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A CRITICAL REVIEW OF THE HEPATOPROTECTIVE ACTIVITY OF *SILYBUM MARIANUM*: EVIDENCE AND MOLECULAR DOCKING WITH MECHANISM

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ABSTRACT

Liver diseases remain a major global health concern owing to their increasing prevalence and the limitations associated with conventional therapeutic approaches. Natural products have gained considerable attention as potential hepatoprotective agents because of their safety profile and diverse pharmacological properties. This review comprehensively discusses the geographical distribution,botanical description, ethnobotanical uses, phytochemical constituents, and pharmacological activities of Silybum marianum, with particular emphasis on the hepatoprotective effects of silymarin. In addition, molecular docking studies involving silibinin and silymarin, in comparison with standard hepatoprotective drugs, revealed promising binding affinities toward key target proteins, supporting their potential as effective hepato protective agents. Collectively, the available evidence indicates that silymarin is a multifunctional phytoconstituent with remarkable therapeutic value in liver diseases. However, further well-designed preclinical and clinical studies are required to establish its long-term efficacy,safety, and broader clinical applications in hepato protection. Mechanism of action to be discussed as Silymarin protects and regenerates the liver by stabilizing cell membranes, scavenging free radicals to boost antioxidant defenses (like glutathione), and inhibiting stellar cell activation to reduce fibrosis.

KEYWORDS: Silybum Marianum, Silymarin, Liver Diseases.

INTRODUCTION

The liver is one of the most vital organs in the human body and performs a wide range of physiological functions, including metabolism, detoxification of xenobiotics, nutrient storage, synthesis of plasma proteins, bile production, and maintenance of biochemical homeostasis.[1] It plays a central role in the metabolism of both endogenous and exogenous substances and is continuously exposed to various harmful agents, such as drugs, alcohol, environmental toxins, industrial chemicals, and infectious pathogens.[2] Consequently, the liver is highly susceptible to injury and the development of chronic liver diseases.[3] Liver disorders, including hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, liver fibrosis, cirrhosis, and hepatocellular carcinoma, remain major causes of morbidity and mortality worldwide.[4] Although several conventional therapeutic agents are available for the treatment and management of liver diseases, their long-term use is often associated with limited efficacy, undesirable side effects, and high treatment costs.[5] These limitations have prompted considerable interest in the discovery and development of safer and more effective hepatoprotective agents derived from natural sources.[6] Medicinal plants have been widely investigated for their hepatoprotective properties owing to their rich phytochemical composition and diverse pharmacological activities. Plant-derived bioactive compounds exhibit antioxidant, anti-inflammatory, antifibrotic, and hepatoregenerative effects, making them promising candidates for the prevention and treatment of liver disorders. Consequently, natural products have emerged as valuable alternatives and complementary therapeutic agents in hepatoprotection.[6]

Geographical distribution of *Silybum marianum*

Silybum marianum (Milk Thistle) is native to the Mediterranean region, southern Europe, North Africa and parts of Asia including India and Iran.[7] It is now widely naturalised in North and South America, Australia and New Zealand.[8] Main countries of cultivation: Germany, Austria, Hungary, China, Iran[9].This plant prefers nutrient rich soils.[10] Distribution is mainly controlled by rainfall, temperature and elevation.[11]

Botanical characteristics of *Silybum marianum*

Silybum marianum is an annual or biennial herb with large shiny green leaves having characteristic white veins.[8] The stem is erect and branched, and can reach a height of 1–2 m .[10] Flowers are purple to reddish purple in colour, borne in large solitary capitula,

surrounded by spiny bracts.[7] The fruit is a black achene with pappus, with the flavonolignan complex silymarin.[11]

Morphological aspect of *Silybum marianum*

Under good environmental conditions the plant grows up to 200 cm in height [10]. The leaves are shiny green, oblong to lanceolate and prominently white-veined [8]. The flower heads are large, globular and purple.[7] Fruits are hard achenes, 6-8 mm long [10]. The seeds are the medicinal part containing about 1.5-3% silymarin.[9]

Fig.1: Whole plant of milk thistle/*Silybum marianum*.

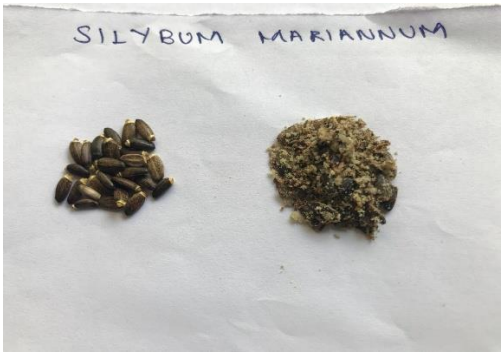

Fig. 2: Seeds and coarse powder of *Silybum marianum*.

Ethnobotanical uses of *Silybum marianum*

Milk thistle has been used in traditional European medicine for >2000 years.[8] The plant has been used in the treatment of liver diseases such as hepatitis, cirrhosis and jaundice.[9] It has also been used for gallbladder diseases and poisoning by toxic mushrooms, especially Amanita phalloides.[12] Traditional practitioners also recommended milk thistle as a digestive aid and general tonic.[7]

Review on silymarin phytochemistry

Silymarin is a complex of flavonolignan extracted from the seeds of *Silybum marianum* [9]. It consists mainly of silybin A and silybin B, which contribute approximately 50–70% of the total silymarin content.[7] The other major constituents are isosilybin A, isosilybin B, silychristin, silydianin and taxifolin.[7] Among these compounds, silybin is considered to be the most biologically active constituent and is mainly responsible for the hepatoprotective effects of silymarin [13].The structures of its components include.

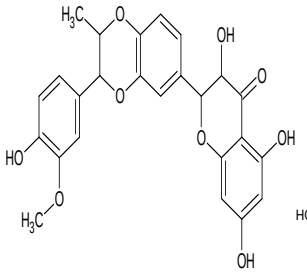

Fig. 3: Silibinin.

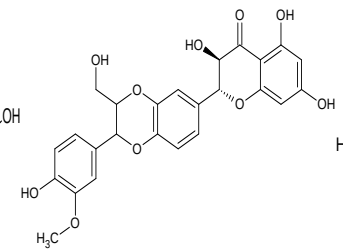

Fig. 4: Isosilybin.

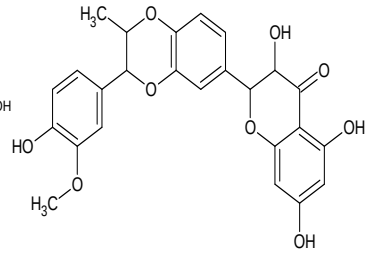

Fig. 5: Silymarin.

Therapeutic potential of *Silybum marianum*

Hepatoprotective activity

Silymarin protected rat liver against carbon tetrachloride-induced hepatotoxicity by reducing lipid peroxidation and preserving membrane integrity.**[14]** clinical and experimental studies and concluded that silymarin exhibits significant hepatoprotective activity in toxic, inflammatory, and chronic liver diseases.**[15]**·silymarin stabilizes hepatocyte membranes, scavenges free radicals, stimulates protein synthesis, and promotes regeneration of liver tissue.[13] Silibinin reduced hepatic fibrosis, inhibited hepatic stellate cell activation, and decreased collagen accumulation in experimental models.**[16]**

MECHANISM

Silymarin stabilizes hepatocyte membranes, scavenges free radicals, protein synthesis, and promotes regeneration of liver tissues.[13] Silibinin reduced hepatic fibrosis, inhibited hepatic stellate cell activation, and decreased collagen accumulation in experimental models.[16]Silymarin raises the intracellular glutathione concentration and improves the activities of antioxidant enzymes such as superoxide dismutase and catalase.[17] Significant reduction of oxidative stress markers in liver tissues by silymarin.[18]

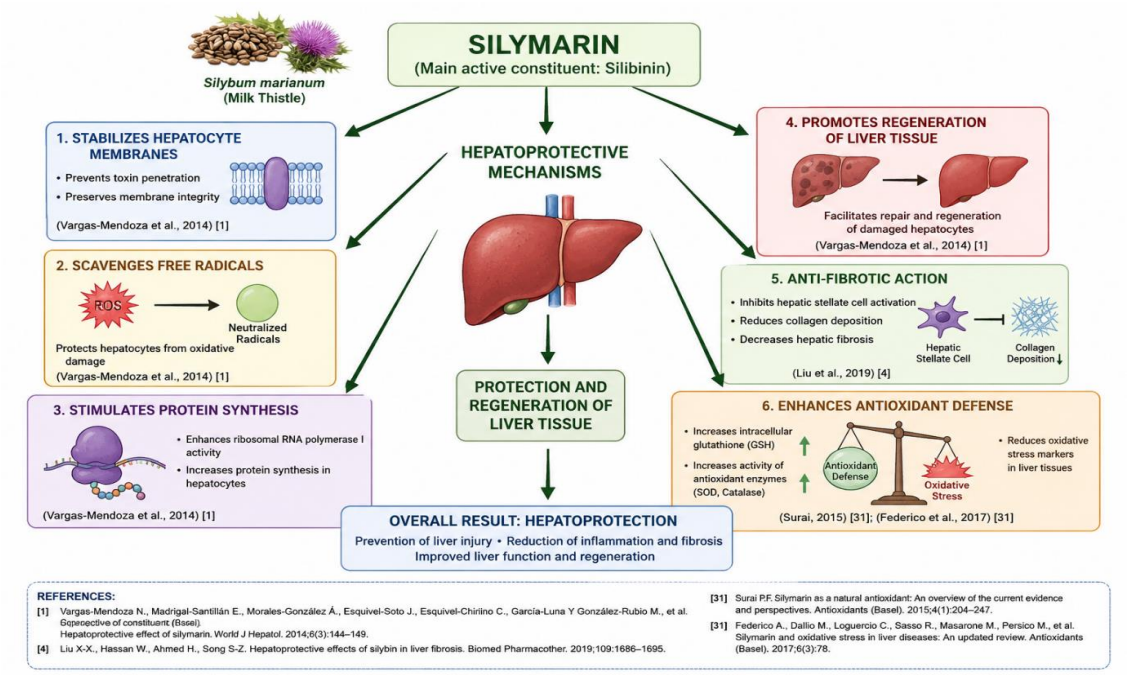

Fig. 6: It represents the schematic mechanisms of silymarin as hepatoprotectives.

Anti-oxidant capacity.

Silymarin functions as a powerful antioxidant by quenching reactive oxygen species and inhibiting lipid peroxidation.[17] Silymarin raises the intracellular glutathione concentration and improves the activities of antioxidant enzymes such as superoxide dismutase and catalase.[17] Significant reduction of oxidative stress markers in liver tissues by silymarin.[18]

Anti-inflammation activity

Silymarin inhibits the activation of NF-κB and hence decreases the inflammatory responses. [13]Silymarin has been found to reduce the production of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6. [15].Silibinin decreases inflammation associated with liver fibrosis.[16]

Anti-diabetic activity

Silymarin has been reported to significantly decrease blood glucose levels and improve glucose tolerance in streptozotocin-induced diabetic rats.[19] Administration of silymarin to patients with type 2 diabetes mellitus resulted in significant reductions in fasting blood glucose and HbA1c levels compared with placebo.[20] In addition, experimental and clinical studies were reviewed which shows that silymarin improves insulin sensitivity and glucose metabolism in diabetic subjects.[21] Silymarin has a protective role against diabetic complications, which resulted in a reduction in oxidative stress and improvement in renal function in patients of diabetic nephropathy.[22]

Anti-cancer activity

The anticancer activity of silymarin against a variety of malignancies by inhibiting tumour growth and progression.[23] silymarin to inhibit cell proliferation in prostate, colon, lung and skin cancer models.[24] Silybin modulates the cell cycle regulatory proteins to induce apoptosis in cancer cells.[25]silymarin inh.ibits angiogenesis and metastasis by regulating multiple signalling pathways involved in tumour progression.[23] Silymarin, with its antiproliferative and chemopreventive properties, may be used as an adjunct therapeutic agent in cancer treatment.[9]

Neuroprotective activity

Silymarin protects neuronal cells from oxidative stress-induced damage.[17] silymarin exerts neuroprotective effects in experimental models of Parkinson's disease through reduction of oxidative stress and neuronal degeneration.[18] The therapeutic potential of silymarin in neurodegenerative disorders and reported its beneficial effects via antioxidant and anti-inflammatory mechanisms.[26] Silymarin could inhibit the progression of Alzheimer's disease via reducing neuroinflammation and oxidative damage.[27] One of the major contributors to the neuroprotective effects is the strong antioxidant activity of silymarin.[17]

Cardioprotective activity

Silymarin confers cardioprotective effects by decreasing oxidative stress and safeguarding myocardial tissues against damage.[17] Silymarin has been shown to enhance cardiovascular health by modulating inflammatory and oxidative stress pathways.[9] The antioxidant properties of silymarin have been reported to be involved in the prevention of cardiovascular damage associated with free radical generation.[17] Silymarin improves lipid metabolism and reduces risk factors for cardiovascular diseases.[15] Silymarin has antiatherogenic activity and is able to reduce the formation of atherosclerotic lesions.[14]

***In silico* molecular docking**

An In Silico molecular docking was performed in CB 2 DOCK and compared the binding affinity with the standard synthetic drug namely Ursodeoxycholic acid, N-Acetylcysteine, Metadoxine & Bifendate, which are used as hepatoprotective. This confirms Silibinin & Silymarin has more or less similar action as compared to standard synthetic drug. Whose dock score/binding affinity is mentioned below.

Table No. 1: binding affinity of phytochemicals with target enzymes.

Target Enzymes	Silybin	Silymarin	Ursodeoxycholic Acid	N-Acetylcysteine	Metadoxine	Bifendate
8BHE	-8.2	-8.6	-9.5	-5.0	-5.5	-7.6
5LDO	-7.7	-7.9	-7.1	-4.8	-5.7	-7.0
2R3X	-9.3	-10.0	-9.7	-4.9	-5.8	-7.3
3NXU	-9.2	-8.9	-9.2	-4.8	-5.5	-6.7
4IQK	-10.4	-10.4	-9.7	-4.8	-6.4	-7.6
2C6U	-8.0	-8.1	-7.9	-4.3	-5.4	-5.8
2HI4	-9.9	-9.0	-7.1	-4.9	-6.6	-7.6

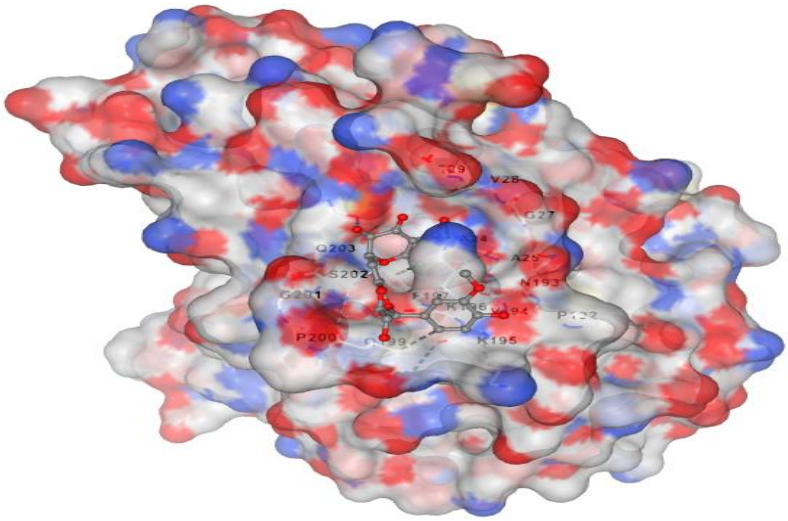

Fig. 7: It shows the interaction of Silibinin with liver enzyme LD50.

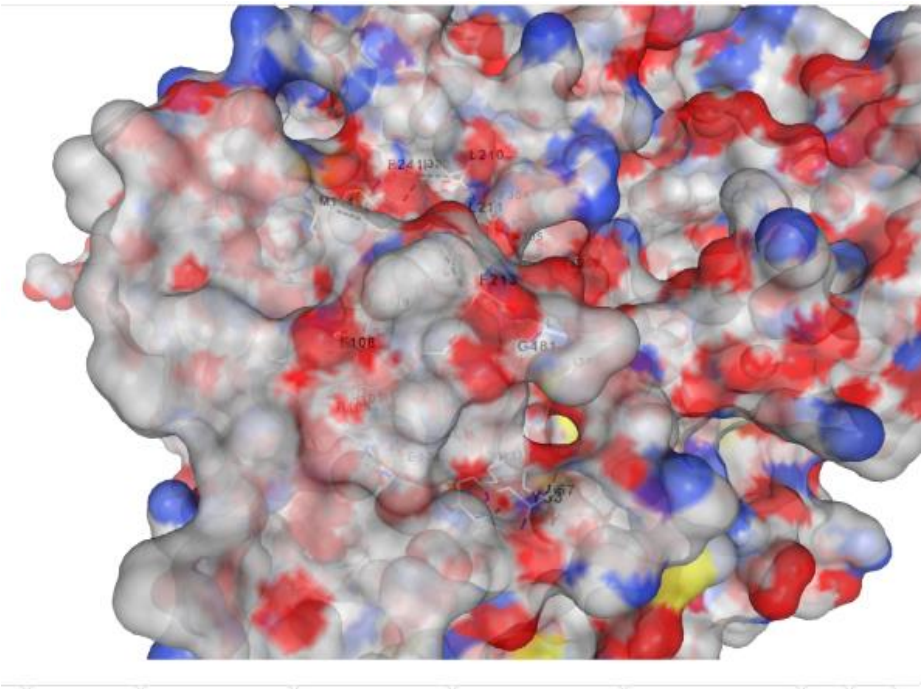

Fig. 8: It shows the interaction of Silymarin with liver enzyme 3NXU.

The molecular docking study revealed that Silibinin and Silymarin have good binding affinities for the selected liver associated target proteins. In several instances, the docking scores of both phytoconstituents were comparable or better than the standard hepatoprotective drugs Ursodeoxycholic acid, N-acetylcysteine, Metadoxine and Bifendate. Among the two compounds, Silymarin had the highest binding affinity to the target protein 2R3X (−10.0 kcal/mol) while both Silibinin and Silymarin showed excellent binding to 4IQK (−10.4 kcal/mol). The positive protein ligand interactions indicate a high scope of modulation of liver associated molecular targets.The docking results validate the hepatoprotective potential of Silibinin and Silymarin and offer computational evidence for their possible mechanism of action. However, molecular docking only predicts the probability of binding, not biological activity. Additional in vitro, in vivo and clinical studies are required to validate these observations, confirm their therapeutic efficacy and safety.

CONCLUSION

Silybum marianum is an important medicinal plant which has been traditionally used for treatment of liver disorders since long time. The main bioactive complex, silymarin, possesses strong antioxidant, anti-inflammatory, antifibrotic and hepatoprotective properties that contribute to the prevention and treatment of various liver diseases. Besides its hepatoprotective effects, there is increasing evidence that C. spinosa has antidiabetic, anticancer, neuroprotective and cardioprotective activities, thus making it a promising multifunctional phytotherapeutic agent.

The molecular docking results discussed in this review further indicate that silibinin and silymarin exhibit good binding affinities towards some important hepatoprotective targets similar to some of the standard drugs, indicating their therapeutic potential. The experimental and clinical evidence is promising, but additional large-scale, randomised clinical trials are needed to confirm long-term efficacy, optimise dosing regimens, improve bioavailability, and develop standardised therapeutic guidelines. In conclusion, silymarin remains one of the promising natural compounds for liver protection and an important candidate for future drug development and clinical research.

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