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Effectiveness of Milk Thistle on Human Body against Diseases: A Comprehensive Review

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Abstract

Milk thistle (Silybum marianum L.) is a baceous plant that belongs to the Asteraceae (daisy) family and is a member of the Carduae clan. Since antiquity, a several diseases has been treated by milk thistle such as to treat liver problems, spleen problems, gallbladder problems, hepatitis, and gallstones. Milk thistle seeds are utilized in herbal remedies, and there are six flavonolignans that make up silymarins: silychristin, silydianin, silybin A& B, isosilybin A & B. Because of its membrane-stabilizing qualities, silymarin is effective in chronic liver disorders. Many disorders, such as anti-cancer, anti-diabetic, anti-hypertenshaion, and anti- Alzheimer's, are caused by S. Marianum. Milk thistle is now utilized in a diversity of supplements, including oil seed and capsules of soft gel.

Keywords: Milk thistle, *Silybum Marianum*, silibinin, Ant oxidant, Protective, health benefits, liver diseases.

INTRODUCTION

Since ancient times, the milk thistle (*Silybum marianum* L.) has been used as a medicine to treat conditions affecting the liver, spleen, gallbladder, hepatitis, and gallstones. *S. marianum* was also used as being a bitter tonic and galactagogue to treat hemorrhoids and dyspeptic illnesses, as well as uterine haemorrhages, constipation, diabetes, hay fever, and varicose veins. (Livolti G, 2015). Silymarins, a family of chemicals found in milk thistle seeds, have been demonstrated to possess hepatoprotective properties, antioxidant, neuroprotective, anti-diabetic, & anticancer characteristics. The silymarins in seeds have six flavonolignans that make up silymarins: silychristin, silydianin, silybin A& B, isosilybin A & B. They are utilised in herbal remedies. (Mudge E *et al.*, 2015).

$C_{25}H_{22}O_{10}$ is the empirical formula for silymarin. The structural similarities between silymarin and steroid hormones are thought to be responsible for its protein synthesis facilitator activity. Silybin is the primary component of silymarin with the highest level of biological activity, accounting for 90% of the herb's component in most preparations. Silymarin is establish throughout the plants, although it has been particularly abundant in the fruits and seeds. Polyphenol, betaine, and essential fatty acids found in milk thistle seeds may contribute to silymarin's anti-inflammatory and hepatoprotective properties. (Das SK *et al.*, 2008).

Because of its membrane-stabilizing qualities, silymarin is effective in chronic liver disorders. It stimulates nucleolar polymerase A and increases ribosomal protein synthesis, promoting hepatocyte regeneration (Neumann U *et al.*, 2010). It possesses immune-modulatory properties and boosts interferon gamma, interleukin 4 and 10 secretion. (Beinhardt S *et al.*, 2012). It has been shown to normalize serum amino transferases in patients with long-lasting liver diseases, particularly continuing hepatitis C virus infection, and to prevent graft re-infection after orthotropic liver transplantation in patients with decompensate chronic

hepatitis C infection by inhibiting HCV particle entry into transplanted liver (Uchenna O *et al.*, 2014).

Silymarin may be the most effective antioxidant known to the environment due to its free scavenger re-activation and good membrane-lipid / water separation. NASH, a variant of NAFLD, is thought to play a role in the cause of oxidative stress, which is thought to be a "second strike" that causes the dramatic inflammatory response seen in NASH. Because patients have elevated levels of serum lipid peroxidation products as well as other symptoms of oxidative stress and low levels of antioxidant enzymes, the properties of silymarin's antioxidant can be very effective as a NASH treatment. In addition, oxidative stress is a critical component of HCV infection activity. Milk corn is found in capsules, tablets, mixtures, and dry powders, as well as phytosomes and liposomes, which are obtained and developed to increase flavonolignan availability (Javed S *et al.*, 2011).

Milk thistle looks to be safe and has a number of health benefits for cirrhosis, alcoholic hepatitis, alcoholic fatty liver, liver poisoning, and viral hepatitis, to name a few. Milk thistle is a medicinal herb which belongs to Asteraceae family and consist of different component such as essential oils, mucilage, tyramine, histamine as well as flavolignans and gamma linoleic acid. Silymarin consist of flavonolignan combination that includes silybin, while silybin is the main active component, and is the main element of milk thistle extract. It is best recognized for its hepatoprotective properties. In addition, research has revealed that it has an important role against the different diseases such as memory loss (Alzheimer disease), cancer, Parkinson's, & diabetic, thus its security is critical. In Salmonella typhimurium strains, silymarin was discovered to be mutagenic in the existence of metabolic enzymes. With its proven hepatoprotective actions, silymarin offers a variety of therapeutic effects, particularly in liver disorders (Vargas-Mendoza N *et al.*, 2014). Silymarin has very important clinical effects against Parkinson and Alzheimer disease. In experimental human hepatocytes, Alcohol-unrelated fatty liver disorder linked to silymarin (Federico A *et al.*, 2017; Marin V *et al.*, 2017). Silybin inhibits oxidative damage, hepatic fat formation, and insulin conflict. In the diabetic patients, silymarin is very help full low down the postprandial plasma glucose and HbA (1c) as well as fasting blood glucose (Hussain SAR, 2007; Voroneanu L *et al.*, 2016).

Therapeutic Significance of Milk Thistle

One of the most important medicinal herbs in the world is S. marianum. Since the first century, milk thistle has been utilized as a medicine throughout Europe. European cuisines have traditionally utilized its petals, roots and leaves as vegetables, and its fruits (achenes) have been used to create alternate to coffee. Silybum marianum seeds have been utilized as a natural liver and bile duct remedy for about 2000 years. Silymarin is a pharmacologically beneficial drug made up of four primary components: silybin from 50 to 60 percent, isosilybin 5 percent, silychristin 20 percent, and silydianin 10 percent (Ding TM *et al.*, 2001). Saturated fatty acids are abundant in milk thistle seeds. The seed has the potential to be used as a source of edible oil and protein for humans. However, before recommending this oil for edible purposes, it may be essential to refine it and feed it for a long time (Khan I *et al.*, 2007).

Role in Liver Improvement

Viral hepatitis

Silibinin is the major pharmacologically active component of silymarin, which is extracted from Silybum marianum milk thistle se.comeds. Silibinin helps the liver by removing toxins, reducing inflammation, and preventing free radical damage (Jennifer N *et al.*, 2020). Viral replication is unaffected by silymarin. Its inhibitory action on the inflammatory and cytotoxic cascade of events generated by viral infection disease may be advantageous in viral hepatitis (Saller R *et al.*, 2001). Its influence on protein synthesis can aid the regeneration process and normalise the liverenzymes (Savita S *et al.*, 1994). If pregnant women are unable to avoid alcohol, silymarin can help protect their unborn child from the harmful effects of alcohol. Silymarin only helps to attenuate some of the effects of alcohol. In NDEA-induced hepatotoxic rats, combination administration of Silymarin and garlic extracts was found to be more helpful than individual extract administration. These investigations suggest that plant extracts can be employed as hepatoprotective drugs with success (Shaarawy SM *et al.*, 2009). One study looked at 24 hepatitis C virus patients, both male and female (HCV) infection who had non-cirrhotic hepatitis and had failed to respond to interferon cure Patients were given oral silymarin in doses 140 mg, 280 mg, 560 mg, and 700 mg three intervals daily for seven days. At a dose of 280 mg, nausea and headache were noted. However, no drug-related side effects have been documented (Hawke RL *et al*, 2010). The principal active component of Silybum marianum, silibinin (silybin A & B), shows that antiviral action against herpes simplex virus type 2 (HSV-2) (Cardile AP *et al.*, 2017). In a metaanalysis study (including people with non-alcoholic liver disorder), taking 140 miligram of silymarin twice 12 weeks daily was shown to be safe, with no reported toxicity (Zhong S *et al.*, 2017). Silybum marianum seed formulas are commonly used in cases of poisoning in Amanita phalloides and in people with alcoholic liver disease (Saller R *et al.*, 2001; Wellington K *et al.*, 2001). For many years, silymarin has been utilized to treat chronic liver-related illnesses. Nonalcoholic fatty liver disease (NAFLD) is a clinical ailment that is not brought on by alcohol but rather by excessive fat buildup in the liver. Silymarin

therapy effectively lowers NAFLD (Cacciapuoti F *et al.,* 2013). According to Onaolapo OJ *et al.,* (2017), silymarin when combined with medications such as L-methionine has capable to protect the organ liver and kidney from acetaminophen overdose.

Anti-Cancer Activity

Cancer survival rates are low in developing countries, which may be due to the lack of effective treatment or late diagnosis. Silibinin resolves many potent chemo-preventive and anti-cancer therapeutic activities in a wide range of commonly found types of epithelial cancers, such as those of the skin, intestine, genital, and chest. Furthermore, many anti-cancer strategies that combine silibinin with other drugs show interactions that reduce drug toxicity and chemo-resistance (Reed D *et al.*, 2020). *S. marianum* could be a viable addition to BC therapy: when paired with chemotherapy medications such carboplatin, cisplatin, and doxorubicin, it has a synergistic effect on cancer cells (Binienda A *et al.,* 2020). In prostate cancer, silibinin derivatives also have anti-cancer effects (Manivannan E *et al.,* 2017). Cancer risk can be lowered, however, by raising public awareness of cancer-causing substances and correct treatment, encouraging physical activity, and eating a well-balanced, high-nutrient diet (Jemal A *et al.,* 2011). Previously, S. marianum was utilized for body detoxification and cleansing. It is currently employed in cancer research. It's also used to lessen the risk of hepatotoxicity during and after chemotherapy. Silybum marianum extract significantly reduces the negative effects of radiodermatitis. Polyphenolic antioxidants derived from Silybum marianum are well acknowledged as one of the most efficient cancer-prevention medicines (Agarwal R, 2000; Le Marchand L, 2002). Other studies have shown that SM can block cell cycle in the G1 / S phase by acting on cyclin-dependent kinase inhibitors such as p15, p21, and p27. SM also suppresses cell kinases & flammable recordings, in added to, that are involved in tumor proliferation of cells, invasion, and metastasis. By reducing the signaling pathways of STAT3 and ERK1 / 2, milk thistle can also reduce proliferation of cells, on cogenesis and genetic expression of iNOS in malignant cells, caspase activation and apoptotic cell death are also produced (Agarwal R *et al.,* 2007).

Antidiabetic Activity

Diabetes (DMT2) is an endocrine system metabolic disorder in which insulin resistance created to regulate glucose uptake into insulin dependent tissues, as well as hyperinsulinemia excess eliminating glucose intolerance. Because DMT2 is linked to an increased risk of heart disease, (Rahimi R *et al.,* 2018). The protective role of milk thistle against stress brought on by diabetes in rats was investigated. It was found that milk thistle lowered MDA and nitric oxide (NO) levels and prevented weight loss caused by diabetes. They also found that SM improved cardio logical metabolism induced by DM2 by altering the lipid profile (Henriksen EJ *et al.,* 2011). As we all know, Silybum marianum has an antioxidant impact since antioxidant medicines have been shown to be beneficial in the therapy of metabolic issues in diabetes (Stolf AM *et al.,* 2017; Ebrahimpour-Koujan S *et al.,* 2018). Another trial involved giving participants twice-daily Berberol tablets containing 588 mg of *Berberis aristata* extract and 105 mg of thorn milk with 45 diabetes and people with hypercholesterolemic. Although Berberol® was less toxic and well tolerated, it produced asthenia and headaches in some people. Additionally, one patient in the Berberol with statins group experienced a headache and short-term constipation, while two out of every 15 patients experienced cramps (Di Pierro F *et al.,* 2015). Silymarin supplementation may enhance T2DM patients' glycemic indices and lipid profiles, according to another study (Ebrahimpour-Koujan S *et al.,* 2018).

Antioxidant Activity

Inhibitors of oxidation are known as antioxidants. Free radicals are created during the chemical process of oxidation, and they can start a cascade of events that damage the cells of organisms. Cardiovascular illnesses, one of the most major causes of death worldwide, have also been linked to oxidative stress. According to the findings of a study, blood levels of free radicals in the group treated with milk thistle were lower than those in the group treated with *Corynebacterium psedotuberculosis*. According to the findings, milk thistle's antioxidant activity helps to prevent and treat oxidative stress. The antioxidant silymarin has been shown to protect against heart issues caused by oxidative stress caused by metals, anticancer medicines, and environmental contaminants (Razavi BM *et al.,* 2016). Oxidative stress has been linked to a variety of problems, including diabetes. Silymarin at 50 mg per kg orally avoided diabetes-induced stress, raised insulin levels, and later reduced glucose levels in diabetic rats by regenerating pancreatic cells (Amniattalab A *et al.,* 2016). The inhibitory activity of PTP1B has been found in flavonoids. These findings suggest that the extraction of milk thistle seeds can be used as a promising antioxidant and anti-diabetic treatment (Qin NB *et al.,* 2017). Extract of Silybum marianum L. was used to test the effect of enhancing memory. Anti-cancer silibinin properties have been discovered to affect the cell cycle, serine or threonine protein kinase, tumour suppressor p53, and survival signalling proteins in skin carcinogenesis (Dheeraj A *et al.,* 2017).

Cardio-Protection

Some of the illnesses that could develop as a result of using SM include ischemia, hypertension, atherosclerosis, vascular dysfunction, and hypertrophy of the heart (Taleb A *et al.,* 2018). During the treatment of acute myocardial infarction (MI), the most common

symptom of ischemic heart disease, myocardial I/R is an unavoidable complication (Eapen ZJ *et al.,* 2012). Silybum marianum promotes cardio-protection and inhibits unfavorable remodeling post-myocardial infarction by reducing oxidative stress and reactive fibrosis, according to a study. Another study discovered that SM intake protects the heart from the negative consequences of a MI and promotes cardiac repair. The antioxidant and anti-fibrotic effects of SM may be responsible for these advantages (Vilahur G *et al.,* 2018). Cardiotoxicity, which is believed to be mediated by oxidative stress and apoptosis activation, limits the use of some chemotherapeutic drugs such as doxorubicin during cancer therapy. Because of its antioxidant and membrane-protective characteristics, silibinin has such cardioprotective benefits (Chlopčíková Š *et al.,* 2004). Regarding SM's immunomodulatory function, it has been found to have immune-stimulatory and immunosuppressive effects on a variety of illnesses, including CVDs that are dose- and time-dependent. In vitro investigations have revealed that milk thistle protects the components of immune system by inhibiting the activation of the MAPK & NF-B signaling pathways and restoring the function of the nuclear factor 2 (Nrf2) signaling pathway. Silymarin appears to decrease both inflammation and oxidative damage through altering NF-B signaling (Kim EJ *et al.,* 2015).

Blood Disorders

Oral tablet use had no negative consequences in kids with acute lymphoblastic leukemia and liver disease. The magnitude and frequency of adverse effects were comparable to the control group. The therapeutic dose of silibinin was 5.1 mg/kg per day, and each capsule delivered a standard dose for 28 days (Ladas EJ *et al.,* 2010). Using 420 mg of silymarin daily for six months, researchers looked into the impact of silymarin on interleukin levels in the blood of beta thalassemia patients, with no adverse effects reported (Balouchi S *et al.,* 2014). For 9 months, beta thalassemia patients were given a dose of silymarin 420 mg / day to reduce iron and serum ferritin levels, as well as desferrioxamine. Silymarin has been found to be safe in this trial, with no side effects (Darvishi Khezri H *et al.,* 2016).

Tuberculosis

Antiretroviral therapy recipients with tuberculosis were given one silymarin (140 mg) tablet every eight hours. At 2 and 4 weeks following the study's start, silymarin did not have any harmful side effects. After eight weeks, this dosage of silymarin in another trial showed no negative effects (Luangchosiri C *et al.,* 2015). Clinical examinations of patients with TB who had poor vision did not show any negative effects after taking 140 mg of silymarin orally three times per day for two weeks. There have also been reports of anorexia and other nausea-related digestive issues (Marjani M *et al.,* 2016).

Anti-Amnesia Effects

In a scopolamine-induced amnesia animal model, methanol extraction of SM seeds inhibited acetylcholinesterase and buteryl cholinesterase in a concentration-dependent manner, with IC 50 values of 110g/mL and 130 g/mL, individually, and also demonstrated anti-amnesia efficacy. In addition, encouraged fit cutting was performed on quercetin, rutin, and morin, and the IFD scores of these compounds were comparable with their experimental acetylcholinesterase inhibitory effects. These chemicals, however, are not the primary components of SM seeds. Further research into measuring and analysing flavonolignans' acetylcholinesterase inhibitory action is needed, according to our findings (Nazir N *et al.,* 2018).

Some other Effect of Milk Thistle

In 60 people with cancer, there were no side effects by taking 140 mg of silymarin twice a day for seven days before taking cisplatin (Momeni A *et al.,* 2015). According to one study, beta thalassemia patients can safely take deferiprone (2040 mg/kg per day) and 140 mg silymarin three times a day for six months. Silymarin also had an iron deficiency, and after discontinuation of treatment, ferritin and iron levels decreased, but the concentrations of serum creatinine, alanine aminotransferase, and aspartate aminotransferase did not alter (A Hagag A *et al.,* 2015). Silymarin's protective effects have been studied in a variety of neurological diseases, including Alzheimer's disease, Parkinson's disease and cerebral ischemia. By lowering oxidative stress, inflammatory cytokines, apoptotic cellular machinery, and estrogen receptor processes, silymarin safeguards the brain (Borah A *et al.,* 2013). According to studies, silybin is made up of two diastereoisomers: silybin A & B. Silybin, is an anti-hepatotoxic medication that has both a 1, 4-dioxane ring and a flavonoid component. It has been demonstrated that the antioxidant activity of silybin is increased by the presence of a 2, 3-double bond in the C-ring of a flavonoid structure (Ahmed B *et al.,* 2003; Khan SA *et al.,* 2011).

Mechanism of Liver Disease

The hydrophobic-hydrophilic interface of the microsomal bilayer is merged with silymarin and its constituents, changing how the acyl chains are packed and regaining the fluidity of the mitochondrial and hepatic microsome membranes. Silymarin seems to function as an antioxidant in ways other than just scavenging the free radicals responsible for lipid peroxidation, but also via altering glutathione and superoxide dismutase enzyme systems, particularly by boosting nuclear transcription components' expression and activation (Vladimir-Knežević S *et al.,* 2015).

Silymarin's hepatoprotective actions appear to be primarily dependent on five characteristics;

- Free radical scavenging activity and the potential to enhance glutathion levels in cells protect against lipid peroxidation (GSH)
- In the presence of xenobiotic damage, the ability to promote membrane stability and regulate membrane permeability
- Capacity to control nuclear expression via a steroid-like effect (because to silymarin's structural resemblance to steroid hormones), followed by tissue regeneration.
- The transformation of latent hepatic stellate cells into activated myofibroblasts, which are responsible for the deposition of collagen fibres that cause cirrhosis, is blocked.

Reduced hepatic inflammation and inflammatory cytokines as a result of anti-inflammatory effect, potentially as a result of reduced tissue damage.

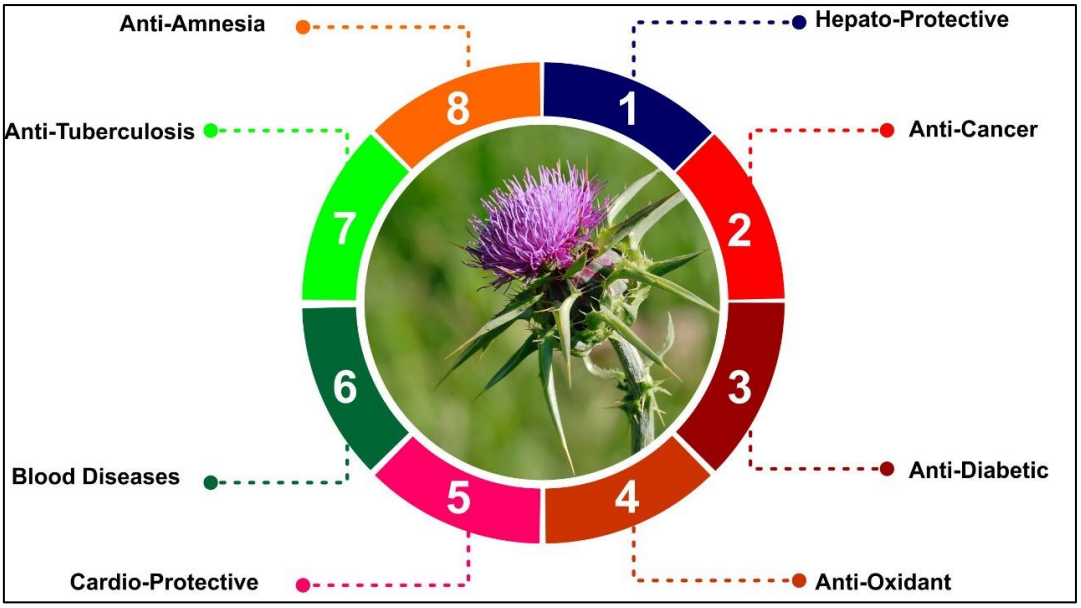

Fig-1: Shows the some therapeutic uses of silymarin

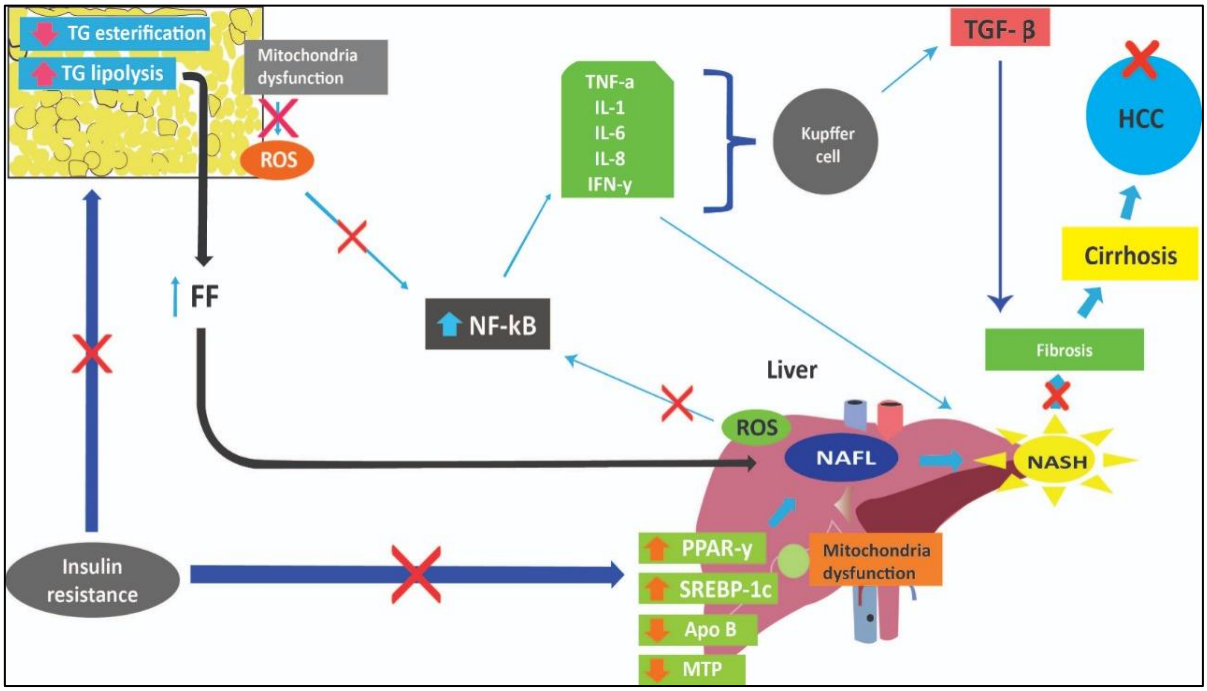

Fig-2: Mechanism of Liver Disease shown in fig

Mechanism of diabetes disease

A prior study found that silibinin concentrations of 50–300 mM have a significant impact on hepatic glucose metabolism. The metabolic processes that contribute to glycaemia maintenance, gluconeogenesis in the fasted state and glycogenolysis and glycolysis in the fed state, were both inhibited by silibinin, supporting the liver's role in silibinin's anti hyperglycemic effect. The processes through which silibinin accomplishes these effects are numerous and complex, as seen in the diagram (Colturato CP *et al.*, 2012).

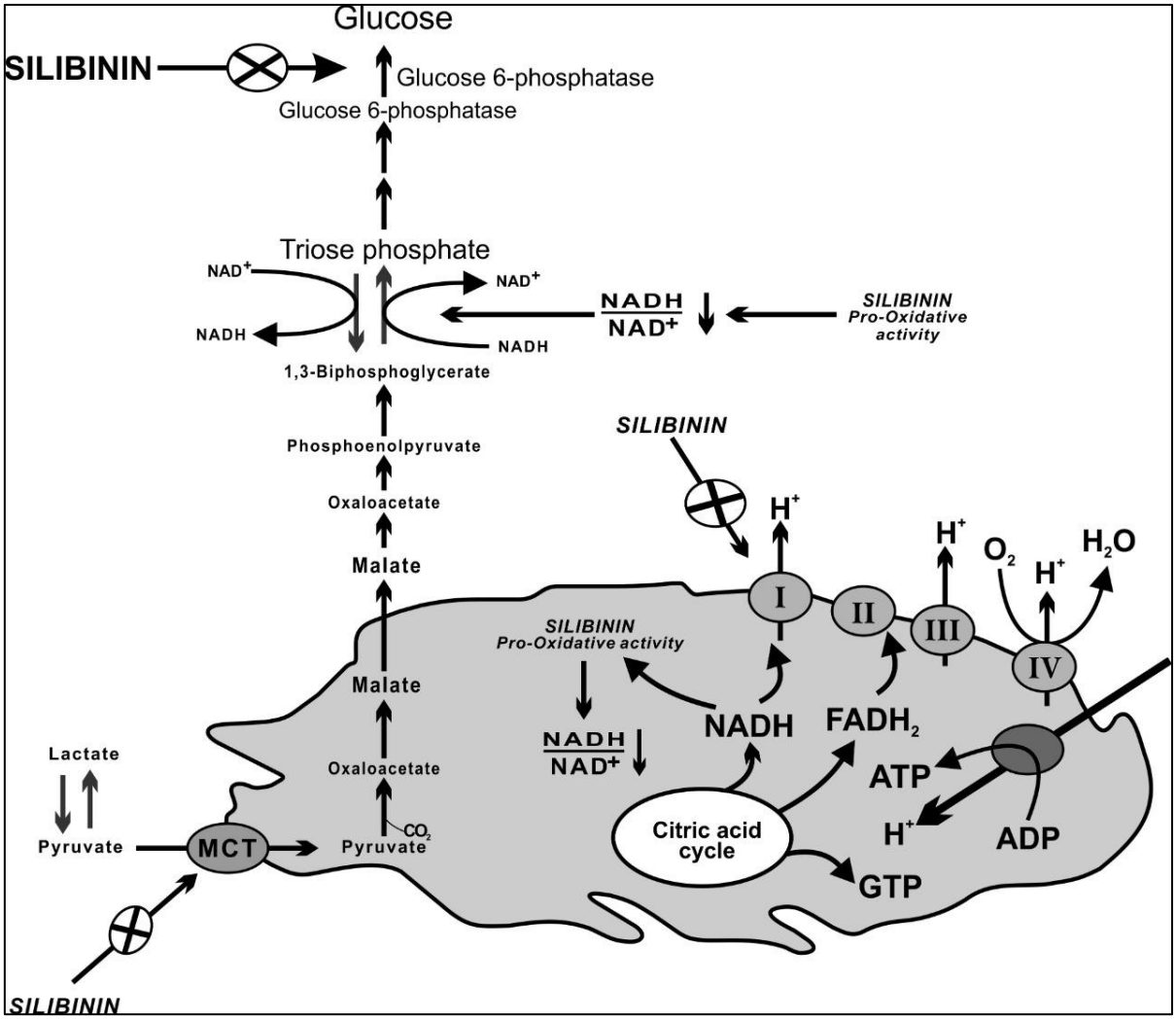

Fig-3: Mechanism of diabetes shown in fig

Mechanism of NAFLD:

NAFLD, or nonalcoholic fatty liver disease, is the primary cause of liver disease in Western countries. It is caused by poor eating habits and a sedentary lifestyle. There are currently no licensed medications for this indication, hence the main therapeutic suggestion as a first step is lifestyle adjustment, which includes both dietary changes and increased physical activity. The discovery of the molecular pathways that cause fat accumulation, oxidative balance deterioration, and liver fibrosis will likely improve both diagnostic and therapeutic approaches Food bioactive substances that control the activation of genes implicated in lipogenesis, fibrogenesis, lipid peroxidation, and inflammation constitute a novel and appealing treatment approach for this disease (Dongiovanni P *et al.*, 2016).

Milk Thistle Supplements

Milk Thistle Oil

Extract from mature milk thistle seeds has been proven to have clinical usefulness in numerous liver illnesses, including hepatitis, cirrhosis, and alcoholic liver disease (Pepping J, 1999). The use of a microwave can improve the yield of oil extraction. Furthermore, the oil extraction yield rose as the treatment time of the extraction process increased; 2 and 4 minute pretreatment milk thistle samples yielded 32.33 percent and 35.41 percent oil by solvent, respectively, compared to non-treated seeds oil (29.43 % (Fathi-Achachlouei B *et al,* 2019). The seeds' oil content ranged from 26 to 31 percent. Linoleic acid had highest value (50–54%) of all the fatty acids, oleic (23–

29%) and palmitic (6.5–8%) acids. The most prevalent sterols were 4-desmethylsterols (between the range of 1,800 to 2,200 lg per gram), 4-monomethylsterols (26–35 lg/g) and dimethylsterols (50–85 lg per g). The concentrations of a-, b-, c-, and d-tocopherols in the oil ranged from 187 to 465 lg/g, 10 to 51 lg/g, 9 to 12 lg/g, and 18 to 80 lg/g, respectively. According to the findings, the extracted oil of seeds is high in fatty acids, vitamin E, and sterols, making it a good choice for mixing with other vegetable oils or using alone in food preparation (Fathi-Achachlouei *et al.*, 2009).

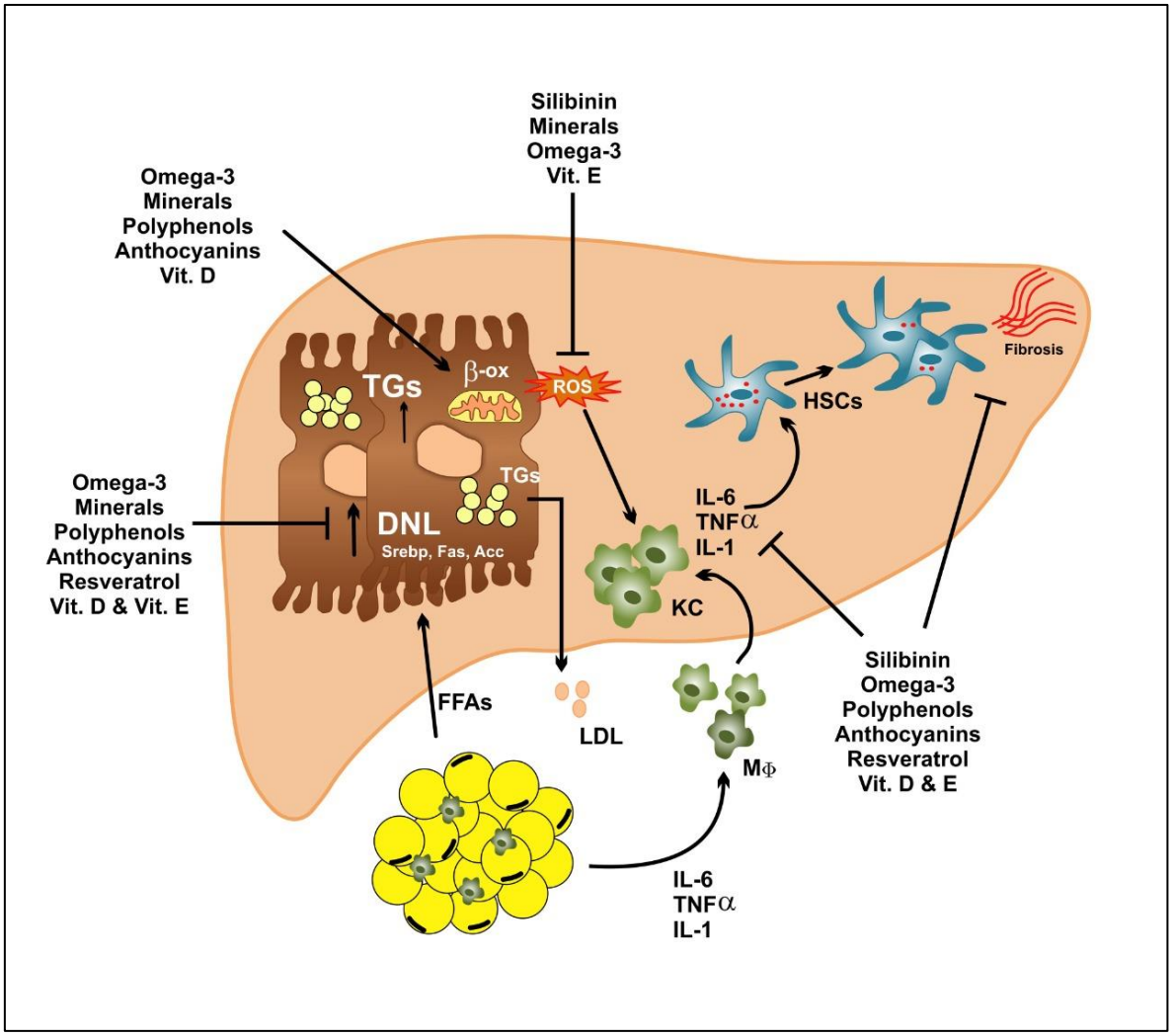

Fig-4: Shows the different steps involved in Mechanism of NAFLD

Milk Thistle Soft-Gel

Silybin was administered with Realsil in two different pharmacological formulations (capsules and granules, both corresponding to 47 mg of silybin). After a week of washout, the data were compared to those obtained by administering silymarin granules and capsules, each containing 58 mg and 80 mg of silybin, respectively. When compared to standard SM tablets, in oily-medium soft-gel capsules, SIB bioavailability is 9.6 times greater when combined with SPC. Several investigations in animals and humans have shown that silybin complexed with phosphatidylcholine has a higher bioavailability than SIB that has not been complexed (Méndez-Sánchez N *et al.*, 2019).

Milk Thistle Capsules

The pulverized dried milk thistle sample was manually put into the empty capsules. Some pills included 200 milligrams of ground sample, whereas others had 400 milligrams of ground material. To avoid contamination, milk thistle was encapsulated in a microbiology laboratory. In a separate investigation, the entire *Silynum marianum* plant will be dried, crushed, and capsules made. The extract will be 200 milligrams each capsule. The albino rats with CCL4-induced hepatitis will be fed these capsules (Khan I *et al.*, 2007).

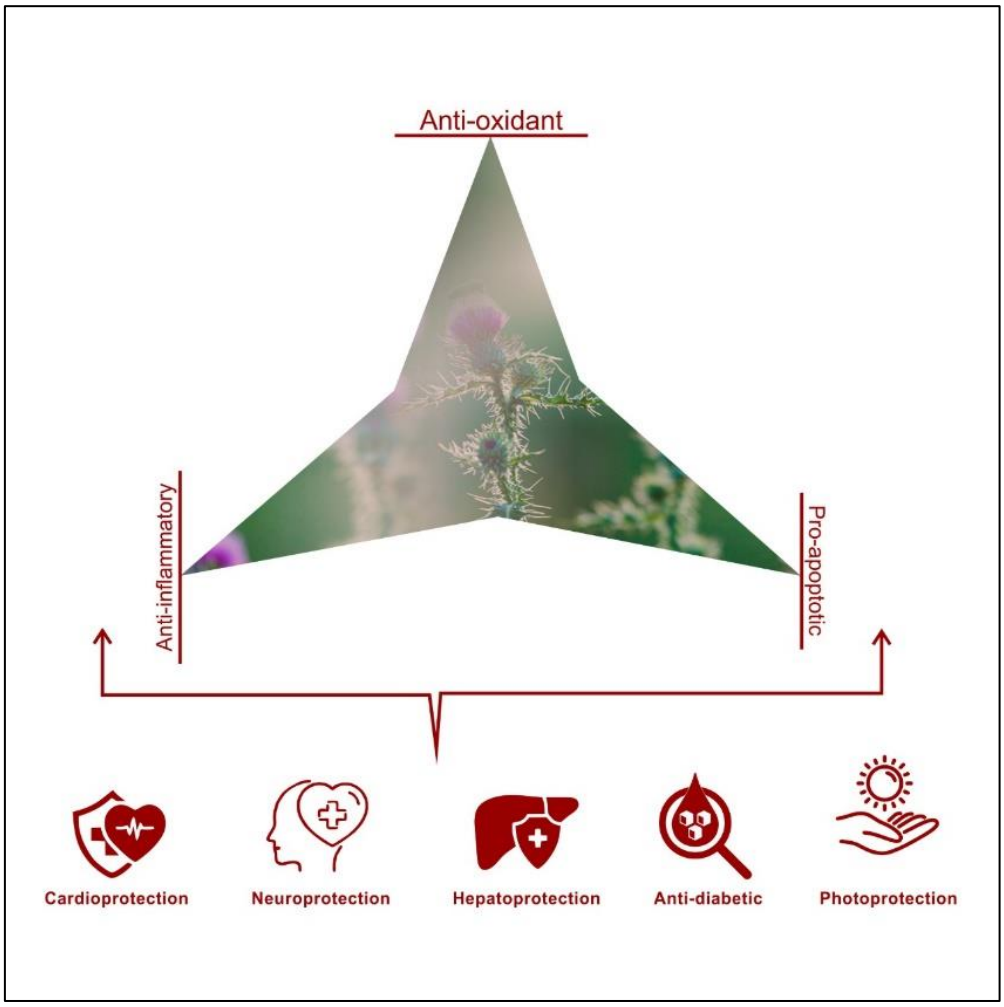

Fig-5: SM and some of its most important features

CONCLUSION

This review demonstrates that *Silybum marianum* is a multifunctional extract capable of producing results in in vitro research, animal studies, and human studies by changing cell signaling pathways. As a result, it has been utilized in photo-protection creams as well as the treatment and prevention of diseases like cancer. Anti-inflammatory, antioxidant, and pro-apoptotic qualities make up the so-called "functional trinity" that is put forth by SM. This triumvirate can be used to prevent the beginning and progression of harmful mechanisms that cause a variety of diseases. Numerous investigations have shown that the *Silybum marianum* extract can be used to treat a wide range of illnesses and diseases. It has been used for millennia. Despite the numerous studies demonstrating the advantages of SM, caution should be used when using it on a large scale in humans because there are still few clinical trials demonstrating the right dosage and the true usefulness of this extract in treating a variety of illnesses. As a result, additional studies are required to confirm the safety of applying the SM to the wide range of illnesses covered in this study.

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