IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"A Comprehensive Review On Milk Thistle: Phytochemistry, Pharmacokinetics, Mechanism Of Action, And Therapeutic Potentials"

Hansika Varshney (Author)
Shri Ram Murti Smarak College of Engineering and Technology Pharmacy Bareilly (U.P) 243202

Rajat Yadav (Corresponding Author)
Assistant Professor
Shri Ram Murti Smarak College of Engineering and Technology Pharmacy Bareilly (U.P) 243202

ABSTRACT

For many years, milk thistle (Silybum marianum) has been used as a herbal cure for a variety of illnesses. A complex blend of flavonolignans, including silibinin (silybin), silychristin, and silidianin, makes up the main active ingredient "SILYMARIN." Research on pharmacology has shown that silymarin possesses strong anti-inflammatory, antifibrotic, and antioxidant characteristics. Mixed results have come from clinical trials examining the effectiveness of milk thistle in treating a variety of liver illnesses, such as liver cirrhosis, hepatitis B and C, non-alcoholic fatty liver disease, and alcoholic liver disease. Because of its well-established safety record and low number of documented side effects, milk thistle is a valuable adjunctive treatment. Silymarin's pharmacokinetics shows that it has limited oral bioavailability and poor water solubility, which make it difficult to employ therapeutically. To improve its absorption and bioavailability, advances in formulation technologies, such as the creation of liposomal, nanoparticles, and phytosomes, have been investigated. The goal of this paper is to give a thorough overview of milk thistle's pharmacological characteristics and pharmacokinetics, as well as its possible application in the treatment of liver illnesses and other ailments such as cancer, viral infection, fibrosis, tumorigenesis, inflammation, etc.

KEY WORDS-

Milk thistle, Silybummarianum, Hepatoprotective, Silymarin, Flavonolignans, Carcinogenic.

INTRODUCTION

For ages, milk thistle (Silybummarianum L. Gaert., Asteraceae) seeds have been used as a herbal remedy, mostly for liver ailments. The "milky white" veins on the leaves, which release a milky sap when split apart, are the source of the common name "milk thistle." Three isomeric flavonolignans—silibinin (silybin), silychristin, and silidianin collectively known as SILYMARIN extracted from dried milk thistle seeds are the medicinally active ingredients of milk thistle seeds. The most physiologically active is silybin. In addition to proteins, fixed oil, silybonol, apigenin, betaine, and free fatty acids, the seeds also include additional flavonolignans that may enhance the health benefits of milk thistle seeds[1,2].A variety of chemical and biological poisons, including metals, fluoride, pesticides, and agents that are cardiotoxic, neurotoxic, hepatotoxic, and nephrotoxic, as well as biological poisons including mycotoxins, snake venoms, and bacterial toxins, are protected against by silybummarianum[3]. It has been shown that

silymarin not only significantly lowers lipid peroxidation but also possesses anti-oxidant, antihypertensive, and hepatoprotective qualities [4,5]. (Figure 1)

Figure 1: Milk thistle (Silybummarianum) flower, leaves, seeds.

BOTANICAL DESCRIPTIONS

The plant milk thistle can grow annually or twice a year. With huge prickly leaves, large purple blooming heads, and powerfully spinescent stems, it is erect, sturdy, and grows to a height of 5 to 10 feet. The stems and leaves release a milky sap when broken. The glabrous leaves have spiky margins and are dark green, oblong, sinuate-lobed, or pinnatified. The veins of the leaves are milky white. The leaves, which start off as a flat rosette, have a diffusely mottled look due to white veins. Every stem has a terminal head that contains a single, enormous, purple, mildly scented flower that ends in sharp spines from June to September, when the plant is in flower. Sharp spines are ridged on the reddish-purple blooms. The transversely wrinkled, 6-7 mm long achenes have a golden ring at the apex and are flecked with a dark grey colour[2].

PRESENT DAY CULTIVATION AND USAGE

Native to Asia Minor, North Africa, Southern Europe, Southern Russia, and Kashmir (India), milk thistle is found in these regions. It was brought to most of Europe, North and South America, and Southern Australia. It is mostly grown as a medicinal plant on dry, stony soils in Europe, Australia, Canada, China, and North and South America. Its lovely foliage has led to its widespread cultivation as an ornamental plant. Ripe seeds are harvested in the latter part of July. Currently, liver illnesses are the primary application for milk thistle seed, its refined extracts, and its active ingredients. It is the most commonly utilized hepatoprotective agent in cases of hepatotoxicity caused by industrial pollutants and mushroom poisoning, as well as chronic inflammatory hepatic illnesses such as hepatitis, jaundice, alcohol abuse, fibrosis, cirrhosis, and fatty infiltration.It is also a common agent in nutraceuticals. The seed tincture has been used in homoeopathy for the treatment of varicose veins, jaundice, gallstones, peritonitis, hemorrhage, and liver diseases. Commercially accessible products include extracts, pills, or capsules containing standardized extract of milk thistle seeds[1,8].

PHYTOCHEMISTRY

The primary and most well-known ingredient in milk thistle extract is silymarin, a complex mixture found in the leaves, seeds, and fruits of the plant. Flavonolignans, which constitute the majority of silymarin, often account for 70–80% of the extract. together with taxifolin, quercetin, and apigenin, among other flavonoids. Several significant flavonolignans, such as silybin, isosilybin, silychristin, and silydianin, are found in silymarin.Among these compounds, silybin is the primary and most physiologically active constituent of silymarin. It is widely recognized for its remarkable therapeutic properties and is often considered thebasis of milk thistle's medicinal actions when compared to other flavonolignans[9]. In addition, silymarin includes diastereomericflavonolignan pairs, A and B, with varying contributions to the overall composition from these pairings[10]. The rich mixture of diastereomers contributes to the complexity of the silymarin and may have an impact on its range of biological activities[11]. (Figure 2)

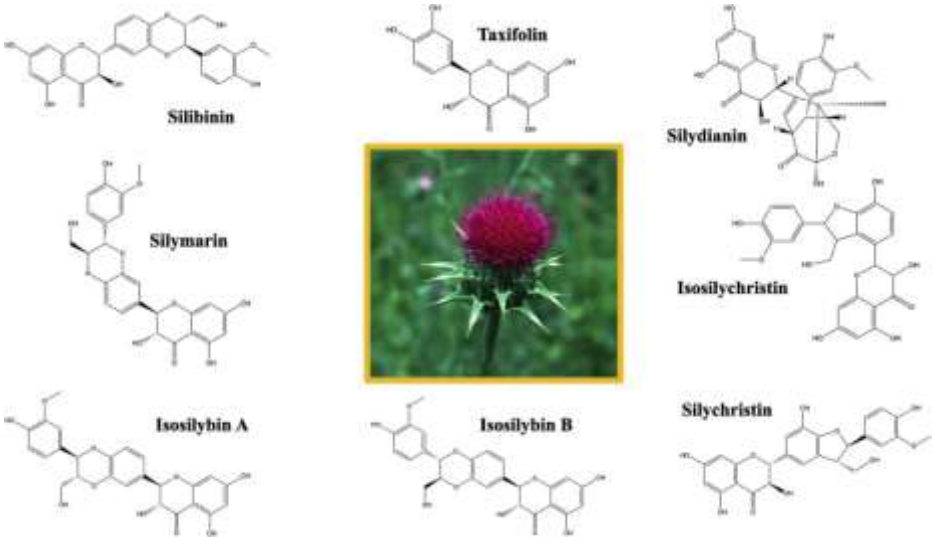

Figure 2: Chemical structures of Milk thistle constituents

PHARMACOKINETICS OF SILYMARIN

The process by which a substance is absorbed, distributed, digested, and eliminated from the body is referred to as pharmacokinetics (PK). A chemical's PK statistics provide details on systemic exposure to the kinetic models. PK is also necessary to determine the therapeutic potential and efficacy of recommended dosages for specific drugs [12, 13]. In most cases, silybin is the dominating molecule and is also regarded as the active metabolite [14]. Experts deem silybin safe when taken orally for up to a week at a dose of up to 1.44 g per day [12,15]. The components of the silymarin are only weakly soluble in water, and studies have shown that 30 minutes later, oral administration of powder extracts only results in plasma concentrations of 20 ng/mL.Conjugatedsilybin made up the majority of the silybin detected in the circulation [16]. Less than 3% of the total dose provided was made up of silybin urine recoveries [17]. (Figure 3)

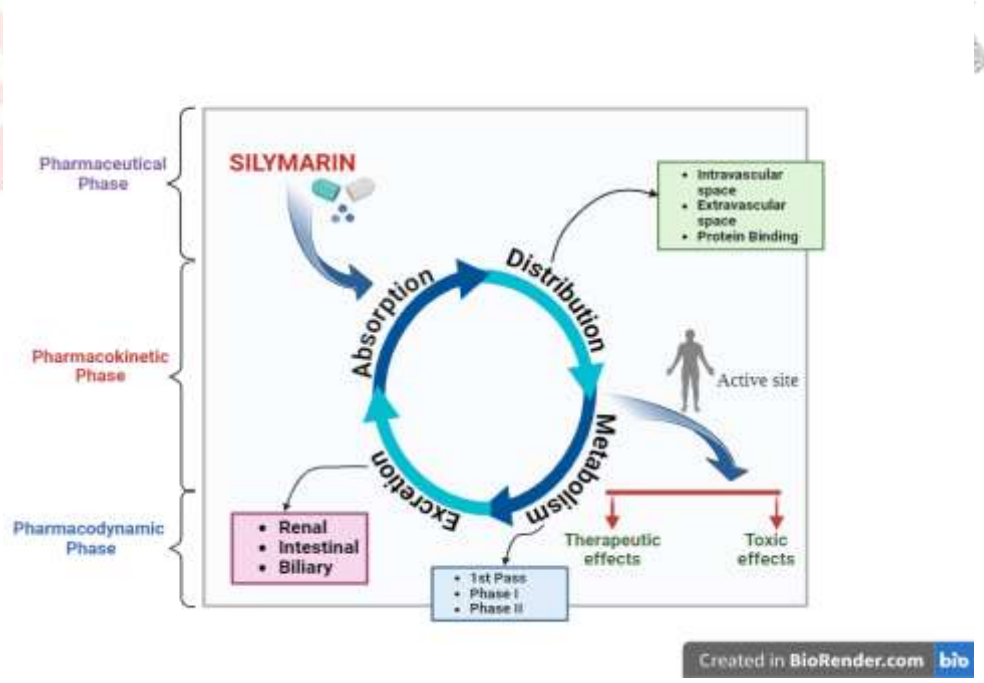

Figure 3: Pharmacokinetics of Silymarin

Absorption-

The accumulation of data from in vitro and in vivo studies indicates that intestinal epithelia absorb silymarin. Silymarin is frequently used as an encapsulated supplement since it is water insoluble. When silymarin is taken orally, it absorbs easily. After six to eight hours, the maximum plasma concentration is

attained. Silymarin has a limited bioavailability because it is only absorbed by the body between 23% and 47% when taken orally [18,19].

Distribution-

It was discovered that silybin exhibits quick tissue dispersion whether it is conjugated or gratis. When silybin was given to mice at a dosage of 50 mg/kg, the concentrations of the substance in the tissues were measured, and it was shown that the peak levels were attained within an hour [20]. Furthermore, studies have looked into the amounts of conjugated and free silybin in connective tissues. According to [21, 22], the Cmax values per gram of silybin for the liver, lungs, stomach, skin, prostate, and pancreas were 8.8/1.6 (mean/SD) and 5.79/1.10 (mean/SD), respectively. According to a study, 70.3 to 46% of rats' blood had silybin bound to proteins [20, 23].

Metabolism-

Silybin is metabolized in phases I and II, with a focus on phase II conjugation mechanisms. Individuals undergo many conjugations of silybin. Research revealed that in human liver microcosms, silybin underwent metabolic degradation. Significantly, three smaller mono-hydroxyl metabolites, one minor di-hydroxyl metabolite, and a major demethylated metabolite were found [20].

Elimination-

Silymarin, conjugated or gratis, is rapidly eliminated in vivo. Silybin's renal excretion, however, is negligible and accounts for only 1% to 2% of the oral dosage over the course of a day. The biliary concentrations of silybin in patients were approximately 100 times higher than the serum concentration, indicating that the liver and bile are the primary organs through which silybin is expelled [24].

MECHANISM OF ACTION

Milk thistle exhibits its hepatoprotective properties by three major mechanisms:

1) Anti-inflammatory-

The capacity of milk thistle to modulate the cytokines that cause inflammation accounts for its anti-inflammatory characteristics. It has been demonstrated that milk thistle suppresses and downregulates the production of COX-2, an important mediator of inflammatory pathways [25, 26]. Additionally, silymarin blocks the Nf-kb-controlled transduction cascade, which is a protein complex that triggers the expression of proinflammatory genes that code for cytokines that are directly implicated in the inflammatory process. Additionally, NF-kB controls inflammatory T cell survival. In mice, silybin was found to lower the levels of proinflammatory cytokines in the liver and plasma while raising IL-10, a cytokine that modulates and suppresses inflammation [27, 28].

2) Antioxidant-

On hepatocytes, milk thistle has also demonstrated antioxidant qualities. It has the ability to suppress free radicals produced by the metabolism of harmful chemicals like carbon tetrachloride, acetaminophen, and ethanol. By directly preventing radical generation and shielding cell membranes from harm caused by free radicals, it promotes the synthesis of proteins. Additionally, it can enhance the amount of scavengers inside cells and function as a free radical scavenger [29].

3) Antfibrotic-

Apart from its anti-inflammatory and antioxidant characteristics, silybin exhibits potential as an antifibrotic agent. This is attributed to its capacity to reduce DNA synthesis induced by platelet-derived growth factor (PDGF) in cells, thereby impeding the conversion of stellate hepatocytes into myofibroblasts. Silybin indirectly inhibits the deposition of collagen fibers that promote the course of liver damage by reducing myofibroblasts [25]. Lastly, silybin has shown a correlation with a noteworthy downregulation of TGF-B, an important regulator in the development of liver fibrosis [30].

THERAPEUTIC POTENTIALS OF SILYMARIN

1. Anti-cancer activity-

1.1 Effect of milk thistle and silymarin on liver cancer -

Silymarin has multiple modes of action against liver cancer. It increases the concentration of apoptotic cells by suppressing the proliferation of HepG2, human hepatocellular carcinoma cells. Because of a rise in cytosolic cytochrome complex (Cyt c) levels, it may also result in a decrease in mitochondrial transmembrane potential. Silymarin achieves this by down-regulating the expressions of anti-apoptotic proteins, such as survivin and Bcl-2, and proliferation-associated proteins, such as proliferating cell nuclear antigen, cyclin D1, c-Myc, and β-catenin, and up-regulating the expressions of proapoptotic proteins, such as p53, Bax, apoptotic protease-activating factor 1, and caspase-3 [31].

1.2 Effect of milk thistle and silymarin on prostate cancer-

Prostate cancer is the most common non-cutaneous cancer among men. According to a study, patients who had radical prostatectomy and received 570 mg of silymarin daily for six months may see a drop in total cholesterol and low-density lipoprotein (LDL), two markers of a blood lipid profile linked to the advancement of prostate cancer [32]. Prostate-specific antigen (PSA) was significantly reduced in individuals with benign prostatic hyperplasia who took 570 mg of silymarin daily for six months [33]. According to a different study, administering silybin in conjunction with ionizing radiation decreased prostate cancer cells' migratory and invasive characteristics and hindered endothelial cell growth [34].

1.3 Effect of milk thistle and silymarin on skin cancer-

Skin cancer is primarily caused by uncontrolled exposure to solar ultraviolet (UV) radiation, especially in the UVB (290–320 nm) and UVC (200–290 nm) ranges. UVB causes a variety of DNA damage and is readily absorbed by skin cells [35]. According to a study that assessed the impact of UVB-induced silybinonphotodamage, silybin could delay apoptosis and hasten the healing of UVB-induced cyclobutane pyrimidine dimers (CPD). Silybin modified the way UVB-induced S phase arrest occurred, reducing both inactivated S phase populations and active DNA synthesis [36].

2. Antioxidant activity-

The recent paper "Evaluation of antioxidant activity and its association with plant development in Silybummarianum L." by Admah et al. (2013) [37] caught our attention. The authors have solely assessed the DPPH-scavenging activity (DSA) of extracts obtained from whole plants and SM leaves at several ages (10 to 100 days post-germination) and have not looked into the impact of different radiation dosages on this activity. The greatest DSA value is 52.98 ± 03%, whereas the maximum DSA was obtained in both leaves and whole plants in 80-day-old plants (60 and 65.43%), according to the authors' abstract for the paper. Lucini developed the evidence for the chemicals from the SM's antioxidant capacity [38]. The authors found no connection between antioxidant potentials and the concentration of certain chemicals, such as silybin. In the ABTS and FRAP tests, the antioxidantcapacity of the components is greater than that of the positive control. The most powerful DPPH inhibitors were found in taxifolin and dehydrodiconifery alcohol-4-β-D-glucoside [39].

3. Hepatoprotective activity-

The plant has been used for liver protection at least since the first century. One of the potential key components of silymarin'shepatoprotective effects may be its antioxidant activity [40]. By lowering CCl4's metabolic activation and functioning as a chain-breaking antioxidant, it protects mice from lipid peroxidation and hepatotoxicity caused by CCl4 [41]. It reduced the development of cirrhosis in rats treated with CCl4, restored increased transaminases to normal levels [42], and shielded against detrimental increases in the membrane ratios of phospholipids, cholesterol, sphingomyelin, and phosphatidylcholine [43]. Rat livers treated with CCl4 had higher collagen content; rats treated with silymarin (50 mg/kg for 5 days) had lower collagen content [44].Hepatic cirrhosis and fibrosis are the final stages of liver injury that are brought on by iron overload [45]. The primary cause of iron-induced hepatotoxicity is oxidative stress brought on by elevated hepatic lipid peroxidation. Serum enzyme levels and iron-induced increased lipid

peroxidation were decreased in rats treated with silymarin [46].After receiving silymarin pretreatment, rats with partial hepatectomy displayed enhanced synthesis of protein, RNA, DNA, and cholesterol, indicating liver regeneration [47].Silymarin most likely triggers a physiological regulator, allowing 10 silybin to attach to a particular polymerase binding site and promote the synthesis of ribosomes [48]. It is most likely able to penetrate the nucleus and particularly stimulate RNA polymerase because of its structural resemblance to steroids. It also counteracts the inactivation of cytochrome P-450 into cytochrome P-420 and raises the contents of cytochromes P-450 and B5, as well as the activity of amidopyrine-D-demethylase, hydroxylases of hexobarbita and aniline, and the respiratory chain of microsomes [49].

4. Anti-inflammatory activity-

Silymarin and silybin, its main ingredient, shown anti-inflammatory properties [50,51,52], as well as the ability to inhibit Kuppfer cells [52] and neutrophil migration [53]. It has been discovered that by inhibiting the enzyme lipoxygenase, it prevents the liver from producing prostaglandins from polyunsaturated fatty acids and leukotrienes.These leukotrienes are among the most harmful substances that can be discovered in humans [54].

5.Immunomodulatory activity-

When endotoxin-free neutralizing anti-II-12 antibody was injected intraperitoneally into mice administered silymarin, the protective effects against UVB-induced reduction of the contact hypersensitive response were eliminated. Moreover, silymarin therapy blocked the reduction of the contact hypersensitivity response induced by UVB in their wild-type mice but not in IL-12 mutant animals. Furthermore, silymarin-treated or non-treated IL-12 knockout mice that received an intraperitoneal (i.p.) injection of IL-12 responded more strongly to contact hypersensitivity than did mice exposed to UVB alone or silymarin plus UVB. These suggest that silymarin can shield mice from UVB-induced immunosuppression and that IL-12 plays a role in mediating this protective effect [55]. Silybin dramatically reduces CD80 and CD86 expression. MHC (Histocompatibility Complex Molecules) class I and class II in the dendritic cells (DCs) generated from murine bone marrow, and was linked to deficiencies in the DCs' expression of lipopolysaccharide (IPS)-induced II-12.DCs treated with silybin demonstrated exceptional efficacy in capturing Ag (antigens) through endocytosis mediated by mannose receptors. It has been shown that silybin inhibits both the nuclear translocation of the NF-kB p65 subunit and the activation of MAPKS (mitogenactivated protein kinases) induced by LPS"[56]. The effects of silybin on caspases may be a normal cell-mediated immune response, and the molecular basis for the silybin-treated DCs demonstrated an anticarcinogenic and anti-inflammatory defective activation of the response and consequences. According to a different study, silymarin may be helpful in reducing the damage to dopaminergic neurons and the development of therapeutic adjuvants that stimulate microglia and produce inflammatory mediators that require immunosuppression, such as immunity to infectious TNF-a and nitric oxide (NO). In a dose-dependent way, it markedly decreased the levels of inducible nitric oxide synthase (INOS) mRNA, protein, and LPS-induced nitrite [57]. When silymarin is administered parenterally, T-lymphocyte activity is suppressed and inflammatory processes are triggered [58]. Silymarin and its active ingredient, silibinin, increase the production of IL-10 while suppressing the intrahepatic expression of TNF-a, IL-2, iNOS, interferon-gamma (y-IFN), and interleukin (II)-4 [57,59,60]. Silymarin may play a role in NF-KB-dependent reporter gene transcription and the inhibition of TNF-induced activation of NF-CB, a nuclear transcription factor [61,62]. It did not interfere with p65's capacity to bind to DNA; instead, it prevented its translocation to the nucleus. Additionally, it inhibited the activation of NF-KB caused by phorbol ester, LPS, okadaic acid, and ceramide, while having no discernible effect on NF-B activation induced by H2O. Silymarin also prevented TNF-induced cytotoxicity and Caspase activation, as well as the activation of mitogen-activated protein kinase and c-Jun N-terminal kinase. It inhibited lipid peroxidation and reactive oxygen intermediate generation brought on by TNF [62].

6. Anti-viral activity-

Silymarin may help treat viral hepatitis even if it has no effect on viral replication because it inhibits the inflammatory and cytotoxic cascade of events that the virus causes[63]. Silymarin inhibits nuclear factor kappa B (NF-kB)-dependent transcription in human hepatoma cells and tumour necrosis factor-alpha (TNF-cz) expression in anti-CD3 stimulated human peripheral blood mononuclear cells, which may help treat patients with chronic hepatitis C [51]. These effects of silymarin are anti-inflammatory and antiviral. Both the human keratinocytes (HaCaT) and the human hepatoma cell (HepG2) lines employed showed decreased

hasal and dioxin-inducible CYP1A1 catalytic activity in response to silybin and dehydrosylibin. In HaCaT cells as opposed to HepG2 cells, the inhibitory impact of the investigated chemicals was more noticeable, and dehydrosilybin was a far more potent inhibitor than silybin [64]. Siybin exhibited a high growth inhibitory effect on HepG2 (hepatitis B virus negative; p53 intact) and Hep38 (hepatitis B virus positive; p53 mutant) cells. Its cytotoxicity was comparatively stronger in Hep3B cells and was linked to the induction of apoptosis. In HepG2, it also resulted in Gl arrest, while in Hep3B cells, it induced both G1 and G2-M arrests. In both cell lines, silybin increased ip1/p27 but lowered the levels of cyclin D1, cyclin D3, cyclin E, cyclin-dependent kinase (CDK-2), and CDK4. Silybin also lowered the G2-M regulator protein levels in Hep3B cells. Moreover. In these HCC cells, silybin significantly reduced CDK2, CDK4, and CDC2 kinase activity [65].

7. Anti-fibrotic activity-

The harmful involvement of hepatic stellate cells and their generated myofibroblasts is crucial to liver fibrogenesis. Freshly isolated rat hepatic stellate cells' proliferation was inhibited by silibinin at a concentration of 10'mol/l, but this effect was undetectable on their viability, morphology, or cytoskeletal architecture. Moreover, it inhibited the transformation of myofibroblasts and down-regulated the profibrogenic transforming growth beta (TGF-B) and extracellular matrix component gene expression [66]. Hepatoprotective effects may be related to changes in TGFB1 and c-myc expression in the liver[67]. One significant component of the possible antifibrotic qualities may be inhibition of hepatic stellate cell transition and proliferation [66].

8. Anti-carcinogenic/anti-tumorigenesis activity-

Long-term silymarin anti-carcinogenic and cancer chemopreventive effects Targeting mostly stage I tumors, silymarin feeding dramatically reduced tumor growth and also caused regression of already-existing tumors [68, 69]. The mechanism underlying these effects may involve inhibition of promoter-induced edema, hyperplasia, proliferation index, and oxidant state. It has been linked to in vivo prostate tumor antiproliferative, pro-apoptotic, and anti-angiogenic efficaciousness [70]. By altering enzyme activity, cell proliferation, and/or PGE(2) concentration, feeding silymarin to rats during the promotion stage of 4-nitroquinoline 1-oxide (4-NQO)-induced rat tumorigenesis has the potential to prevent tongue squamous cell carcinoma [71]. There have also been reports of tumorigenesis models in human prostate, breast, and cervical carcinoma cells. Only in the case of cervical cancer cells did silibinin treatment cause a considerable and time-dependent suppression of both DNA synthesis and cell growth, together with a significant loss of cell viability [72]. It is commonly known that oxidative stress and immunological suppression brought on by ultraviolet (UV) light are major factors in the development of skin cancer. Applying silymarin topically on mouse skin inhibits the development of photocarcinogenesis. It was discovered to be connected to the suppression of myeloperoxidase activity and infiltrating leukocytes, specifically the CD11b+ cell type [73]. Silymarin decreased the number of UVB-induced H+O-producing cells and INOS-expressing cells concurrent with a decrease in H+O and nitric oxide production. Silymarin also enhanced the levels of the immunostimulatory cytokine, IL-12, and decreased the UVB-induced enhancement of the immunosuppressive cytokine, interleukin (IL)-10 [55,73]. The inhibition of photocarcinogenesis in mice may be linked to silymarin's ability to reduce UVB-induced oxidative stress and immunosuppression [73]. In human lung cancer cells, both small cell and non-small cell, silybin considerably inhibits growth, causes a mild cell cycle arrest, and causes a strong apoptotic death. It causes G1 arrest, which stops cell development and causes androgen-dependent human prostate cancer LNCaP cells to differentiate [74, 75]. The phosphorylation state of proteins associated with retinoblastoma (Rh) is crucial for promoting the advancement of the cell cycle. They stimulate growth when they are hyperphosphorylated, but they inhibit growth when they are hypophosphorylated. With the help of their catalytic subunits, cyclins, cyclin-dependent kinases (CDKs) phosphorylate Rb, releasing transcription factor E2Fs from Rb-E2F complexes and promoting cell division.The levels of CDK4 and CDK2, respectively, decreased after silybin therapy, although cyclin D1 and cyclin E protein levels remained unchanged. The transcription factors E2F3, E2F4, and E2F5, in that order, have significantly decreased in protein levels. The hypophosphorylation of Rb-related proteins that siybin causes may contribute to its anti-carcinogenic and cancer-prevention effects in various cancer models, including PCA. The primary cause of this impact was a significant drop in the quantity of Rb phosphorylated at particular serine sites [76,77]. Silybin successfully prevents constitutive activation of NF-KB in advanced human prostate carcinoma

DU145 cells and suppresses the development of human prostate cancer cells (PCA) both in vitro and in vivo [78]. Nuclear levels of the NF-KB subunits, p65 and p50, were likewise lowered in accordance with this. Treatment with silybin led to a marked rise in IkappaBalpha (inhibitory KB-C) and a corresponding drop in phospho-IkappaBalpha. IKKalpha kinase activity is dose-dependently decreased by silybin. Silibinin's inhibitory action on IKKalpha and downstream effectors can occur without an upstream trigger. Additionally, silybin prevents TNFco-induced NF-B activation through the IkappaBalpha pathway, which makes DU145 cells more susceptible to INF-co-induced death [61].

CONCLUSION-

There are many different methods utilized in the search and usage of herbal remedies. These methods are typically regarded as safer and superior to conventional medical practice because they are natural or stem from deeply held beliefs about wellness and health, whether they be religious, philosophical, or otherwise. A well-researched plant for treating a variety of ailments is Silybummarianum, and silymarin is one of the most used medications. The lipid, biliary, immunomodulatory, and anti-inflammatory properties of milk thistle seed are demonstrated. In addition, it possesses antiviral and anticancer activities. Except for minor gastrointestinal and allergic reactions, milk thistle seed formulations are safe, well-tolerated, and do not have any significant negative effects on humans. It may encourage more clinical research if silymarin and its bioactive ingredients are made available for sale as medications. Its composition can also be used to help prevent and cure a variety of medical conditions. Additionally, milk thistle seems to have a favorable safety profile, with minimal adverse effects documented and typically good tolerance in the majority of people. Ultimately, even though milk thistle shows promise, it should be used cautiously and preferably with medical advice. In order to more effectively incorporate milk thistle into traditional medical practice, future research should concentrate on clarifying the exact mechanisms of action, ideal dosages, and long-term effects.

REFERENCES

1. DerMarderosian, A. The Reviews of natural products. 1st ed. Facts and Comparisons: St. Louis, Missouri, 2001.

2. Evans, W.C. Trease and Evans pharmacognosy. 15th ed. Reed Elsevier India Pvt. Ltd.: New Delhi, 2002.

3. Brandon-Warner E, Eheim AL, Foureau DM, Walling TL, Schrum LW, McKillop IH. Silibinin (Milk Thistle) potentiates ethanol-dependent hepatocellular carcinoma progression in male mice. *Cancer Lett.* 2012;326:88–95. [PMC free article] [PubMed] [Google Scholar]

4. Brantley SJ, Oberlies NH, Kroll DJ, Paine MF. Two flavonolignans from milk thistle (Silybummarianum) inhibit CYP2C9-mediated warfarin metabolism at clinically achievable concentrations. *J PharmacolExpTher.* 2010;332:1081–1087. [PMC free article] [PubMed] [Google Scholar]

5. Chambers CS, Holečková V, Petrásková L, Biedermann D, Valentová K, Buchta M, et al. The silymarin composition… and why does it matter? *Food Res Int.* 2017;100:339–353. [PubMed] [Google Scholar]

6. Chen CH, Huang TS, Wong CH, Hong CL, Tsai YH, Liang CC, et al. Synergistic anti-cancer effect of baicalein and silymarin on human hepatoma HepG2 Cells. *Food ChemToxicol.* 2009;47:638–644. [PubMed] [Google Scholar]

7. Chevreau N, inventor. *LIFEVANTAGE Corp, assignee. Topical compositions and methods for reducing oxidative stress. United States patent US 20160166626A1.* 2016 Jun 16;

8. Barceloux, D.G. Medical Toxicology of Natural Substances. John Wiley & Sons, Inc.: New Jersey, 2008.

9.FizaAmjad, RidaZainab, Muhammad Akram, Umme Laila, MominaIftikhar, Adonis Sfera, PragneshParmar. A Review on Anti-tuberculosis Properties of Medicinal Plants. IAIM, 2023; 10(10): 1-9.

10.Muhammad Akram, Muhammad Amjad Chishti, Umme Laila, RidaZainab, MominaIftikhar, Muhammad Talha Khalil, AtheerKadhimIbadi, AymenHawani, Adonis Sfera, PragneshParmar. Herbal Remedies with potential COVID-19 Activities. IAIM, 2023; 10(9): 27-36.

11.Parmar P. Evolution of Toxicology in India: From Safety Concerns to Comprehensive Science. AdvClinToxicol, 2023; 8(3): 000275. DOI:10.23880/act-16000275

12. Zhu HJ, Brinda BJ, Chavin KD, Bernstein HJ, Patrick KS, Markowitz JS. An assessment of pharmacokinetics and antioxidant activity of free silymarinflavonolignans in healthyvolunteers: a dose escalation study. *Drug MetabDispos*. 2013;**41**(9):1679-85. [PubMed ID: 23835761]. [PubMed Central ID: PMC3876803]. https://doi.org/10.1124/dmd.113.052423.

13. Das SK, Mukherjee S, Vasudevan DM. Medicinal properties of milk thistle with special reference to silymarin–an overview. *Natural Product Radiance*. 2008;**7**(2):182-92.

14. Zhang W, Hong R, Tian T. Silymarin's Protective Effects and Possible Mechanisms on Alcoholic Fatty Liver for Rats. *BiomolTher (Seoul)*. 2013;**21**(4):264-9. [PubMed ID: 24244810]. [PubMed Central ID: PMC3819898]. https://doi.org/10.4062/biomolther.2013.020.

*15.*Hoh C, Boocock D, Marczylo T, Singh R, Berry DP, Dennison AR, et al. Pilot study of oral silibinin, a putative chemopreventive agent, in colorectal cancer patients: silibinin levels in plasma, colorectum, and liver and their pharmacodynamic consequences. *Clin Cancer Res*. 2006;**12**(9):2944-50. [PubMed ID: 16675592]. https://doi.org/10.1158/1078-0432.CCR-05-2724.

*16.*Sornsuvit C, Hongwiset D, Yotsawimonwat S, Toonkum M, Thongsawat S, Taesotikul W. The Bioavailability and Pharmacokinetics of Silymarin SMEDDS Formulation Study in Healthy Thai Volunteers. *Evid Based Complement Alternat Med*. 2018;**2018**:1507834. [PubMed ID: 30108644]. [PubMed Central ID: PMC6077530]. https://doi.org/10.1155/2018/1507834.

*17.*Xu Y, Li J, He B, Feng T, Liang L, Huang X. In vitro Dissolution Testing and Pharmacokinetic Studies of Silymarin Solid Dispersion After Oral Administration to Healthy Pigs. *Front Vet Sci*. 2022;**9**:815198. [PubMed ID: 35300217]. [PubMed Central ID: PMC8921073]. https://doi.org/10.3389/fvets.2022.815198.

18. Koltai T, Fliegel L. Role of Silymarin in Cancer Treatment: Facts, Hypotheses, and Questions. *J Evid Based Integr Med*. 2022;**27**:2515690X211068826. [PubMed ID: 35018864]. [PubMed Central ID: PMC8814827]. https://doi.org/10.1177/2515690X211068826.

19. Javed S, Kohli K, Ali M. Reassessing bioavailability of silymarin. *Altern Med Rev*. 2011;**16**(3):239-49. [PubMed ID: 21951025].

20. Xie Y, Zhang D, Zhang J, Yuan J. Metabolism, Transport and Drug-Drug Interactions of Silymarin. *Molecules*. 2019;**24**(20). [PubMed ID: 31615114]. [PubMed Central ID: PMC6832356]. https://doi.org/10.3390/molecules24203693.

21. Calani L, Brighenti F, Bruni R, Del Rio D. Absorption and metabolism of milk thistle flavanolignans in humans. *Phytomedicine*. 2012;**20**(1):40-6. [PubMed ID: 23072776]. https://doi.org/10.1016/j.phymed.2012.09.004.

22. Wu JW, Lin LC, Tsai TH. Drug-drug interactions of silymarin on the perspective of pharmacokinetics. *J Ethnopharmacol*. 2009;**121**(2):185-93. [PubMed ID: 19041708]. https://doi.org/10.1016/j.jep.2008.10.036.

23. Nasri H. Silymarin and its properties; a nephrology viewpoint. *J Ren Endocrinol*. 2015;**1**(1). e09.

24. Aziz M, Saeed F, Ahmad N, Ahmad A, Afzaal M, Hussain S, et al. Biochemical profile of milk thistle (SilybumMarianum L.) with special reference to silymarin content. *Food SciNutr*. 2021;**9**(1):244-50. [PubMed ID: 33473288]. [PubMed Central ID: PMC7802570]. https://doi.org/10.1002/fsn3.1990.

25. Loguercio C, Festi D. Silybin and the liver: from basic research to clinical practice. World J Gastroenterol. 2011 May 14;17(18):2288-301. [PMC free article] [PubMed]

26. Abenavoli L, Bellentani S. Milk thistle to treat non-alcoholic fatty liver disease: dream or reality? Expert Rev GastroenterolHepatol. 2013 Nov;7(8):677-9. [PubMed]

27. Schümann J, Prockl J, Kiemer AK, Vollmar AM, Bang R, Tiegs G. Silibinin protects mice from T cell-dependent liver injury. J Hepatol. 2003 Sep;39(3):333-40. [PubMed]

28. Beyoğlu D, Idle JR. Metabolomic insights into the mode of action of natural products in the treatment of liver disease. BiochemPharmacol. 2020 Oct;180:114171. [PubMed]

29. Trouillas P, Marsal P, Svobodová A, Vostálová J, Gazák R, Hrbác J, Sedmera P, Kren V, Lazzaroni R, Duroux JL, Walterová D. Mechanism of the antioxidant action of silybin and 2,3-dehydrosilybin flavonolignans: a joint experimental and theoretical study. J PhysChem A. 2008 Feb 07;112(5):1054-63. [PubMed]

30. Fabregat I, Moreno-Càceres J, Sánchez A, Dooley S, Dewidar B, Giannelli G, Ten Dijke P., IT-LIVER Consortium. TGF-β signalling and liver disease. FEBS J. 2016 Jun;283(12):2219 32. [PubMed]

31. Lu W, Lin C, King TD, Chen H, Reynolds RC, Li Y. Silibinin inhibits Wnt/β-catenin signaling by suppressing Wnt co-receptor LRP6 expression in human prostate and breast cancer cells. *Cell Signal.* 2012;24:2291–2296. [PMC free article] [PubMed] [Google Scholar]

31. Ramakrishnan G, Augustine TA, Jagan S, Vinodhkumar R, Devaki T. Effect of silymarin on N-nitrosodiethylamine induced hepatocarcinogenesis in rats. *ExpOncol.* 2007;29:39–44. [PubMed] [Google Scholar]

33. Ramakrishnan G, Lo Muzio L, Elinos-Báez CM, Jagan S, Augustine TA, Kamaraj S, et al. Silymarin inhibited proliferation and induced apoptosis in hepatic cancer cells. *Cell Prolif.* 2009;42:229–240. [PMC free article] [PubMed] [Google Scholar]

34. Ramakrishnan G, Raghavendran HR, Vinodhkumar R, Devaki T. Suppression of N-nitrosodiethylamine induced hepatocarcinogenesis by silymarin in rats. *ChemBiol Interact.* 2006;161:104–114. [PubMed] [Google Scholar]

35. Tooiserkani F, Hormati A, Moradi H, Ali asl F. A Glimpse of Silybummarianum from the perspective of Iranian traditional medicine and modern studies. *Qom Univ Med Sci J.* 2019;13:78–86. [Google Scholar]

36. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65:87–108. [PubMed] [Google Scholar]

37.Ahmad N, Abbasi BH, Fazal H. Evaluation of antioxidant activity and its association with plant development in SilybummarianumL. Industrial Crops and Products. 2013a; 49:164-168.

38.Lucini L, Kane D, Pellizzoni M, Ferrari A, Trevisi E, RuzickovaG et al. Phenolic profile and in vitro antioxidant power of different milk thistle [Silybummarianum(L.) Gaertn.] Cultivars. Industrial Crops and Products. 2016; 83:11-16.

39.Qin NB, Jia CC, Xu J, Li DH, Xu FX, Bai J et al. New amides from seeds of Silybummarianum with potential antioxidant and antidiabetic activities. Fitoterapia.2017a; 119:83-89.

40. Feher J, Lang I, Nekam K, Csomos G, Muzes G and Deak G, Effect of silibinin on the activity and expression of superoxide dismutase in lymphocytes from patients with chronic alcoholic liver disease, Free RadicresCommun, 1987, 3(6), 373-377.

41. Lettéron P, Labbe G, Degott C, Berson A, fromenty B, Delaforge M, Larrey D and Pessayre D, Mechanism for the protective effects of silymarin against carbon Tetrachloride-induced lipid peroxidation and Hepatotoxicity in mice. Evidence that Silymarin acts both as an inhibitor of Metabolic activation and as a chain-breaking antioxidant, BiochemPharmacol, 1990,39(12), 2027-2034.

42. Sharma A, Chakraborti KK and Handa SS, anti-hepatotoxic activity of some Indian Herbal formulations as compared to Silymarin, Fitoterapia, 1991, 62, 229-235.

43. Muriel P and Mourelle M, The role of membrane composition in ATPase activities of cirrhotic rat liver: effect of silymarin, J ApplToxicol, 1990, 10(4), 281-284.

44. Favari L and Perez-Alvarez V, Comparative effects of colchicines and silymarin on CCl4 –chronic liver damage in rats, Arch Med Res, 1997, 28, 11-17.

45. Pulla Reddy A and Lokesh BR, Effect of Curcumin and eugenol on iron-inducedHepatic toxicities in rats, Toxicology, 1996,107, 39-45.

46. Bhattacharya A, Ramanathan M, Ghosal and Bhattacharya SK, Effect of WithaniaSomniferaglycowithanolides on ironInducedheopatotoxicity in rats, Phytother Res, 2000, 14, 568-570.

47. Srivastava S, Srivastava AK, Srivastava S, Patnaik GK and Dhawan BN, Effect of picroliv and Silymarin on liver regeneration in rats, Indian J Pharmacol, 1994, 26, 19-22.

48. Schopen RD, Lange OK and Panne C, searching for a new therapeutic principle. Experience with hepatic therapeutic agent Legalon, Medical Welt, 1969, 20, 888-893.

49. Saratikov AS, Vengerovskii AI and Sedykh IM, The correction with hepatic protectors of structural metabolic disorders in the liver in D-galactosamine poisoning, FarmakolToksikol, 1990, 53(2), 38-40.

50. Dehmlow C, Murawski N and de Groot H, Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells, Life Sci, 1996,58(18), 1591-1600

51. Polyak SJ, Morishima C, Shuhart MC, WangCC, Liu Y and Lee DY, Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaBsignaling, and HCV infectionby standardized Silymarin,Gastroenterology, 2007, 132(5),1925-1936.

52. Dehmlow C, Erhard J and de Groot H,Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin, Hepatology, 1996,23(4), 749-754.

53. De La Puerta R, Martinez E, Bravo L andAhumada MC, Effect of silymarin on different acute inflammation models and on leukocyte migration, J PharmPharmacol, 1996, 48(9), 968-970.

54. Fiebrich F and Koch H, Silymarin, an inhibitor of lipoxygenase, Experientia,1979, 35(12), 1548-1560.

55. Meeran SM, Katiyar S, Elmets CA and KatiyarSK, Silymarin inhibits UV radiation-induced immunosuppression through augmentation of interleukin-12 in mice, MolCancerTher, 2006, 5(7), 1660-1668.

56. Lee JS, Kim SG, Kim HK, Lee TH, JeongYI,Lee CM, Yoon MS, Na YJ, Suh DS, Park NC,Choi IH, Kim GY, Choi YH, Chung HY andPark YM, Silibinin polarizes Th1/Th2 immune responses through the inhibition of immunostimulatory function of dendritic cells, J Cell Physiol, 2007, 210(2),385-397.

57. Wang MJ, Lin WW, Chen HL, Chang YH, OuHC, Kuo JS, Hong JS and Jeng KC, Silymarin protects dopaminergic neurons against lipopolysaccharide-induced neurotoxicity by inhibiting microglia activation, EurJNeurosci, 2002, 16(11), 2103-2112.

58. Johnson VJ, He Q, Osuchowski MF andSharma RP, Physiological responses of a natural antioxidant flavonoid mixture,silymarin, in BALB/c mice: III. Silymarin inhibits T-lymphocyte function at low doses but stimulates inflammatory processes at high doses, Planta Med, 2003, 69(1),44-49.

59. Schumann J, Prockl J, Kiemer AK, VollmarAM, Bang R and Tiegs G, Silibinin protects mice from T cell-dependent liver injury(small star, filled), J Hepatol, 2003,39(3), 333-340.

60. Wilasrusmee C, Kittur S, Siddiqui J, BruchD, Wilasrusmee S and Kittur DS, In vitroimmunomodulatory effects of ten commonly used herbs on murine lymphocytes, J AlternComplementMed, 2002, 8(4), 467-475.

61. Dhanalakshmi S, Singh RP, Agarwal C andAgarwal R, Silibinin inhibits constitutive andTNFalpha-induced activation of NF-kappaB and sensitizes human prostate carcinomaDU145 cells to TNFalpha-induced apoptosis,Oncogene, 2002, 21(11), 1759-1767.

62. Manna SK, Mukhopadhyay A, Van NT andAggarwal BB, Silymarin suppresses TNF-induced activation of NF-kappa B, c-Jun N-terminal kinase, and apoptosis, J Immunol,1999, 163(12), 6800-6809.

63. Saller R, Meier R and Brignoli R, The use ofsilymarin in the treatment of liver diseases, Drugs, 2001, 61(14), 2035-2063.

64. Dvorák Z, Vrzal R and Ulrichová J, Silybin and dehydrosilybin inhibit cytochrome P4501A1 catalytic activity: a study in human keratinocytes and human hepatomacells,CellBiolToxicol, 2006, 22(2), 81-90.

65. Varghese L, Agarwal C, Tyagi A, Singh RP andAgarwal R, Silibinin efficacy against human hepatocellular carcinoma, ClinCancerRes, 2005, 11(23), 8441-8448.

66. Fuchs EC, Weyhenmeyer R and Weiner OH, Effects of silibinin and of a synthetic analogue on isolated rat hepatic stellate cells andmyofibroblasts, Arzneimittelforschung,1997, 47(12), 1383-1387.

67. He Q, Osuchowski MF, Johnson VJ andSharma RP, Physiological responses to a natural antioxidant flavonoid mixture,silymarin, in BALB/c mice: I induction of transforming growth factor beta1 and c-myc in liver with marginal effects on other genes,Planta Med, 2002, 68(8), 676-679.

68. Singh RP, Dhanalakshmi S, Tyagi AK, ChanDC, Agarwal C and Agarwal R, Dietary feeding of silibinin inhibits advance human prostateCarcinoma growth in athymic nude mice and increases plasma insulin-like growth factor-binding protein-3 levels. Cancer Res,2002, 62(11), 3063-3069.

69. Lahiri-Chatterjee M, Katiyar SK, Mohan RR and Agarwal R, A flavonoid antioxidant,silymarin, affords exceptionally high protection against tumour promotion in theSENCAR mouse skin tumourigenesismodel,Cancer Res, 1999, 59(3), 622-632.

70. Singh RP, Sharma G, DhanalakshmiS,Agarwal C and Agarwal R, Suppression of advanced human prostate tumour growth inathymic mice by silibinin feeding is associated with reduced cell proliferation, increased apoptosis, and inhibition of angiogenesis, Cancer Epidemiol Biomarkers Prev, 2003, 12(9),933-939.

71. Yanaida Y, Kohno H, Yoshida K, Hirose Y,Yamada Y, Mori H and Tanaka T, Dietarysilymarin suppresses 4-nitroquinoline1-oxide-induced tongue carcinogenesis in male F344 rats, Carcinogenesis, 2002,23(5), 787-794.

72. Bhatia N, Zhao J, Wolf DM and Agarwal R, inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison withsilymarin, Cancer Lett, 1999, 147(1-2),77-84.

73. Katiyar SK, Treatment of silymarin, a plant flavonoid, prevents ultraviolet light-induced immune suppression and oxidative stress in mouse skin, Int J Oncol, 2002, 21(6),1213-1222.

74. Sharma Y, Agarwal C, Singh AK and AgarwalR, Inhibitory effect of silibinin on ligand binding to erbB1 and associatedmitogenicsignaling, growth and DNA synthesis in advanced human prostate carcinoma cells, MolCarcinog, 2001,30(4), 224-236.

75. Zhu W, Zhang JS and Young CY, Silymarin inhibits function of the androgen receptor by reducing nuclear localization of the receptor in the human prostate cancer cell line LNCaP, Carcinogenesis, 2001,22(9), 1399-1403.

76. Tyagi A, Agarwal C and Agarwal R, Inhibition of retinoblastoma protein (Rb) phosphorylation at serine sites and anincrease in Rb-E2F complex formation bysilibinin in androgen-dependent human prostate carcinoma LNCaP cells: role in prostate cancer prevention, MolCancerTher, 2002, 1(7), 525-532.

77. Tyagi A, Agarwal C and Agarwal R, The cancer preventive flavonoid silibinincauseshypophosphorylation of Rb/p107 and Rb2/P130 via modulation of cell cycle regulators in human prostate carcinoma DU145 cells, cell Cycle, 2002, 1(2), 137-142.

78. Dhanalakshmi S, Agarwal P, Glode LM andAgarwal R, Silibinin sensitizes human prostate carcinoma DU145 cells to cisplatin- and carboplatin-induced growth inhibition and apoptotic death, Int J Cancer, 2003,106(5), 699-705.