of silymarin. The nontraditional use of silymarin may make a breakthrough as a new approach to protect other organs in addition to liver.

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