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MILK THISTLE (*SILYBUM MARIANUM*): AN OVERVIEW ABOUT ITS PHARMACOLOGY AND MEDICINAL USES WITH AN EMPHASIS ON ORAL DISEASES

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ABSTRACT

Milk thistle (Silybum marianum L.) is a baceous plant that belong to the Asteraceae family and is a member of Cardue clan. Since antiquity, a several diseases have been treated by milk thistle such as liver disease, spleen problem, gallbladder problem, hepatitis and gallstones. Milk thistle seed are utilised in herbal remedies, and there are six flavonolignans that make up silymarin: silychristin, silydianin, silybin A&B, isosilybin A & B. because of its membrane stabilizing qualities, silymarine is effective in chronic liver disease. 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 and stimulation of 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. Milk thistle is now utilized in a diversity of supplement, including oil seed and soft gelatine capsule.

KEYWORDS: Milk thistle, silymarin, Silybum marianum, silydianin.

INTRODUCTION

Since ancient times, the milk thistle has been used as medicine to treat condition affecting the liver, spleen, gallbladder, hepatitis and gallstones. Silybum marianum was also used as a bitter tonic and galactagogue to treat haemorrhoids, constipation, diabetes, hay fever, and varicose veins.[1] C25H22O10 is the empirical formula for silymarin. The structural similarities between silymarin and steroid hormones are thought to be responsible for protein synthesis facilitator activity. Polyphenol, betaine, and essential fatty acids found in milk thistle seed may contribute to silymarin's anti-inflammatory and hepatoprotective properties.[2]

Apart from the liver disease, silymarin effects have also been indicated in various illnesses of different organ such as prostate, lungs, central nervous system, kidneys, breast, pancreas and skin.[3] Silymarin has ability to antagonize the toxin of Amanita phalloides (poisonous basidiomycete fungus).[4]

The long-term effect of the use of milk thistle brings about the following side effects: allergy, insomnia, itching, bloating and diarrhoea. Because of the lack of conclusive findings on the safety of milk thistle, it is not advisable to be used by children and pregnant women and if it is to be used it must be recommended by doctor.

- **The general benefits of milk thistle are**

1. It provides safety for the liver against invading disease.
2. It manages and slows down the deterioration of the brain processes due to advancing age.
3. It contributes to the treatment of cancer
4. It aids in increasing the breast milk production in lactating mothers.
5. It helps in reducing the high sugar blood level of diabetic patients.

Silybum marianum seeds have been utilized as a natural liver and bile duct remedy for 2000 years. Silymarin is a pharmacologically beneficial drug made up of four

primary components: silybin (50 to 60%), isosilybin(5%), silychristin(20%), and silydianin(10%).[5]

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.

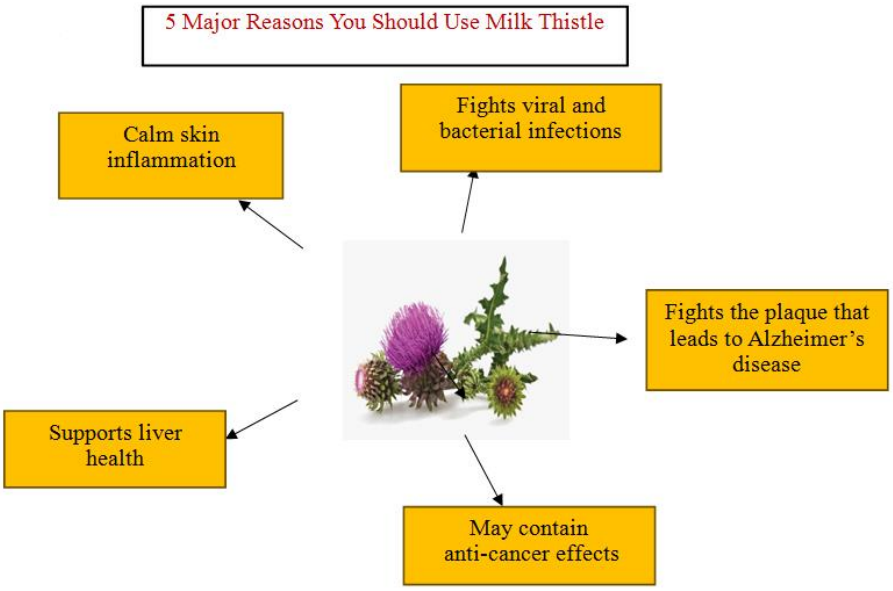


Figure 1: Therapeutic effect of Milk Thistle.

- **Anti-oxidant properties of silymarin**

Reactive oxygen species (ROS), which are mostly linked to detoxification activities are spontaneous created in the liver as part of necessary metabolic reactions. Excessive fatty acid oxidation and exposure to high quantities of toxins, such as alcohol or hepatotoxic medication can result in aberrant ROS generation and the depletion of endogenous antioxidants. Hepatocytes, Kupffer cells, endothelial cells and inflammatory leukocytes, ethanol is known to encourage the generation of free radicals.[6] This imbalance referred to as oxidative stress has been linked to the onset of several liver conditions including liver fibrosis.[7]

In vitro research has demonstrated that Silibinin has potent anti-ROS qualities including the capacity to scavenge peroxyl anions and hydroxyl, superoxide anion radicals, hypochlorous acid, and nitric oxide.[8] It has been demonstrated that silibinin treatment reduces ROS production in Kupffer cells, silymarin the precursor to silibinin can increase glutathione production and hence increase liver tissue' anti-oxidant properties.[9]

In several different method silymarin protects liver cells. It prevents lipid peroxidation, which supports the maintenance of endogenous protective antioxidant glutathione levels and stabilize membrane permeability.[10] Silymarin a natural flavonoid complex from milk thistle has been shown to inhibit the production of pro-inflammatory cytokines, such as TNF-α, INF-ϒ, IL-2 and IL-4, which are crucial in the inflammatory cascade and immune response. This has significant therapeutic implications for hepatoprotection, as it shields against damage from harmful substances like carbon tetrachloride, which trigger oxidative stress and inflammation. Silymarin mechanism involves suppressing NF-kB activation, which regulates the expression of pro-inflammatory genes. This makes silymarin a promising candidate for addressing hepatic disorder linked to inflammation and oxidative stress.[11]

The regulation of inflammation in the liver is achieved by inhibiting hepatic nuclear factor kappa B activation. Nuclear factor kappa B is a key transcription factor involved in inflammation, immune response and cell survival. It down regulates inflammatory mediators like interleukins, TNF-α which are involved in various diseases. NF-kB inhibition also modulates cellular signalling pathway such as the mitogen activated protein kinase (MAPK) pathway, potentially mitigating damage to cellular components. Therefore, targeting nuclear factor kappa B as a therapeutic strategy is crucial in hepatic inflammatory conditions.[12]

Silymarin a natural compound from milk thistle plant has hepatoprotective mechanism that prevents the reception of xenobiotics, including toxic substances found in mushrooms, by hepatocyte surfaces. It inhibits organic ion uptake transporter, which facilitate the transport of substances across the membranes. This prevents harmful substances from entering hepatocytes, reducing the risk of cellular damage. Silymarin's interference with these transporters is part of its broader hepatoprotective mechanism, contributing the overall defence against toxic insults.[13] Silibinin is the major active constituents of silymarin, is renowned for its potent antioxidant effects, which involve scavenging reactive oxygen species (ROS) and inhibiting oxidative stress

pathways.[14] These antioxidant properties are frequently cited as the primary drivers of silibinin's hepatoprotective benefits.

One of the mechanisms responsible for the decrease in oxidative stress is the protective effect of silymarin on mitochondrial structure and function. Silymarin protects mitochondria from pathological events by triggering pro-survival cell signalling. For example, silymarin supplementation is shown is shown to optimize electron transport chain, decreasing electron leakage and ROS formation and directly reducing activities of ROS producing enzymes in the mitochondria.[15]

Silibinin was evaluated for its protective effect against beta-adrenergic agonist isoproterenol-induced injury in cultured rat neonatal cardiac myocytes.[16] It was shown that silibinin addition was associated with increased SOD activity and upregulated mitochondrial membrane potential and with a prevention of mitochondrial dysfunction and cell injury.[17]

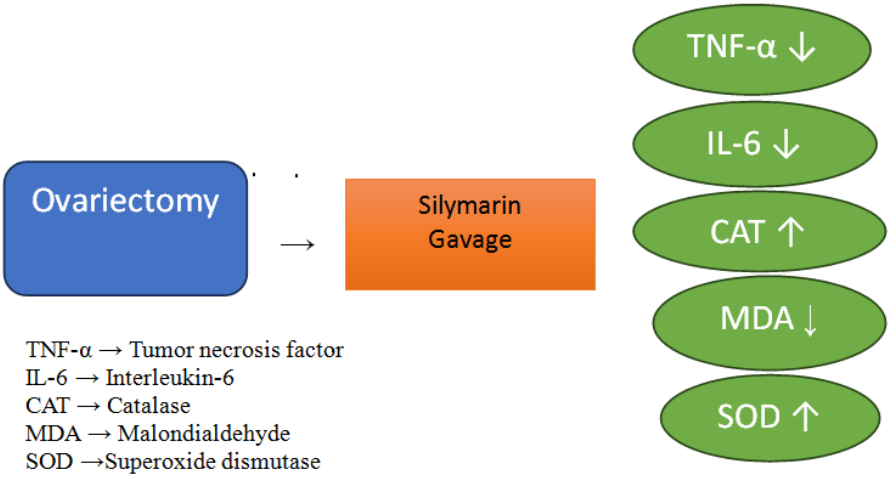
Cardiovascular illness, one of the most major causes of death worldwide, have also been linked to oxidative stress. According to the finding of the study, blood levels of free radicals in the group treated with milk thistle were lower than those in the group treated with Corynebacterium pseudotuberculosis. 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.[18] 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.[19] The inhibitory activity of PTP1B (protein tyrosine phosphatase 1B) has been found in flavonoids. These findings suggest that extraction of milk thistle seeds can be used as a promising anti-diabetic and anti-oxidant treatment.[20] Extract of Silybum marianum L. was used to test the effect of enhancing memory.

Toxin exposure can cause oxidative stress in hepatocytes, leading to the generation of reactive oxygen species (ROS) and oxidative stress. Silymarin, specifically silibinin, counteracts these harmful effects by preventing TNF-α development and exhibit antioxidant activities.

- **The role of silymarin in Mitigating Inflammation and Cognitive impairment Induced by Ovariectomy**

Estrogen is primarily produced in the ovaries and after menopause when their production stops estrogen levels in the bloodstream decrease drastically. This decrease in estrogen levels is significant because it can lead to an increased risk of chronic kidney disease, which is more frequently observed after menopause. Estrogen normally helps to reduce renal superoxide production and protect the kidneys from oxidative damage.[21] The effects of menopause on oxidative stress and inflammation are particularly important in the field of osteoporosis because all these factors contribute to bone loss.[22] Estrogen which can cross blood brain barrier and are also endogenously produced in the brain from cholesterol have been shown to affect various aspects of mitochondrial function. Specially they modulate ATP and reactive oxygen species (ROS) production, oxidant defence, mitochondrial membrane potential and calcium levels.[23,24]

Sex steroid such as estrogen can modulate behaviour, cognitive and memory. Estradiol a form of estrogen has a crucial trophic effect on memory and executive function in basal forebrain and hippocampus. Estrogens also mediate neurotransmitter interactions in the prefrontal cortex which is related to executive functions.[25,26] Specifically rats that underwent ovariectomy showed a significant increase in hydrogen peroxide production in liver mitochondria and peroxisomes, as well as a decrease in antioxidant enzyme activity.[27] On the other way estrogen can protect against the progression of chronic liver diseases by reducing inflammation, improving mitochondrial functions and lowering oxidative stress levels.[28] Milk thistle particularly its active compound silibinin can interact with estrogen levels and act as a weak estrogen agonist. Milk thistle contains silibinin which has been shown to bind to estrogen receptors, particularly Erβ and can exhibit estrogen like effect.[29]



Silymarin is a compound from milk thistle that has six flavonoid isomers, with silybin being most active.[28,29] Certain amounts of silymarin can lower the secretion of IL-1β and TNF-α, inhibit phosphorylation of p65 NF-kB and p38 MAPK (mitogen activated protein kinase), and block NF-kB activation by decreasing p65 subunit phosphorylation.[30,31]

Luo et al. found that 1 month of ERT improved spatial learning capacity and myelin sheath in OVX rats. Another study found that silymarin injection also improved spatial learning capacity in OVX rats. These finding suggest that estrogen and silymarin injection may be effective in improving memory after menopause.[32]

A study by Tao et al. showed that administration of ammonium ferric citrate to OVX rats resulted in decreased level of SOD2 and total antioxidant capacity and increased levels of MDA in serum. However, treatment with silymarin reduced oxidative stress in the serum of these rats. That's why we can conclude that silymarin is able to reduce oxidative stress by decreasing MDA and increasing SOD2 levels.[33]

- **Anti-cancer activity of Silymarin**

Low cancer survival rates in developing nations could be caused by delayed diagnosis or ineffective therapy. The first observation of silymarin's possible benefits in cancer is the 1991 publication by Mehta and Moon.[34] They demonstrated that silymarin could prevent cancer in mice mammary glands treated with tetradecanoylphorbol acetate (TPA) and dimethylbenzanthracene (DMBA).

In a variety of frequently occurring epithelial cancer types, including those of the skin, gut, genital, and chest, silibinin has numerous strong chemopreventive and anti-cancer therapeutic effects. A derivative of silibinin exhibits anti-cancer properties in prostate cancer.[35] S. Marianum was used to cleanse and detoxify the body. Currently, it is used in studies on cancer. During and after chemotherapy, it is also used to reduce the risk of hepatotoxicity. Extract from Silybum marianum considerably lessens the harmful effects of radiodermatitis. One of the most effective medications for preventing cancer is the polyphenolic antioxidant that is extracted from silybum marianum.[35] By interacting with cyclin-dependent kinase inhibitors like p15, p21, and p27, SM can stop the cell cycle in the G1/S phase. Additionally, SM inhibits flammable recordings and cell kinase, which are implicated in tumor cell invasion, metastasis, and proliferation. Milk thistle can also decrease cell proliferation by inhibiting the STAT3 and ERK1/2 signaling pathways. It also has an effect on the cogenesis and genetic expression of iNOS(inducible nitric oxide synthase) in cancerous cells, which results in caspase activation and apoptotic cell death.[36]

Additionally, silymarin inhibits the cytosolic glutathione S-transferase in the rat liver, though this function does not directly suggest anticancer potential.[37] Silymarin exhibits anti-inflammatory properties comparable to indomethacin, scavenges reactive oxygen species, inhibits the metabolism of arachidonic acid in human cells, and shields skin from UV rays and carcinogens.[38] Scambia et al.examined silymarin's antiproliferative properties on human ovarian and breast cancer cell lines and discovered that it inhibited their growth.[39]

=> Silymarin Synergizes with Anticancer Drugs to Induce Apoptosis <=

Drug toxicity and chemo-resistance are decreased by interactions between silibinin and other medications in several anti-cancer treatments.[40] Combination of silymarin with paclitaxel has a synergistic effect that can i) raise the Bax/Bcl-2 ratio by inhibiting the expression of the Bcl-2 gene in gastric and prostate cancer cell lines.[41,42] Combinations of silibinin with platinum compounds, such as cisplatin, carboplatin, and oxidovanadium complex, were similarly successful in triggering apoptosis.[47,48] A combination of doxorubicin and silibinin that works together to trigger and stop the cell cycle during the G2/M phase can also work together to increase apoptosis in lung tumor cells[44], prostate cancer cells[46], breast cancer cells[45], and hepatoma cells.[43]

Silymarin coadministered with chemotherapeutic drugs has the ability to reduce toxicity in normal organs. It protects adults and children receiving leukemia treatment from the liver and renal toxicity brought on by methotrexate.[49,50] Silibinin reduced the nephrotoxicity of cisplatin without compromising its antitumoral efficacy.[51] Despite being less effective than quercetin in this regard, it shields the heart from doxorubicin toxicity.[52] Silymarin reduced docetaxel central and peripheral neurotoxicity.[53] Silymarin reduced hepatotoxicity in patients with nonmetastatic breast cancer receiving doxorubicin/cyclophosphamide paclitaxel.[54]

- **The Therapeutic Potential of Milk Thistle in Diabetes**

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.[55]

A randomized controlled trial tested milk thistle on people with type II diabetes.

The study involved 40 diabetic adults, aged 25-50, who were on anti-diabetic medications. They were given either a pill containing 140 mg of silymarin (an extract of milk thistle), or a placebo, three times daily for 45 days.[56]

Compared with the placebo, milk thistle extract[56]

- Reduced fasting blood sugar by 11%,
- Reduced blood insulin levels by 14%,
- Reduced insulin resistance, when cells ignore insulin's signal to remove sugar from the blood, by 26%,
- Reduced triglyceride levels by 24%,
- Raised HDL ("good") cholesterol by 7%,
- Reduced the **triglyceride-to-HDL** ratio by 28%
- Increased insulin sensitivity, how well cells respond to insulin, by over 5.5%.

Several studies have proposed the hepatoprotective effects of silymarin on diabetes.[57] These medications reduce MDA (a final lipid-oxidized product) and raise SOD (an antioxidant enzyme) levels in rats with non-alcoholic fatty liver disease (NAFLD). Its antioxidant action may contribute to this effect. Milk thistle also effectively protected the liver from lipid accumulation and severe hepatic changes.

The development of human islet amyloid polypeptide deposits in pancreatic beta-cells is a critical factor in the declining ability to produce insulin in the great majority of patients with type 2 diabetes. Through the inhibition of fibrillation, enhancement of oligomerization, and reduction of beta-cell cytotoxicity of human islet amyloid polypeptide (hIAPP) in a dose-dependent manner, silibin appears to be able to increase the viability of pancreatic beta-cells.[58] Silibin has been demonstrated to reduce hepatic glucolysis via inhibiting pyruvate kinase (PK) and lowering DHA phosphorylation, both of which are caused by a drop in ATP levels. The entire antioxidant capacity is unlocked at concentrations between 25 μM and 100 μM. Silibin suppresses ROS generation due to DHA metabolism even at a low dose of 10 Mm.[59]

Prior studies have demonstrated that, in comparison to its traditional variation, the use of silibin nanoparticles significantly increases its hypoglycemic effect in STZ-induced diabetic mice. Additionally, as compared to animals treated with traditional silibin, the levels of HbA1c, insulin, cholesterol, triglycerides, liver enzyme levels, and antioxidant status parameters (such as glutathion (GSH), catalase, and superoxide dismutase (SOD)) are comparable to those of healthy controls. Another study found that silimarin was effective in bringing the levels of SOD, glutathione peroxidase (GSHPx), and catalase (CAT) back to levels comparable to the control group. This suggests that silimarin is a free-radical scavenger that can shield the pancreas from additional harm caused by alloxan.[60,61]

- **Role of silymarin in Viral Hepatitis**

The potential of silymarin as a supportive treatment for viral hepatitis has been limited by the availability of safe and effective direct antiviral medications. However, silymarin may benefit those with acute or chronic hepatitis, according to a number of studies. Since silymarin is only authorized for liver support and not for the direct treatment of viral hepatitis, this distinction is crucial. For the HALT-C trial, patients with advanced fibrosis or cirrhosis who had not responded to traditional treatment supplied baseline data on silymarin use.[62,63] At the time of the baseline assessment, 16% of the 1049 patients had been using silymarin for an average of 35 months, and 16% had previously taken it for an average of 6 months. Although silymarin had no effect on clinical outcomes, its use was significantly associated with a later onset of histologic liver disease, as seen by lower levels of hepatic collagen in biopsies.[64,65]

In another study, low-dose multivitamin supplements or the commercial silymarin formulation (Eurosil 85®) were used to treat Egyptian patients with chronic hepatitis C. Both groups' weight loss and fatigue symptoms had considerably improved from the start at the 12-month follow-up. After using silymarin, patients experienced significant relief from their heartburn and nausea symptoms. The silymarin group saw fewer cases of jaundice and black urine, while the difference was not statistically significant.[66]

The Eurosil 85® silymarin formulation significantly reduced symptoms in an 8-week randomized, placebo-controlled investigation of acute viral hepatitis patients in Egypt. Patients who received silymarin saw a quicker

resolution of biliary retention symptoms, including dark urine, jaundice, and scleral icterus, in comparison to those who got a placebo.

Indirect bilirubin levels in silymarin recipients were significantly decreased at day 56. Nevertheless, no discernible variations in any hepatocellular damage markers were found across the groups.[67]

Numerous research has looked into silymarin's possible synergistic benefits when used with traditional antiviral medications. Sbstances like interferon. Although initial results point to a potential additive advantage, further extensive, carefully planned studies are required to provide definitive confirmation of these findings.

The use of silymarin for viral hepatitis has not received much attention because direct antiviral medications are now readily available; however, our findings suggest that silymarin could be helpful in supportive therapy.

- **Role of silymarin in Renal protection**

The impact of silymarin has been examined in rat models of diabetes mellitus produced by alloxan. Renal tissue is harmed by reactive oxygen species (H2O2, O2, and OH) produced by alloxan.[68,69] Twenty days following a nine-week course of alloxan, silymarin was administered, and it effectively treated the kidney tissue damage. It exerts anti-oxidant effects via increasing the expression of genes for antioxidant enzymes and other crucial protective defences against damage from free radicals that include catalase, glutathione peroxidase, and superoxide dismutase. Thus, silymarin may be utilized as a medication to treat diabetic nephropathy.[70] Glomerular filtration is reduced by oxidative stress (ROS). Vitamin E or silymarin treatment improved the change in serum creatinine. amounts in the dogs treated with gentamicin.[71]

According to study, silybin has been shown to be useful in preventing free oxygen radical damage to tubular epithelium during cold ischemia and the reperfusion phase of renal transplants. Another study indicates that silymarin has a protective effect against toxicity caused by tacrolimus.[72] Furthermore, the kidney damage caused by paracetamol, cisplatin, vincristine, vancomycin, colistin, and diclofenac was well prevented by silybin and/or silymarin.[73,74]

A few studies have demonstrated silymarin's potential effectiveness in treating diabetic nephropathy. Silymarin has also been found to be effective in reducing proteinuria in type 2 diabetes.[75] This reduction in proteinuria was related to antioxidant and anti-inflammatory effects of silymarin.[76-83] The impact of adding silymarin to renin-angiotensin system inhibitors on proteinuria in individuals with type 2 diabetes who had overt nephropathy was examined by Fallahzadeh et al. This study found that silymarin may lower the amount of albumin, TNF-α, and malondialdehyde excreted in the urine of patients with diabetic kidney disease.[84] Therefore, in addition to regulating metformin blood sugar, a combination of silymarin, renin-angiotensin system inhibitors, and angiotensin receptor blockers may have additive kidney protective properties to prevent or stop the onset of diabetic nephropathy.

Silymarin & cisplatin

According to another study, silymarin reduces cisplatin's nephrotoxic effects without lowering its anti-tumour activity. When silymarin was given before to cisplatin, its reno-protective were more noticeable.[85]

Silymarin and doxorubicin

Doxorubicin, an anthracycline, is widely used to manage several malignancies, mainly Hodgkin lymphoma and breast cancer. El-Shitany's research revealed that male Albino rats given a single intraperitoneal dose of 10 mg/kg of doxorubicin experienced nephrotoxicity. Doxorubicin significantly raised the levels of plasma creatinine, urea, LDH, and creatine phosphokinase (CPK). One month following the treatment of doxorubicin, microscopic analysis of the kidneys revealed tubular congestion, tubular cast, and interstitial glomerular congestion with broad Bowman's space, proximal tubular degeneration, vascular tubular degeneration, and bleeding. A group of rats received 50 mg/kg of silymarin as a pretreatment one week prior to receiving an injection of doxorubicin, and then every day after that for revealed a significant decrease in plasma CPK and LDH after one month, by 82% and 43%, respectively, in comparison to the group that received doxorubicin treatment.

The creation of an iron-doxorubicin complex, which produces free radicals and ROS and oxidatively damages lipid membranes and cellular components, was suggested to be the cause of doxorubicin-induced nephrotoxicity. Because silymarin has antioxidant and ROS-scavenging qualities, it may be able to reverse this damage. Silymarin may counteract this damage through its antioxidant and ROS scavenging properties.[86]

Silymarin and Acetaminophen - Induced Nephrotoxicity

The powerful analgesic acetaminophen may cause adverse effects on the kidneys, particularly in cases of chronic interstitial nephritis.[87] The effects of milk thistle on nephrotoxicity brought on by a single IP dose of 750 mg/kg were assessed by Ramachandran et al. Male Wistar albino rats given acetaminophen. Silymarin was employed as a common reno protection agent in this investigation. Oral silymarin administrations at a 50 mg/kg dosage significantly improved kidney function. Antioxidant activity markers such glutathione peroxidase, catalase, and superoxide dismutase showed a little decline and remained within almost normal levels in the silymarin-treated animal group.[88]

- **Potential therapeutic effects of milk thistle in eye diseases**

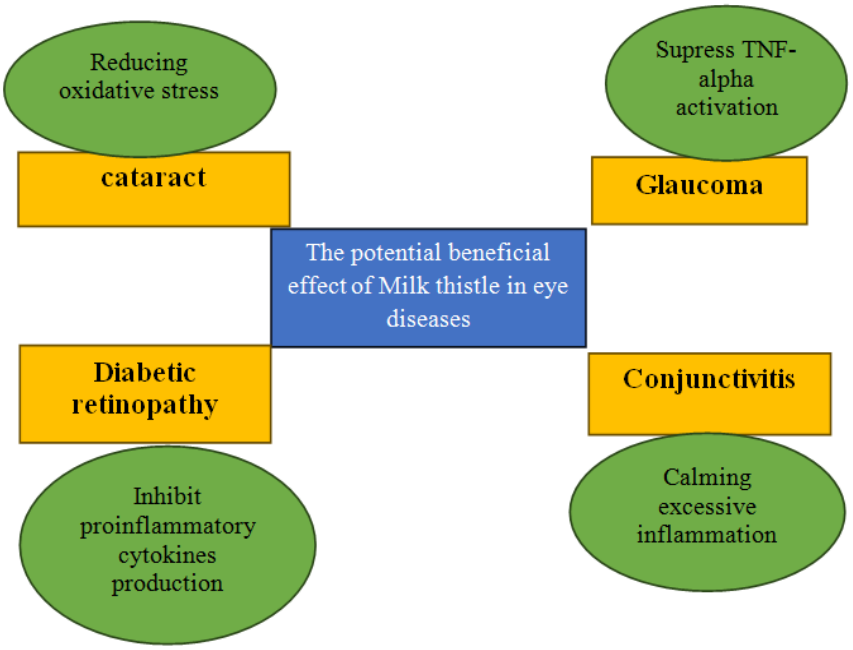
Eye diseases have become a significant public health concern worldwide, with increasing prevalence and burden on healthcare systems.[89] As the population ages and lifestyles change, it is anticipated that the prevalence of eye conditions such cataracts, age-related macular degeneration (AMD), and glaucoma would rise.[90]

It has been discovered that the different bioactive substances present in Silybum marianum offer a variety of possible therapeutic benefits. For instance, silymarin may have anti-inflammatory properties by lowering the expression of inflammatory mediators and preventing the synthesis of pro-inflammatory cytokines.[91] By scavenging free radicals and guarding against oxidative stress, it has also been shown to have antioxidant benefits. Because of these characteristics, Silybum Marianum is a desirable option for treating a number of illnesses, particularly those affecting the eyes.[92] Traditional Chinese medicine holds that the liver and eyes are related, and that the liver's bile drainage promotes blood detoxification, which benefits the eyes. Silymarin is also considered by Ayurveda as a remedy for yellowish sclera, which might result from liver failure.[93]

Shen et al. investigated the potential benefits of silymarin on retinal ganglion cell models of glaucoma. By comparing the levels of certain apoptotic markers in cells exposed to blue light with and without silymarin, the study examined the impact of silymarin on blue light-induced apoptosis in retinal ganglion cells. The findings suggested that silymarin might be used to treat glaucoma.[94]

Another study by Lin et al. looked for various indicators of AMD in rats in order to examine the impact of silibinin on AMD. The findings suggested that silibinin may help treat AMD and stop retinal edema and neovascularization by in vivo VEGF and hypoxia.[95]

Goswami et al. conducted an ex vivo study on corneas extracted from rabbits and demonstrated that silymarin may be helpful in the case of vesicant-inflicted ocular injury, but the treatment should be carried out on time, not too late after exposure to nitrogen mustard.[96]



Glaucoma => TNF (Tumor Necrosis factor) -alpha plays a role in glaucoma, as does oxidative stress, silymarin supress TNF-alpha activation and blocked oxidative stress. One study showed that silymarin inhibited glial cell proliferation in CNS cells. Glial cell hyperactivation is known to underlie the optic nerve damage in glaucoma.

Cataract => According to qualitative analyses, silymarin has a faint positive effect on cataract in diabetic rats.[97] In another in vitro study, silymarin significantly suppressed the progression of cataract in rats by reducing oxidative stress.[98]

Diabetic Retinopathy => Silymarin improved glucose and lipid profiles, scavenged reactive oxygen species, and inhibited proinflammatory cytokines production.[99] Therefore, silymarin may be useful to prevent diabetic complications.

Conjunctivitis => Silymarin can inhibit certain inflammatory signalling pathways, calming excessive inflammation in ocular tissues.

Pharmacological activity related to ocular disease

Several pharmacological activities of Silybum marianum have been identified that may be beneficial in the treatment of ocular diseases. A promising one is its anti-VEGF (Vascular Endothelial Growth Factor) activity.[100] VEGF is a critical factor in the pathogenesis of various ocular diseases, including AMD (Age Related Macular Degeneration) and diabetic retinopathy. According to studies, silymarin can prevent eyesight loss by lowering neovascularization and VEGF synthesis and activity.[101]

Additionally, Silybum marianum has been shown to possess antibacterial qualities, which may make it helpful in the management of eye infections.[102] Research has demonstrated that silymarin exhibits broad-spectrum antibacterial activity against a variety of bacteria, such as Pseudomonas aeruginosa and Staphylococcus aureus, which are frequently linked to ocular infections.[103] Silybum marianum has strong anti-inflammatory properties that may help treat a number of eye conditions, such as uveitis and "dry eye syndrome".[104] Silybum marianum has strong antioxidant qualities that could help treat conditions of the eyes, such as AMD and cataracts.[105] Silymarin helps prevent eyesight loss by scavenging free radicals and guarding against oxidative stress, which lessens retinal cell damage.[106] Overall, the pharmacological activities of Silybum marianum make it a promising candidate for the treatment of various ocular diseases, and further research is warranted to explore its potential therapeutic benefits Silybum marianum appears to be a safe and well-tolerated medication, but patients should always consult with their healthcare provider before starting any new medication or supplement.[107]

Overall, the potential therapeutic effects of Silybum marianum in the treatment of ocular diseases are promising, but further research is needed to establish its efficacy and safety in this context. With more research, Silybum marianum could prove to be a valuable addition to the treatment options available for ocular diseases.

Anti-Parkinson Potential of Silymarin

One of the most common neurodegenerative diseases in the world is Parkinson's disease. The cause of Parkinson's disease is nigrostriatal pathway malfunction leading to the death of dopaminergic neurons in the Substantia Nigra pars compacta (SNc).[108] There are currently no effective treatments for this illness; yet, dopaminergic drugs are still utilized for the principal treatment for Parkinson's disease that aims to reduce motor symptoms.[108] The available medications that are currently in practice for management of PD include levodopa, dopamine agonists (ropinirole, bromocriptine, cabergoline), MAOIs (selegiline), amantadine, anticholinergics (trihexyphenidyl), carbidopa, and entacapone.[109]

Many in vitro and in vivo studies have disclosed potential neuroprotective properties of silymarin using several models of Parkinson's Disease.[110] Major processes linked to silymarin's antioxidant properties include scavenging free radicals, increasing cellular glutathione levels, and enhancing superoxide dismutase activity. Silymarin has neuroprotective properties through oxidative stress suppression, and it can be used to treat neurodegenerative conditions such traumatic brain injury, Parkinson's disease, and Alzheimer's disease.[111] According to reports, silymarin reduces damage to dopaminergic neurons by preventing microglia from activating and by preventing the production of inflammatory mediators including NO and tumor necrosis factor-alpha (TNF-α).[112] According to reports, silymarin preserved dopaminergic neurons and reduced SN apoptosis, maintaining striatal dopamine levels. The antiapoptotic effect of silymarin is because of the suppression of protein P-p53, Bax, and caspase-9 expression.[113] Research connected these effects to silymarin's anti-inflammatory and antioxidant properties.[114] Silybum marianum, having the restored DA content and also preserved TH-positive neurons in the SN.[113] It has been also documented from some studies that silymarin reduces level of α-synuclein protein and increasing dopamine level.[115]

Furthermore, silibinin, the primary active component of silymarin and another flavonoid, has demonstrated very positive antiparkinsonian effects in PD by boosting the TH (Tyrosine hydroxylate)-positive fibers, preventing MMP disruption, and reducing the cell death of dopaminergic neurons in the ST and SN.[116]

Anti-Parkinson's targets of silymarin

→ By acting through inhibition of neuroinflammation[117]
→ Inhibition of CYP 2E1 expression leads to free radical formation[118]
→ Prevention of oxidative stress[118]
→ It maintains mitochondrial integrity and function and inhibits mitochondrial apoptotic pathway.[119]
→ Modulation of estrogen receptors.

The binding affinity of silymarin for estrogen receptor β in CNS regions has also been reported. Estrogen attenuates toxin-induced neurotoxicity, prevents lipid peroxidation, acting synergistically with antioxidants such as glutathione.[120]

Silymarin – promising pharmacological agent to treat Polycystic Ovary Syndrome

The imbalance between pro-oxidants and antioxidants may be the cause of female pregnancy problems like infertility, endometriosis, PCOS, preeclampsia, abortion, and miscarriage.[121] The anti-angiogenesis properties of silymarin decrease follicular cell proliferation, which lowers testosterone synthesis, and raise corpus luteum because progesterone hormone levels rise.[122] In addition to lowering testosterone levels, silymarin has hepatoprotective properties, can boost the synthesis of SHBG protein, and inhibits inflammation and cyclooxygenase (COX) by decreasing cysts.[122,123]

Silymarin lowers blood glucose levels, inhibits gluconeogenesis, and affects glucose 6-phosphatase, all of which reduce PCOS symptoms. By blocking cyclooxygenase-2 (COX-2) and lipoxygenase, silymarin lowers inflammation in PCOS and has a positive effect on lowering blood glucose levels by reducing oxidative stress.[122,123]

The impact of silymarin on PCOS in rats produced by estradiol valerate was examined in a 2014 study by Nebuni et al. Rats were given silymarin at doses of 20 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, and 300 mg/kg for 14 days in this investigation.[123] According to reports, the group that received silymarin treatment experienced a drop in body weight, abdominal circumference, and the quantity and size of cysts. They found no cysts at high dosages (300 mg/kg), which may be because silymarin has anti-inflammatory qualities. Different doses of silymarin had positive effects such as a decrease in estradiol, testosterone, and LH and a significant increase in FSH and progesterone hormones due to the appearance of corpus luteum cysts in the ovary.[124] According to the encouraging results of earlier studies, milk thistle seeds could be a useful tactic to address the several PCOS issues, including IR, dyslipidemia, oxidative stress, and inflammation.

Effect of Silymarin on Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease. This can be treated with antioxidant and anti-inflammatory compounds. Acetic acid-induced colitis in rats has been successfully treated with silymarin doses of 50 mg and 100 mg per kg. The treatment of 100 mg/kg of silymarin has been shown to minimize macroscopic damage, crypt damage, and inflammation.[125]

Silymarin's beneficial effects were assessed in the randomized clinical research on patients with ulcerative colitis. Silymarin was prescribed to them as part of their regular treatment; six months later, the oral dosage was reduced to 140 mg per day. High dosages of silymarin can cause headaches, diarrhoea, nausea, and vomiting. These adverse symptoms were transient, but there were no hazardous or dangerous side effects.[126] The nanosilymarin medication for colitis patients was developed by Hoseini et al. Rats with ulcerative colitis were used in their experiments. They gave rats with ulcerative colitis oral doses of 50, 100, and 200 mg/kg of nano silymarin for 14 days. The findings show that by blocking the TLR4/NFκB molecular pathway, nanosilymarin decreased colon inflammation in rats.[127]

Silymarin's limited solubility results in low bioavailability despite its potential pharmacological action. Therefore, the pharmacokinetic properties of silymarin are also a focus of this review.

Absorption and metabolism of silymarin

Silymarin has oral absorption only about 23-47% and quick phase II conjugation, leading to poor bio-availability.[128] Silymarin suffers from low bioavailability due to poor water solubility.[128] However, efflux transporters on the apical side of the intestinal epithelium further throttled the absorption of silymarin.

The Caco-2 cell monolayer model was used to investigate the intestinal absorption of silybin.[129] The measure mean-efflux ratios of silybin A and silybin B were 5.05 and 4.62, respectively, indicating an active transport mechanism. Moreover, MK571 (a multidrug resistance associated protein (MRP2)-specific inhibitor) significantly decreased the efflux ration of silybin, while Ko143 (a breast cancer resistance protein (BCRP)-specific inhibitor) and cyclosporin A were less potent, suggesting that intestinal efflux of silybin is mediated by MRPs and possibly BCRP. Studies carried out with Madin-Darby canine kidney cells II (MDCKII) lines overexpressing transporter and a sandwich culture hepatocyte model confirmed that the transporters involved in the absorption and excretion of silybin are MRP2 and BCRP, but not P-bp.[129]

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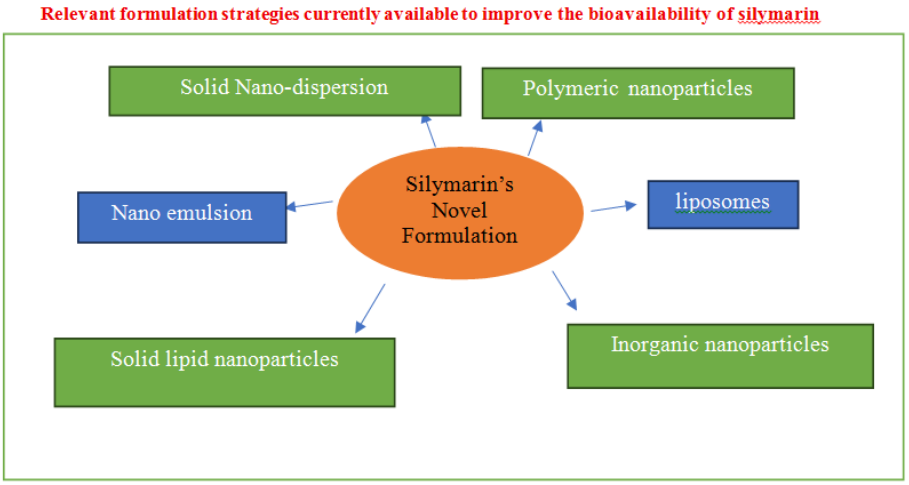
Formulation Strategies for Enhancing the Bioavailability of Silymarin

A renowned hepatoprotective, antioxidant, antiviral, and anticancer medication, silymarin has several drawbacks, including poor water solubility, ineffective intestinal absorption, the presence of several components, and a higher metabolism. Experts in the fields of colloidal and pharmaceutical sciences have been working to propose silymarin-based formulations with improved stability and solubility, increased bioavailability, and effective therapeutic performances, as evidenced by an increasing number of scientific reports in the literature.[130,131] Researchers may now use a variety of solubilization techniques to entrap silymarin and other weakly water-soluble active plant components in aqueous nanovesicle.[132] For example, an effective nanoencapsulation makes it possible for phenolics and antioxidants to passively enter the lymphatic and blood

circulatory systems from the intestinal lumen, significantly increasing their bioavailability.[133,134] As a result, silymarin-based formulations have started to be made using cutting-edge methods and have been shown to improve their therapeutic efficacy against a number of illnesses.[135]

Formulation Strategies Designed to Improve the Bioavailability of Silymarin

Many formulations have been created to increase silymarin's solubility and bioavailability; the majority of these formulations are primarily intended for oral use.



1. Lipid-based Formulations

Lipid-based formulations, which involve incorporating the active lipophilic component into inert lipid vehicles, are used to increase the oral bioavailability of drug compounds that are poorly soluble in water. These formulations include oils, surfactant dispersions, pro liposomes and liposomes, solid lipid nanoparticles and lipid nanocarriers, micro- or nano emulsions, and self-emulsifying formulations. These lipid formulations can be broadly divided into two groups, namely, liquid oil-in-water (O/W) emulsions (LEs) and solid lipid nanoparticles (SLNs). SLNs are novel lipid-based formulations which are constituted exclusively of biodegradable lipids such as highly purified triglycerides, monoglycerides, hard fats, complex glyceride mixtures or even waxes, which are solid at physiological temperature.[135]

2. Micro- and Nano Emulsions

For oral or topical administration, the formulations based on both microemulsion and nano emulsion techniques are made using food-acceptable or generally recognized as safe (GRAS) ingredients to improve the permeability of silymarin and boost solubility and stability. For example, O/W microemulsions were formulated to incorporate 2% w/w of Silymarin as a potential dermal delivery system.[136] According to a recent study, a commercial SLM extract could be fully dissolved at a dosage of 40 mg/mL in a nano emulsion made with 2.5 g of Cremophor® EL/Labrafil® as the surfactant/cosurfactant mixture and 2.5 g of Labrasol® (20%) as the oil phase. a ratio of 1.5:1, with 60% of the remaining mass being deionized water.[137]

3. Polymer-based Nanocarriers

Researchers have developed a number of methods in the literature to effectively encapsulate Silymarin in biocompatible and biodegradable polymeric nano systems, including solid nano dispersions, composites, and polymeric micelles.

All things considered, they offer a very effective method for dispersing a medication that is not very water soluble within an inert hydrophilic polymer matrix. For quick dissolving, the loaded medication is released as extremely small particles while the polymeric erosion continues.[138]

4. Inclusion in Polymeric Matrices

As Sonali et al. explained, selecting the right formulation technique is essential to maximizing the performance of the finished product. They compared co-precipitation, spray drying, and kneading methods when creating SLM-loaded solid dispersions with HPMC acting as a hydrophilic polymeric carrier.[139] In vitro studies suggested the following enhancement in Silymarin dissolution compared to pure drug.

By employing the ESE(Emulsification/Solvent Evaporation) approach and the freeze-drying process using P188 as the polymer, Zhao et al. developed another formulation of SLM (containing 33% of SIL) loaded NPs with a particle size of approximately 100 nm. Very high Silymarin concentrations with a long retention duration were seen in the liver, and the absorption of SLM NPs in the organs was noticeably greater than that of the drug suspension.[120]

REFERENCES

1. Livolti, G. Potential therapeutic effects of milk thistle. EuroMediterranean Biomedical Journal, 2015; 10(13): 168-172.
2. Das, S. K., Mukherjee, S., & Vasudevan, D. Medicinal properties of milk thistle with special reference to silymarin–An overview. Natural Product Radiance, 2008; 7(2): 182-192.
3. Gazak R, Walterova D, Kren V. Silybin and silymarin - New and emerging applications in medicine. Curr Med Chem., 2007; 14: 315-338.
4. Tůmová L, Tůma J, Megušar K, Doleža M Substituted Pyrazinecarboxamides as Abiotic Elicitors of Flavolignan Production in Silybum marianum (L.) Gaertn Cultures in Vitro. Molecules, 2010; 15(1): 331-340. doi:10.3390/molecules15010331
5. Ding, T. M., Tian, S. J., Zhang, Z. X., Gu, D. Z., Chen, Y. F., Shi, Y. H., & Sun, Z. P. Determination of active component in silymarin by RP-LC and LC/MS. Journal of Pharmaceutical and Biomedical Analysis, 2001; 26(1): 155-161.
6. Rombolà, L., Scuteri, D., Marilisa, S., Watanabe, C., Morrone, L. A., Bagetta, G., & Corasaniti, M. T. Pharmacokinetic interactions between herbal medicines and drugs: Their mechanisms and clinical relevance. Life, 2020; 10(7): 106.
7. Sprouse, A. A., & Van Breemen, R. B. Pharmacokinetic interactions between drugs and botanical dietary supplements. Drug Metabolism and Disposition, 2016; 44(2): 162–171.
8. Pellicoro, A., Ramachandran, P., Iredale, J. P., & Fallowfield, J.A. Liver fibrosis and repair: Immune regulation of wound healing in a solid organ. Nature Reviews. Immunology, 2014; 14(3): 181–194.
9. Sozen, H., Celik, O. I., Cetin, E. S., Yilmaz, N., Aksozek, A., Topal, Y., Cigerci, I. H., & Beydilli, H. Evaluation of the protective effect of silibinin in rats with liver damage caused by itraconazole. Cell Biochemistry and Biophysics, 2015; 71: 1215–1223.
10. Wadhwa, K., Pahwa, R., Kumar, M., Kumar, S., Sharma, P. C., Singh, G., Verma, R., Mittal, V., Singh, I., Kaushik, D., & Jeandet, P. Mechanistic insights into the pharmacological significance of silymarin. Molecules, 2022; 27(16): 5327.
11. Camini, F. C., & Costa, D. C. Silymarin: Not just another antioxidant. Journal of Basic and Clinical Physiology and Pharmacology, 2020; 31(4): 20190206.
12. Perez-Araluce, M., Jüngst, T., Sanmartin, C., Prosper, F. Plano, D., & Mazo, M. M. Biomaterials-based antioxidant strategies for the treatment of oxidative stress diseases. Biomimetics, 2024; 9(1): 23.
13. Mansour, A., Eisa, M., Abdelghany, T., & Salama, S. Silymarin ameliorates diethylnitrosamine-induced liver fibrosis in Wistar rats. Al-Azhar Journal of Pharmaceutical Sciences, 2022; 66(2): 246–266.
14. Kadoglou, N. P., Panayiotou, C., Vardas, M., Balaskas, N., Kostomitsopoulos, N. G., Tsaroucha, A. K., & Valsami, G. A comprehensive review of the cardiovascular protective properties of Silibinin/Silymarin: A new kid on the block. Pharmaceuticals, 2022; 15(5): 538.
15. Zhou, B.; Wu, L.J.; Tashiro, S.; Onodera, S.; Uchiumi, F.; Ikejima, T. Silibinin protects rat cardiac myocyte from isoproterenol-induced DNA damage independent on regulation of cell cycle. Biol. Pharm. Bull., 2006; 29: 1900-1905
16. Ligeret, H.; Brault, A.; Vallerand, D.; Haddad, Y.; Haddad, P.S. Antioxidant and mitochondrial protective effects of silibinin in cold preservation-warm reperfusion liver injury. J. Ethnopharmacol, 2008; 115: 507-514
17. Detaille, D.; Sanchez, C.; Sanz, N.; Lopez-Novoa, J.M.; Leverve, X.; El-Mir, M.Y. Interrelation between the inhibition of glycolytic flux by silibinin and the lowering of mitochondrial ROS production in perifused rat hepatocytes. Life Sci., 2008; 82: 1070-1076.
18. Razavi, B. M., & Karimi, G. Protective effect of silymarin against chemical-induced cardiotoxicity. Iranian Journal of Basic Medical Sciences, 2016; 19(9): 916.
19. Amniattalab, A., Malekinejad, H., Rezabakhsh, A., Rokhsartalab-Azar, S., & Alizade-Fanalou, S. Silymarin: a novel natural agent to restore defective pancreatic β cells in streptozotocin (STZ)-induced diabetic rats. Iranian Journal of Pharmaceutical Research, 2016; 15(3): 493.
20. Qin, N. B., Jia, C. C., Xu, J., Li, D. H., Xu, F. X., Bai, J., & Hua, H. M. New amides from seeds of Silybum marianum with potential antioxidant and antidiabetic activities. Fitoterapia, 2017; 119: 83-89.
21. Sangeetha, N.; Viswanathan, P.; Balasubramanian, T.; Nalini, N. Colon cancer chemopreventive efficacy of silibinin through perturbation of xenobiotic metabolizing enzymes in experimental rats. Eur. J. Pharmacol, 2012; 674: 430-438.
22. Mohamad N.-V., Ima-Nirwana S., and Chin K.-Y., Are oxidative stress and inflammation mediators of bone loss due to estrogen deficiency? A review of current evidence, *Endocrine, Metabolic & Immune Disorders—Drug Targets*, 2020; 20(9): 1478–1487, https://doi.org/10.2174/1871530320666200604160614.
23. Ventura-Clapier R., Piquereau J., Veksler V., and Garnier A., Estrogens, estrogen receptors effects on cardiac and skeletal muscle mitochondria, *Frontiers in Endocrinology*, 2019; 10, https://doi.org/10.3389/fendo.2019.00557, 2-s2.0-85072724534, 557.
24. Rettberg J. R., Yao J., and Brinton R. D., Estrogen: a master regulator of bioenergetic systems in the brain and body, *Frontiers in Neuroendocrinology*, 2014; 35(1): 8–30, https://doi.org/10.1016/j.yfrne.2013.08.001, 2-s2.0-84892882368.

25. Zhang W., Guo L., and Liu D., Concurrent interactions between prefrontal cortex and hippocampus during a spatial working memory task, *Brain Structure and Function*, 2022; 227(5): 1735–1755, https://doi.org/10.1007/s00429-022-02469-y.
26. Gava G., Orsili I., Alvisi S., Mancini I., Seracchioli R., and Meriggiola M. C., Mood and sleep in menopausal transition: the role of menopause hormone therapy, *Medicina (Kaunas)*, 2019; 55: 10, https://doi.org/10.3390/medicina55100668, 2-s2.0-85072916203, 668.
27. Robeva R., Mladenović Dšan, Vesković M., Hrnčić D., Bjekić-Macut J., Stanojlović O., Livadas S., Yildiz B. O., and Macut D., The interplay between metabolic dysregulations and non-alcoholic fatty liver disease in women after menopause, *Maturitas*, 2021; 151: 22–30, https://doi.org/10.1016/j.maturitas.2021.06.012.
28. Koltai T. and Fliegel L., Role of silymarin in cancer treatment: facts, hypotheses, and questions, *Journal of Evidence-Based Integrative Medicine*, 2022; 27, https://doi.org/10.1177/2515690X211068826.
29. Mohamad N.-V., Ima-Nirwana S., and Chin K.-Y., Are oxidative stress and inflammation mediators of bone loss due to estrogen deficiency? A review of current evidence, *Endocrine, Metabolic & Immune Disorders—Drug Targets*, 2020; 20(9): 1478–1487.
30. Lovelace E. S. and Polyak S. J., Natural products as tools for defining how cellular metabolism influences cellular immune and inflammatory function during chronic infection, *Viruses*, 2015; 7(12): 6218–6232, https://doi.org/10.3390/v7122933, 2-s2.0-84949484670.
31. Azarfar K., Yaghmaei P., Amoli M. M., Hayati-Roodbari N., and Ebrahim-Habibi A., Local insulin-derived amyloidosis model confronted with silymarin: histological insights and gene expression of MMP, TNF-*α*, and IL-6, *International Journal of Molecular Sciences*, 2022; 23(9), https://doi.org/10.3390/ijms23094952, 4952.
32. Luo Y., Xiao Q., Chao F., He Q., Lv F., Zhang L., Gao Y., Qiu X., Huang C., Li Y., Wang S., Jiang R., Gu H., and Tang Y., 17*β*-estradiol replacement therapy protects myelin sheaths in the white matter of middle-aged female ovariectomized rats: a stereological study, *Neurobiology of Aging*, 2016; 47: 139–148, https://doi.org/10.1016/j.neurobiolaging.2016.07.023, 2-s2.0-84984813538.
33. Tao Z.-S., Li T.-L., and Wei S., Silymarin prevents iron overload induced bone loss by inhibiting oxidative stress in an ovariectomized animal model, *Chemico-Biological Interactions*, 2022; 366, https://doi.org/10.1016/j.cbi.2022.110168, 110168.
34. Manivannan, E., Amawi, H., Hussein, N., Karthikeyan, C., Fetcenko, A., Moorthy, N. H. N., & Tiwari, A. K. Design and discovery of silybin analogues as antiproliferative compounds using a ring disjunctive–Based, natural product lead optimization approach. European Journal of Medicinal Chemistry, 2017; 133: 365-378.
35. Agarwal, R. Cell signaling and regulators of cell cycle as molecular targets for prostate cancer prevention by dietary agents. Biochemical pharmacology, 2000; 60(8): 1051-1059.
36. Agarwal, C., Tyagi, A., Kaur, M., & Agarwal, R. Silibinin inhibits constitutive activation of Stat3, and causes caspase activation and apoptotic death of human prostate carcinoma DU145 cells. Carcinogenesis, 2007; 28(7): 1463-1470.
37. Bartholomaeus AR, Bolton R, Ahokas JT. Inhibition of rat liver cytosolic glutathione S transferase by silybin. Xenobiotica, 1994; 24(1): 17-24. 0.3109/00498259409043217
38. Dehmlow C, Murawski N, de Groot H. Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells. LifeSci., 1996; 58(18): 1591-1600. https://doi.org/10.1016/0024-3205(96)00134-8
39. Scambia G, De Vincenzo R, Ranelletti PO, et al. Antiproliferative effect of silybin on gynaecological malignan cies: synergism with cisplatin and doxorubicin. Eur J Cancer, 1996; 32(5): 877-882. https://doi.org/10.1016/0959-8049(96) 00011-1
40. Reed, D., Raina, K., & Agarwal, R. Anti cancer Effects of Silibinin: The Current Status in Cancer Chemoprevention. Natural Products for Cancer Chemoprevention: Single Compounds and Combinations, 2020; 161-208.
41. Zhang Y., Ge Y., Ping X., Yu M., Lou D., Shi W. Synergistic apoptotic effects of silibinin in enhancing paclitaxel toxicity in human gastric cancer cell lines. Mol. Med. Rep., 2018; 18: 1835–1841. doi: 10.3892/mmr.2018.9129. [DOI] [PubMed] [Google Scholar]
42. Dogan Sigva Z.O., Balci Okcanoglu T., Biray Avci C., Yilmaz Susluer S., Kayabasi C., Turna B., Dodurga Y., Nazli O., Gunduz C. Investigation of the synergistic effects of paclitaxel and herbal substances and endemic plant extracts on cell cycle and apoptosis signal pathways in prostate cancer cell lines. Gene, 2019; 687: 261–271. doi: 10.1016/j.gene.2018.11.049
43. Li W.G., Wang H.Q. Inhibitory effects of Silibinin combined with doxorubicin in hepatocellular carcinoma; an in vivo study. J. BUON, 2016; 21: 917–924.
44. Tyagi A.K., Singh R.P., Agarwal C., Chan D.C., Agarwal R. Silibinin strongly synergizes human prostate carcinoma DU145 cells to doxorubicin-induced growth Inhibition, G2-M arrest, and apoptosis. Clin. Cancer Res., 2002; 8: 3512–3519.
45. Molavi O., Narimani F., Asiaee F., Sharifi S., Tarhriz V., Shayanfar A., Hejazi M., Lai R. Silibinin sensitizes chemo-resistant breast cancer cells to chemotherapy. Pharm. Biol., 2017; 55: 729–739. doi: 10.1080/13880209.2016.1270972.

46. Singh R.P., Mallikarjuna G.U., Sharma G., Dhanalakshmi S., Tyagi A.K., Chan D.C., Agarwal C., Agarwal R. Oral silibinin inhibits lung tumor growth in athymic nude mice and forms a novel chemocombination with doxorubicin targeting nuclear factor kappaB-mediated inducible chemoresistance. Clin. Cancer Res., 2004; 10: 8641–8647. doi: 10.1158/1078-0432.CCR-04-1435.
47. Zhang Y., Ge Y., Ping X., Yu M., Lou D., Shi W. Synergistic apoptotic effects of silibinin in enhancing paclitaxel toxicity in human gastric cancer cell lines. Mol. Med. Rep., 2018; 18: 1835–1841. doi: 10.3892/mmr.2018.9129.
48. Dogan Sigva Z.O., Balci Okcanoglu T., Biray Avci C., Yilmaz Susluer S., Kayabasi C., Turna B., Dodurga Y., Nazli O., Gunduz C. Investigation of the synergistic effects of paclitaxel and herbal substances and endemic plant extracts on cell cycle and apoptosis signal pathways in prostate cancer cell lines. Gene, 2019; 687: 261–271. doi: 10.1016/j.gene.2018.11.049.
49. Mehta RG, Moon RC. Characterization of effective chemopreventive agents in mammary gland in vitro using an initiation-promotion protocol. Anticancer Res., 1991; 11(2): 593-596. PMID: 1905902
50. Invernizzi R, Bernuzzi S, Ciani D, Ascari E. Silymarine during maintenance therapy of acute promyelocytic leukemia. Haematologica, 1993; 78(5): 340-341. PMID: 8314167.
51. Gaedeke J, Fels LM, Bokemeyer C, Mengs U, Stolte H, Lentzen H. Cisplatin nephrotoxicity and protection by silibinin. Nephrol Dial Transplant, 1996; 11(1): 55-62. https://doi.org/10.1093/ndt/11.1.55
52. Psotová J, Chlopcíková Š, Grambal F, Šimánek V, Ulrichová J. Influence of silymarin and its flavonolignans on doxorubicin-iron induced lipid peroxidation in rat heart microsomes and mitochon dria in comparison with quercetin. Phytother Res., 2002; 16(S1): 63-67. https://doi.org/10.1002/ptr.811
53. Yardım A, Kucukler S, Özdemir S, et al. Silymarin alleviates docetaxel-induced central and peripheral neurotoxicity by reducing oxidative stress, inflammation and apoptosis in rats. Gene, 2021; 769: 145239.
54. Moezian GSA, Javadinia SA, Sales SS, Fanipakdel A, Elyasi S, Karimi G. Oral silymarin formulation efficacy in management of AC-Tprotocol induced hepatotoxicity in breast cancer patients: a randomized, triple blind, placebo-controlled clinical trial. J Oncol Pharm Pract, 2021; 10781552211006182. https://doi.org/10.1177/10781552211006182
55. Rahimi, R., Karimi, J., Khodadadi, I., Tayebinia, H., Kheiripour, N., Hashemnia, M., & Goli, F. Silymarin ameliorates expression of urotensin II (U-II) and its receptor (UTR) and attenuates toxic oxidative stress in the heart of rats with type 2 diabetes. Biomedicine & Pharmacotherapy, 2018; 101: 244-250.
56. Ebrahimpour-Koujan S, Gargari BP, Mobasseri M, et al. Lower glycemic indices and lipid profile among type 2 diabetes mellitus patients who received novel dose of Silybum marianum (L.) Gaertn. (silymarin) extract supplement: A Triple-blinded randomized controlled clinical trial. *Phytomedicine*, May 15, 2018; 44: 39-44.
57. Kheiripour N., Karimi J., Khodadadi I., Tavilani H., Taghi Goodarzi M., and Hashemnia M., Hepatoprotective effects of silymarin on liver injury via irisin upregulation and oxidative stress reduction in rats with type 2 diabetes, *Iranian Journal of Medical Sciences*, 2019; 44(2): 108–117.
58. Cheng B, Gong H, Li X, Sun Y, Zhang X, Chen H, Liu X, Zheng L, Huang Kl. Silibinin inhibits the toxic aggregation of human islet amyloid polypeptide. Biochem Biophys Res Commun, 2012; 419(3): 495–499. doi: 10.1016/j.bbrc.2012.02.042.
59. Detaille D, Sanchez C, Sanz N, Lopez-Novoa JM, Leverve X, El-Mir MY. Interrelation between the inhibition of glycolytic flux by silibinin and the lowering of mitochondrial ROS production in perifused rat hepatocytes. Life Sci., 2008; 82(21-22): 1070–1076. doi: 10.1016/j.lfs.2008.03.
60. Soto C, Recoba R, Barron H, Alvarez C, Favari L. Silymarin increases antioxidant enzymes in alloxan-induced diabetes in rat pancreas. Comp Biochem Physiol Part C Toxicol Pharmacol, 2003; 136(3): 205–212. doi: 10.1016/s1532-0456(03)00214-x
61. Das S, Roy P, Pal R, Auddy RG, Chakraborti AS, Mukherjee A. Engineered silybin nanoparticles educe efficient control in experimental diabetes. Plos One., 2014; 9(7): e101818. doi: 007.10.1371/journal.pone.0101818.
62. Fengyun, C. Silymarin combined with diammonium glycyrrhizinate for prevention and treatment of liver injury induced by chemotherapy in acute leukemia. China Medicine, 2012; 7: 902.
63. Vincenzi, B., Russo, A., Terenzio, A., Galvano, A., Santini, D., Vorini, F., Antonelli- Incalzi, R., Vespasiani-Gentilucci, U., & Tonini, G. The use of SAMe in chemotherapy-induced liver injury. Critical Reviews in Oncology/Hematology, 2018; 130: 70–77.
64. Hagag, A. A., Elgamsy, M. A., El-Asy, H. M., & Mabrouk, M. M. Protective role of silymarin on the hepatic and renal toxicity induced by MTX-based chemotherapy in children with acute lymphoblastic leukemia. Mediterranian Journal of Hematology and Infectious Diseases, 2016; 8(1): e2016043.
65. Jiang, G., Sun, C., Wang, X., Mei, J., Li, C., Zhan, H., Liao, Y., Zhu, Y., & Mao, J. Hepatoprotective mechanism of *Silybum marianum* on nonalcoholic fatty liver disease based on network pharmacology and experimental verification. Bioengineered, 2022; 13(3): 5216–5235.
66. Ladas, E. J., Kroll, D. J., Oberlies, N. H. Cheng, B., Ndao, D. H., Rheingold, S. R., & Kelly, K. M. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in

childhood acute lymphoblastic leukemia (ALL). Cancer, 2010; 116(2): 506–513.
67. Weiskirchen, R. Hepatoprotective and anti-fibrotic agents: It's time to take the next step. Frontiers in Pharmacology, 2016; 6: 303. [DOI] [PMC free article] [PubMed] [Google Scholar]
68. Sha S, Baliga R, Rajapurkar M, Fonseca V. Oxidants in chronic kidney disease. J Am Soc Nephrol 2007; 18: 16-28.
69. Soto C, Mena R, Luna J, Cerbón M, Larrieta E, Vital P, et al. Silymarin induces recovery of pancreatic function after alloxan damage in rats. Life Sci., 2004; 75: 2167-2180.
70. Soto C, Pérez J, García V, Uría E, Vadillo M, Raya L. Effect of silymarin on kidneys of rats suffering from alloxan-induced diabetes mellitus. Phytomedicine, 2010; 17: 1090-1094.
71. Varzi HN, Esmailzadeh S, Morovvati H, Avizeh R, Shahriari A, Givi ME. Effect of silymarin and vitamin E on gentamicin-induced nephrotoxicity in dogs. J Vet Pharmacol Ther., 2007; 30: 477-481.
72. Ferjani H, El Arem A, Bouraoui A, Achour A, Abid S, Bacha H, Boussema-Ayed I. Protective effect of mycophenolate mofetil against nephrotoxicity and hepatotoxicity induced by tacrolimus in Wistar rats. J Physiol Biochem, 2016; 72(2): 133–44.
73. Sonnenbichler J, Scalera F, Sonnenbichler I, Weyhenmeyer R. Stimulatory effects of silibinin and silicristin from the milk thistle Silybum marianum on kidney cells. J Pharmacol Exp Ther., 1999; 290(3): 1375–83.
74. Nouri A, Heidarian E. Nephroprotective effect of silymarin against diclofenacinduced renal damage and oxidative stress in male rats. J Herbmed Pharmacol, 2019; 8(2): 146-52.
75. *Brantley SJ, Oberlies NH, Kroll DJ, Paine MF. Two flavonolignans from milk thistle (Silybum marianum) inhibit CYP2C9-mediated warfarin metabolism at clinically achievable concentrations. J. Pharmacol Exp Ther., 2010; 332: 1081–7. doi: 10.1124/jpet.109.161927.* [DOI] [PMC free article] [PubMed] [Google Scholar]
76. *Vessal G, Akmali M, Najafi P, Moein MR, Sagheb MM. Silymarin and milk thistle extract may prevent the progression of diabetic nephropathy in streptozotocin-induced diabetic rats. Ren Fail., 2010; 32: 733–9. doi: 10.3109/0886022X.2010.486488.* [DOI] [PubMed] [Google Scholar]
77. *Soto C, Pérez J, García V, Uría E, Vadillo M, Raya L. Effect of silymarin on kidneys of rats suffering from alloxan-induced diabetes mellitus. Phytomedicine, 2010; 17: 1090–4. doi: 10.1016/j.phymed.2010.04.011.* [DOI] [PubMed] [Google Scholar]
78. *Meyers CM, Briggs JP. Silymarin for diabetic nephropathy: the challenges of botanical product research. Am J Kidney Dis., 2012; 60: 887–9. doi: 10.1053/j.ajkd.2012.09.002.* [DOI] [PubMed] [Google Scholar]
79. *Jose MA, Abraham A, Narmadha MP. Effect of silymarin in diabetes mellitus patients with liver diseases. J Pharmacol Pharmacother, 2011; 2: 287–9. doi: 10.4103/0976-500X.85952.* [DOI] [PMC free article] [PubMed] [Google Scholar]
80. *Turgut F, Bayrak O, Catal F, Bayrak R, Atmaca AF, Koc A. et al. Antioxidant and protective effects of silymarin on ischemia and reperfusion injury in the kidney tissues of rats. Int Urol Nephrol, 2008; 40: 453–60. doi: 10.1007/s11255-008-9365-4.* [DOI] [PubMed] [Google Scholar]
81. *Vessal G, Akmali M, Najafi P, Moein MR, Sagheb MM. Silymarin and milk thistle extract may prevent the progression of diabetic nephropathy in streptozotocin-induced diabetic rats. Ren Fail., 2010; 32: 733–9. doi: 10.3109/0886022X.2010.486488.*
82. *Soto C, Pérez J, García V, Uría E, Vadillo M, Raya L. Effect of silymarin on kidneys of rats suffering from alloxan-induced diabetes mellitus. Phytomedicine, 2010; 17: 1090–4. doi: 10.1016/j.phymed.2010.04.011.*
83. *Dashti-Khavidaki S, Shahbazi F, Khalili H, Lessan-Pezeshki M. Potential renoprotective effects of silymarin against nephrotoxic drugs: a review of literature. J Pharm Pharm Sci., 2012; 15: 112–23. doi: 10.18433/j3f88s.* [DOI] [PubMed] [Google Scholar]
84. Fallahzadeh MK, Dormanesh B, Sagheb MM, Roozbeh J, Vessal G, Pakfetrat M. et al. Effect of addition of silymarin to renin-angiotensin system inhibitors on proteinuria in type 2 diabetic patients with overt nephropathy: a randomized, double-blind, placebo-controlled trial. Am J Kidney Dis., 2012; 60: 896–903. doi: 10.1053/j.ajkd.2012.06.005.
85. Estela B. Behling, Milena C. Sendao, Heloisa D.C. Francescato, Lusania M.G. Antunes, Roberto S. Costa, Maria de Lourdes P. Bianchi. Comparative study of multiple dosage of quercetin against cisplatin-induced nephrotoxicity in rat kidney. Pharmacol Rep., 2006; 58: 526-532.
86. Nagla A. El-Shitany, Sahar El-Haggar, Karema El Desoky. silymarin prevents adriamycin-induced cardiotoxicity and nephrotoxicity in rats. Food Chem Toicol, 2008; 46: 2422-2428. 24.
87. Cynthia A. Naughton. Drug-Induced Nephrotoxicity. Am Fam Physician, 2008; 78: 743 750.
88. Vinayagam Ramachandran, Ramalingam Sarvanan, Boobalam Raja. Attenuation of oxidative stress by syringic acid on acetaminophen-induced nephrotoxic rats. Comp Clin Path, DOI 10.1007/s00580-011 1327-z,2010
89. Wang B, Congdon N, Bourne R, Li Y, Cao K, Zhao A, Yusufu M, Dong W, Zhou M, Wang N. Burden of vision loss associated with eye disease in China 1990–2020: findings from the global burden of Disease Study 2015. Br J Ophthalmol, 2018; 102(2): 220–4.

90. Keel S, Lingham G, Misra N, Block S, Bourne R, Calonge M, Cheng C-Y, Friedman DS, Furtado JM, Khanna R. Toward universal eye health coverage—key outcomes of the World Health Organization package of eye care interventions: a systematic review. JAMA Ophthalmol, 2022; 140: 1229.
91. Polyak SJ, Morishima C, Shuhart MC, Wang CC, Liu Y, Lee DY. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaB signaling, and HCV infection by standardized silymarin. Gastroenterology, 2007; 132(5): 1925–36.
92. Köksal E, Gülçin I, Beyza S, Sarikaya O, Bursal E. In vitro antioxidant activity of silymarin. J Enzyme Inhib Med Chem., 2009; 24(2): 395–405.
93. Akbarzadeh T, Sabourian R, Saeedi M, Rezaeizadeh H, Khanavi M, Ardekani MRS. Liver tonics: review of plants used in Iranian tradi tional medicine. Asian Pac J Trop Biomed, 2015; 5(3): 170–81.
94. Karimi R, Bakhshi A, Dayati P, Abazari O, Shahidi M, Savaee M, Kafi E, Rahmanian M, Naghib SM. Silymarin reduces retinal microvascular damage in streptozotocin-induced diabetic rats. Sci Rep., 2022; 12(1): 15872.
95. Shen Y, Zhao H, Wang Z, Guan W, Kang X, Tai X, Sun Y. Silibinin declines blue light-induced apoptosis and inflammation through MEK/ERK/CREB of retinal ganglion cells. Artif Cells Nanomed Biotechnol, 2019; 47(1): 4059–65.
96. Lin CH, Li CH, Liao PL, Tse LS, Huang WK, Cheng HW, Cheng YW. Silibinin inhibits VEGF secretion and age-related macular degeneration in a hypoxia-dependent manner through the PI-3 kinase/Akt/mTOR pathway. Br J Pharmacol, 2013; 168(4): 920–31.
97. Borymska W, Zych M, Dudek S, Kaczmarczyk-Sedlak I. Silymarin from milk thistle fruits counteracts selected pathological changes in the lenses of type 1 diabetic rats. Nutrients, 2022; 14(7): 1450.
98. Fallah Huseini H, Zaree A, Babaei Zarch A, Heshmat R. The effect of herbal medicine Silybum marianum (L.) Gaertn. Seed extract on galactose induced cataract formation in rat. J Med Plants, 2004; 3(12): 58–62.
99. Rahimi R, Karimi J, Khodadadi I, Tayebinia H, Kheiripour N, Hashemnia M, Goli F. Silymarin ameliorates expression of urotensin II (U-II) and its receptor (UTR) and attenuates toxic oxidative stress in the heart of rats with type 2 diabetes. Biomed Pharmacother, 2018; 101: 244–50.
100. Attia GM, Elmansy RA, Algaidi SA. Silymarin decreases the expression of VEGF-A, iNOS and caspase-3 and preserves the ultrastructure of cardiac cells in doxorubicin induced cardiotoxicity in rats: a possible protective role. Int J Clin Exp Med., 2017; 10(2): 4158–73.
101. Sadighi S, Dashti-Khavidaki S, Shahbazi F, Mirzania M, Shahi F, Abdollahi A, Ghahremani MH. The effects of concomitant use of silymarin and chemotherapy on solid tumors: a pilot randomized controlled trial. Basic Clin Cancer Res., 2017; 9(2): 13–9.
102. Dhouibi I, Jridi M, Flamini G, Jabeur H, Masmoudi M, Bouaziz M. Volatile and phenolic contents and antioxidant and antibacterial proper ties of Tunisian milk thistle and mastic oils. Euro-Mediterr J Environ Integr, 2020; 5: 1–12.
103. Mahmoudi Rad Z, Nourafcan H, Mohebalipour N, Assadi A, Jamshidi S. Antibacterial effect of methanolic extract of milk thistle seed on 8 species of gram-positive and negative bacteria. J Plant Res (Iran J Biol), 2022; 35(4): 776–85.
104. Hussain R. Dose-dependent anti-inflammatory effect of silymarin in experimental animal model of chronic inflammation. Afr J Pharm Pharmacol, 2009; 3(5): 242–7.
105. Lucini L, Kane D, Pellizzoni M, Ferrari A, Trevisi E, Ruzickova G, Arslan D. Phenolic profile and in vitro antioxidant power of different milk thistle [Silybum marianum (L.) Gaertn.] Cultivars. Ind Crops Prod., 2016; 83: 11–6.
106. Srivastava S., Sammi S. R., Laxman T. S., Pant A., Nagar A., Trivedi S., et al. Silymarin promotes longevity and alleviates Parkinson's associated pathologies in *Caenorhabditis elegans*. *J. Funct. Foods*, 2017; 31: 32–43. 10.1016/j.jff.2017.01.029
107. Goswami DG, Kant R, Tewari-Singh N, Agarwal R. Efficacy of anti-inflammatory, antibiotic and pleiotropic agents in reversing nitrogen mustard-induced injury in ex vivo cultured rabbit cornea. Toxicol Lett., 2018; 293: 127–32.
108. Heydari M, Rauf A, Thiruvengadam M, Chen X, Hashempur MH. Clinical safety of natural products, an evidence-based approach. Front Pharmacol, 2022; 13: 960556.
109. Surmeier, D. J.; Obeso, J. A.; Halliday, G. M. Nat. Rev. Neurosci, 2017; 18: 101-113.
110. Nakaoka S., Ishizaki T., Urushihara H., Satoh T., Ikeda S., Yamamoto M., et al. Prescribing pattern of anti-Parkinson drugs in Japan: a trend analysis from 2005 to 2010. *PLoS One*, 2014; 9: e99021. 10.1371/journal.pone.0099021
111. Ullah, H.; Khan, H. Front. Pharmacol, 2018; 9: 422.
112. Kittur S., Wilasrusmee S., Pedersen W. A., Mattson M. P., Straube-West K., Wilasrusmee C., et al. Neurotrophic and neuroprotective effects of milk thistle (*Silybum marianum*) on neurons in culture. *J. Mol. Neurosci*, 2002; 18: 265–269. 10.1385/JMN:18:3:265
113. Abushouk A. I., Negida A., Ahmed H., Abdel-Daim M. M. Neuroprotective mechanisms of plant extracts against MPTP induced neurotoxicity: future applications in Parkinson's disease. *Biomed. Pharmacother*, 2017; 85: 635–645. 10.1016/j.biopha.2016.11.074
114. Křen V., Walterova D. Silybin and silymarin-new effects and applications. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub*, 2005; 149: 29–41. 10.5507/bp.2005.002

115. Kumar, H.; Kim, I.S.; More, S.V.; Kim, B.W.; Bahk, Y.Y. and Choi, D.K. (2013). Gastrodin protects apoptotic dopaminergic neurons in a toxin-induced Parkinson's disease model.
116. Lee, Y.; Park, H.R.; Chun, H.J. and Lee, J. (2015). Silibinin prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease via mitochondrial stabilization. J. Neurosci.
117. Stojkovska I., Wagner B. M., Morrison B. E. Parkinson's disease and enhanced inflammatory response. *Exp. Biol. Med.*, 2015; 240: 1387–1395. 10.1177/1535370215576313
118. Singhal N. K., Srivastava G., Patel D. K., Jain S. K., Singh M. P. Melatonin or silymarin reduces maneb- and paraquat-induced Parkinson's disease phenotype in the mouse. *J. Pineal Res.*, 2011; 50: 97–109. 10.1111/j.1600-079X.2010.00819.
119. Fernández-Moriano C., González-Burgos E., Gómez-Serranillos M. P. Mitochondria-targeted protective compounds in Parkinson's and Alzheimer's diseases. *Oxid. Med. Cell. Longev*, 2015; 2015: 408927. 10.1155/2015/408927
120. Singh M., Dykens J. A., Simpkins J. W. Novel mechanisms for estrogen-induced neuroprotection. *Exp. Biol. Med.*, 2006; 231: 514–521. 10.1177/153537020623100505
121. Manokaran, K.; Bhat, P.; Nayak, D.; Baskaran, R.; Paramasivam, P.; Ahmed, S. F.; Balaji, V. E.; Ranganath Pai, K.; Balaji, V. Oxidative Stress and Female Reproductive Disorder: A Review. *Asian Pac. J. Reprod*, 2022; 11(3): 107–116.
122. Kayedpoor P, Mohamadi S, Karimzadeh-Bardei L, Nabiuni M. Anti-inflammatory Effect of Silymarin on Ovarian Immunohistochemical Localization of TNF-α Associated with Systemic Inflammation in Polycystic Ovarian Syndrome.
123. Nabiuni M, Kayedpoor P, Mohammadi S, Karimzadeh L. Effect of silymarin on estradiol valerate- induced polycystic ovary syndrome. MEDICAL SCIENCES, 2015; 25(1): 16-26. URL:
124. Dupuis ML, Conti F, Maselli A, et al. The natural agonist of estrogen receptor β silibinin plays an immunosuppressive role representing a potential therapeutic tool in rheumatoid arthritis. *Front Immunol*, 2018; 9: 1903.
125. Atarbashe, R. K.; Abu-Raghif, A. The Therapeutic Effects of Ambrisentan on Experimentally Induced Colitis in a Male Rat's Models. *Ann Trop Med. Public Health*, 2020; 23(4).
126. Rastegarpanah, M.; Malekzadeh, R.; Vahedi, H.; Mohammadi, M.; Elahi, E.; Chaharmahali, M.; Safarnavadeh, T.; Abdollahi, M. A Randomized, Double Blinded, Placebo-Controlled Clinical Trial of Silymarin in Ulcerative Colitis. *Chin. J. Integr. Med*., 2015; 21(12): 902–906.
127. Hoseini, M.; Mohammadi, S.; Mohammadi-Hamaneh, A.; Akbarzadeh, T.; Abdollahi, A.; Jaafari, M. R.; Rezayat, S. M. An Experimental Model on the Protective Impact of Nanosilymarin on Ulcerative Colitis Induced by TNBS in Rats: The Inclusion of TLR4/NF-Kb Pathway. *Nanomed. J*., 2022; 9(3): 216–222Z.
128. Yuan Z.W., Li Y.Z., Liu Z.Q., Feng S.L., Zhou H., Liu C.X., Liu L., Xie Y. Role of tangeretin as a potential bioavailability enhancer for silybin: Pharmacokinetic and pharmacological studies. Pharmacol. Res., 2018; 128: 153-166. doi: 10.1016/j.phrs.2017.09.019
129. Jancova P., Anzenbacherova E., Papouskova B., Lemr K., Luzna P., Veinlichova A., Anzenbacher P., Simanek V. Silybin is metabolized by cytochrome P450 2C8 in vitro. Drug Metab. Dispos, 35: 2035-2039. doi: 10.1124/dmd.107.016410
130. Abenavoli, L.; Izzo, A.A.; Mili´c, N.; Cicala, C.; Santini, A.; Capasso, R. Milk thistle (Silybum marianum): Aconcise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother. Res., 2018; 32: 2202–2213.
131. Bijak, M. Silybin, a major bioactive component of milk thistle (Silybum marianum L. Gaernt.)—Chemistry, Bioavailability, and Metabolism. Molecules, 2017; 22: 1942.
132. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.R.; del Pilar Rodriguez-Torres, M.; Acosta-Torres, L.S.; Diaz-Torres, L.A.; Grillo, R.; Swamy, M.K.; Sharma, S.; et al. Nano based drug delivery systems: Recent developments and future prospects. J. Nanobiotechnol, 2018; 16: 71–103.
133. Obeid, M.A.; Al Qaraghuli, M.M.; Alsaadi, M.; Alzahrani, A.R.; Niwasabutra, K.; Ferro, V.A. Delivering natural products and biotherapeutics to improve drug efficacy. Ther. Deliv., 2017; 8: 947–956.
134. Li, Z.; Jiang, H.; Xu, C.; Gu, L. A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals. Food Hydrocoll, 2015; 43: 153–164.
135. Agarwal, R.; Agarwal, C.; Ichikawa, H.; Singh, R.P.; Agarwal, B.B. Anticancer potential of silymarin: From bench to bed side. Anticancer Res., 2006; 26: 4457–4498.
136. Panapisal, V.; Charoensri, S.; Tantituvanont, A. Formulation of microemulsion systems for dermal delivery of silymarin. Pharm. Sci. Tech., 2012; 13: 389–399.
137. Piazzini, V.; Rosseti, C.; Bigagli, E.; Luceri, C.; Bilia, A.R.; Bergonzi, M.C. Prediction of permeation and cellular transport of silybum marianum extract formulated in a nanoemulsion by using PAMPA and caco-2 cell models. Planta Med., 2017; 83: 1184–1193.
138. Ma, X.; Williams, R.O. Polymeric nanomedicines for poorly soluble drugs in oral delivery systems: An update. J. Pharm. Investig, 2018; 48: 61–75.