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MILK THISTLE (*SILYBUM MARIANUM*) : A REVIEW


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ABSTRACT

Milk thistle (Silybum marianum, family-Compositae) is widespread throughout the world. Milk thistle's common name comes from the white markings on the leaves and its milky white sap used traditionally by nursing mothers to increase milk. Milk thistle appears to be safe and have multiple health benefits on various liver conditions viz; liver cirrhosis, alcoholic hepatitis, alcoholic fatty liver, liver poisoning, and viral hepatitis. Primary chemical constituents of Milk Thistle include flavolignans (silymarin), tyramine, histamine, gamma linoleic acid, essential oil, mucilage, and bitter principle. Available evidence is not sufficient to suggest whether milk thistle may be more effective for some liver diseases than others or if effectiveness might be related to duration of therapy or chronicity and severity of liver disease.

Key Words: Milk Thistle, Liver diseases, Liver poisoning, Silymarin, Tyramine, Hiatamine.

INTRODUCTION

Herbal plants are used as medicines in folk and traditional medicinal practice based on the use of plants and plant extracts. Finding healing powers in plants is an ancient idea. People in all continents have used hundreds, if not thousands, of indigenous plants for treatment of various ailments dating back to prehistory.

Milk thistle (*Silybum marianum*), a member of the Compositae family, is an annual or biennial native to the Mediterranean, but now widespread throughout the world. The main stem is stout, ridged with branching. Milk thistle has the white patches, or marbling along the veins of the dark green leaves. The broad leaves are deeply lobed, and basal leaves can be 20 inches long and 10 inches wide. The leaf margins are yellow and tipped with woody spines 1/8" to 1/2" long. The leaves are alternate, and clasping to the stem. The stem leaves are smaller and not quite as lobed. Each stem ends in a solitary composite flower head, about two inches in diameter, consisting of

purple disc flowers. The flower head of milk thistle differs from other thistles with the presence of broad leathery bracts that are also tipped with stiff spines ¾ inch to two inches long. The seeds are heavy, ¼ inch long, flat, smooth, and shiny and the color ranges from black to brown mottled and have a tuft of minutely barbed bristles, which is deciduous, and falls off in a ring when the seeds mature [1]

Fig. 1

Fig. 2

Thistle is sometimes called

Common Names—Milk thistle, Mary thistle, Holy thistle, Silymarin,).

Milk thistle's common name comes from the white markings on the leaves and its milky white sap used traditionally by nursing mothers to increase milk. However it is best known for its use as a liver protectant and decongestant, which can be traced to the Greeks and Pliny the Elder (23-79AD), who wrote that it was excellent for "carrying off bile." The famous English herbalist Culpepper (1616-1654) used milk thistle to cleanse the liver and spleen, and to treat jaundice and gallstone [2] .

Milk thistle appears to be safe and have multiple health benefits on various liver conditions viz; liver cirrhosis, alcoholic hepatitis, alcoholic fatty liver, liver poisoning, and viral hepatitis.There is no current evidence to indicate that milk thistle directly affects the Hepatitis C Virus (HCV).

the available evidence on the mechanisms of action appears promising [3]. Preliminary studies in animals show that milk thistle may help protect the liver from injury by a variety of toxins ("poisons" such as drugs, viruses, alcohol, radiation, and poisonous mushrooms) and limit the damage from them[4, 5]. To date, the most reliable milk thistle studies on people show that milk thistle does not cure liver disease, but that milk thistle may improve the way the liver works in patients with cirrhosis.

The aerial parts including seeds are used to make medicines. The seeds are more commonly used to protect the liver from damage caused by hepatitis viruses as well as alcohol and other substances. Compounds found in milk thistle — sylibin, sylimarin — act as antioxidants and also stimulate the repair of the liver. In recent experiments using milk thistle and human liver cells, the researchers found that relatively small concentrations of milk

thistle significantly slow down the activity of the liver enzyme CYP3A4 by 50% to 100%.[6]

PHYTOCHEMICAL STUDIES:

Primary chemical constituents of Milk Thistle include flavolignans (silymarin), tyramine, histamine, gamma linoleic acid, essential oil, mucilage, and bitter principle. The dried fruit of Milk Thistle contains the flavonoid complex known as silymarin - the constituent responsible for the medical benefits of the plant. The principal extract of milk thistle, silymarin (4% to 6% in ripe fruit), is composed of several polyphenolic tlavonolignans. The major component (60%) is silybin (also known as silibinin or silybinin), and it is also the most biologically active; other components include silichristin (also known as silychristin, silycristine or silicristin), a metabolic stimulant, and silydianin. Silymarin is found in highest concentrations in the fruit of the plant. Other constituents are flavonoids, a fixed oil (16% to 18%), betaine, trimethylglycine and amines. Milk thistle seed contains 1.5-3% flavone lignans, collectively referred to as silymarin;20-30% fixed oil, of which approximately 60% is linoleic acid, approximately 30% is oleic acid, and approximately 9% is palmitic acid; 25-30% protein; 0.038% tocopherol; 0.63% sterols, including cholesterol, campesterol, stigmasterol, and sitosterol; and some mucilage. The three principle components of silymarin are the flavanolignans silybin, silychristin, and silidianin[7].

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PHARMACOLOGICAL STUDIES:

Effect on liver:

A different review of the literature, performed for the U. S. Department of Health and Human Services, found that, while there is strong evidence of legitimate medical benefits, the studies done to date are of such uneven design and quality that no firm conclusions about degrees of effectiveness for specific conditions or appropriate dosage can yet be made[8].

A review of studies of silymarin and liver disease which are available on the web shows an interesting pattern in that studies which tested low dosages of silymarin concluded that silymarin was ineffective[9], while studies which used significantly larger doses concluded that silymarin was biologically active and had therapeutic effects[10].

Reviews of the literature covering clinical studies of silymarin vary in their conclusions. A review using only studies with both double-blind and placebo protocols concluded that milk thistle and its derivatives "does not seem to significantly influence the course of patients with alcoholic and/or hepatitis B or C liver diseases"[11]

Extracts of milk thistle have been recognized as "liver tonics" for many centuries[12] Research into the biological activity of silymarin and its possible medical uses has been conducted in many countries since the 1970s, but the quality of the research has been uneven. Milk thistle has been reported to have protective effects on the liver and to greatly improve its function. It is typically used to treat liver cirrhosis, chronic hepatitis (liver inflammation), toxin-induced liver damage (including the prevention of severe liver damage from Amanita phalloides ('death cap' mushroom poisoning), and gallbladder disorders[13] .

Toxin-induced liver damage:

This class of drugs is known to cause liver damage from oxidation of lipids. Patients taking silymarin in the study had less hepatic damage from the oxidation of lipids than patients taking the placebo. The efficacy of silymarin in preventing drug-induced liver damage in patients taking psychotropic drugs long-term has been investigated[14] .

Research suggests that extracts of milk thistle prevent and repair damage to the liver from toxic chemicals and medications. Workers who

had been exposed to vapors from toxic chemicals (toluene and/or xylene) for 5-20 years were given either a standardized milk thistle extract (80% silymarin) or placebo for 30 days[15]. The workers taking the milk thistle extract showed significant improvement in liver function tests (ALT and AST) and platelet counts vs. the placebo group.
In a 2009 study published in the journal Cancer, milk thistle showed promise in reducing the liver damaging effects of chemotherapy in a study of 50 children[16].

Anti carcinogenic effect:
Preliminary laboratory studies also suggest that active substances in milk thistle may have anti-cancer effects. One active substance known as silymarin has strong antioxidant properties and has been shown to inhibit the growth of human prostate, breast, and cervical cancer cells in test tubes. Further studies are needed to determine whether milk thistle is safe or effective for people with these forms of cancer[17].
Oxidative stress is one of the key players in skin carcinogenesis, and therefore identifying nontoxic strong antioxidants to prevent skin cancer is an important area of research. In both animal and cell culture studies, it has been shown that silymarin, a polyphenolic flavonoid antioxidant, exhibits preventive and anticancer effects against skin cancer. For example, silymarin strongly prevents both photo carcinogenesis and skin tumor promotion in mice, in part, by scavenging free radicals and reactive oxygen species and strengthening the antioxidant system. It was also found that this effect of silymarin is by inhibiting endogenous tumor promoter tumor necrosis factor alpha in mouse skin, a central mediator in skin tumor promotion. In mechanistic studies, silymarin inhibits mitogenic and cell survival signaling and induces apoptosis. Furthermore, silymarin effectively modulates cell-cycle regulators and check points toward inhibition of proliferation, and growth arrest in G0-G1 and G2-M phases of the cell cycle. Thus, due to its mechanism-based chemo preventive and anticancer effects in experimental models, silymarin is important for the prevention and/or therapy of skin cancer, as well as other cancers of epithelial origin in humans[18].

Anti oxidant effect:
As an antioxidant, silymarin scavenges free radicals that can damage cells exposed to toxins. Silymarin has been said to be at least ten times more potent in antioxidant activity than vitamin E [19]. It increases glutathione in the liver by more than 35% in healthy subjects and by more than 50% in rats [20]. Glutathione is responsible for detoxifying a wide range of hormones, drugs, and chemicals. High levels of glutathione in the liver increases its capacity for detoxification. Silymarin also increases the level of the important antioxidant enzyme superoxide dismutase in cell cultures [21]. It stimulates protein synthesis in the liver, which results in an increase in the production of new liver cells to replace the damaged ones [22]. Silymarin inhibits the synthesis of leukotrienes (mediators of inflammation, which can result in psoriasis, among other things) [23].

Milk Thistle for mushroom poisoning:
In Germany, Milk Thistle is highly recognized as a potent cure for both liver disease and as the only anti-dote for Death Cap mushroom poisoning. The German equivalent to the US Federal Drug Administration (FDA), the Commission E, encourages and allows Milk Thistle as a regulated herb for preventative and curative purposes. In fact, in Western Europe, Milk Thistle is regularly found as an antidote in hospitals and medical centers for poisoning form Death Cap mushrooms. It is proven that if given in time, intravenous Milk Thistle will lower the mortality rate of this deadly fungus [24] .

Lowering Cholesterol levels:
Studies continue to be encouraging and one

such study indicates that the active component, silybin, in Milk Thistle is just as effective in lowering cholesterol levels in animals as a common drug probucol. The study concluded that silybin is also effective for increasing HDL (good) cholesterol levels, all without the side effects commonly associated with prescription drugs [25].

Silymarin is neither well absorbed in water nor by the gastrointestinal tract, so high standardized concentrations are best to assure sufficient absorption into the blood stream. As well, because Milk Thistle is not water soluble, its effectiveness as a tea is doubtful. Many companies market the Milk Thistle tea, however only 10 percent of the actual active plant ingredients are actually absorbed [26].

Bladder:

Milk Thistle is both a demulcent so it stimulates bile flow and is a natural for treating a wide array of Gall Bladder diseases and Symptoms. Milk Thistle can calm down an inflamed Gall Bladder while at the same time clearing out any stagnation that might be present. When using Milk Thistle to combat Gall Bladder symptoms, it is important to verify that there are no Gall Stones present which would be too large for the gall bladder to pass. The only way that this can be known is to visit your local physician and get a clearance from them to proceed [27].

Milk thistle silibinin modulates cyclin-dependent kinase inhibitors -cyclin-dependent kinases - cyclin cascade and activates caspase 3 causing growth inhibition and apoptotic death of human bladder transitional cell carcinoma cells [28]. In another study, milk thistle silibinin decreased survivin levels and caspases-PARP cleavages, in accord with a strong apoptotic death and growth inhibition of Human bladder transitional-cell papilloma cells [29]. And, milk thistle silymarin was found to be effective in preventing OH-BBN-induced bladder carcinogenesis in mice [30].

Breast Cancer:

An in vitro study has suggested a possible synergism between milk thistle silibinin and conventional cytotoxic agents for breast cancer treatment [31].Milk thistle extract may exert a strong anti carcinogenic effect against breast cancer involving inhibition the threshold kinase activities of cyclin-dependent kinases and associated cyclins, leading to a G1 arrest in cell cycle progression [32].

Prostate Cancer:

Extracts of Milk Thistle possess anti cancer activities on human prostrate carcinoma. In prostate cancer, milk thistle silibinin exerts its anti-cancer effect probably via epidermal growth factor receptor, insulin-like growth factor receptor type I and nuclear factor kappa B signaling [33]. Isosilybin A and B might be the most effective suppressors of prostate-specific antigen secretion by androgen-dependent LNCaP cells. Researchers suggested that milk thistle extracts enriched for isosilybin A or B might possess improved potency in prostate cancer prevention and treatment [34]. Finally, milk thistle silibinin was found to able to down regulate 5alpha-dihydrotestosterone, thus, milk thistle may be beneficial to prostate [35] .

Effect on heart:

Milk thistle extract, silymarin, protects cardiomyocytes against doxorubicin-induced oxidative stress via cell membrane stabilization effect, radical scavenging and iron chelating potency [36].

Immune modulation:

A study of mice showed milk thistle silymarin could prevent UVB-induced immuno-suppression and oxidative stress probably by inhibiting the infiltration of leukocytes, and myeloperoxidase activity [37].

A study demonstrated that milk thistle was

immunostimulatory in vitro. Milk thistle increased lymphocyte proliferation in both mitogen and MLC assays. These effects of Milk Thistle were associated with an increase in interferon gamma, interleukin (IL)-4 and IL-10 cytokines in the MLC. The immunostimulatory effect increased in response to increasing doses of Milk Thistle [38].

Nervous system:

In a cell study, milk thistle silymarin significantly inhibited the LPS-induced activation of microglia and the production of inflammatory mediators, such as tumour necrosis factor-alpha and nitric oxide (NO), and reduced the damage to dopaminergic neurons [39] and Milk thistle extract protected cultured rat hippocampal neurons against oxidative stress-induced cell death [40].

ADVERSE EFFECT:

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According to the German Commission E, there are no reported side effects with milk thistle within the recommended doses. Rare cases of milk thistle having a laxative effect have been reported. Human studies have reported stomach upset, heartburn, and transient headaches; however, none of these symptoms were attributed to supplementation with milk thistle, and supplementation was not discontinued [41] One human dosing study reported nausea, heartburn, and dyspepsia in patients treated with 160 mg/day, dyspepsia in patients treated with 240 mg/day, and postprandial nausea and meteorism in patients treated with 360 mg/day. None of these side effects were dose related.

Silymarin has been well tolerated in high doses. Silymarin has been used in pregnant women with intrahepatic cholestasis at doses of 560 mg/day for 16 days, with no toxicity to the patient or the fetus [42].The published data on silymarin use in children focuses on intravenous doses of 20 to 50 mg/kg body weight for mushroom poisoning [43]. Silymarin has also proved nontoxic in rats and mice when administered in doses as high as 5,000 mg/kg body weight. Rats and dogs have received silymarin at doses of 50 to 2,500 mg/kg body weight for a 12-month period. Investigations, including postmortem analyses, showed no evidence of toxicity.

It is not known whether milk thistle may reduce, enhance, or have no effect on the effectiveness of chemotherapy. Silymarin decreases the activity of the cytochrome P450 enzyme system, which is involved in the clearance of certain chemotherapy drugs [44]. However, the dose at which inhibition is observed is high and not achieved with oral intake of silymarin [45]. Milk thistle may also interact adversely with chemotherapy drugs that exert their cytotoxic effects through generation of free radicals. Silymarin and its metabolite inhibit P-glycoprotein-mediated cellular efflux, leading to potentiation of doxorubicin cytotoxicity. No trials have been performed to support or negate these theoretical considerations. No effects on indinavir and alcohol pharmacokinetics have been observed. Enhancement of anti arrhythmic effects of amiodarone in rats has been observed [46].

CLINICAL STUDIES OF MILK THISTLE IN HUMANS:

Sixteen prospective trials were identified. Fourteen were randomized, blinded, placebo controlled studies of milk thistle's effectiveness in a variety of liver diseases. In one additional placebo-controlled trial, blinding or randomization was not clear, and one placebo controlled study was a cohort study with a placebo comparison group.

Seventeen additional trials used nonplacebo controls; two other trials studied milk thistle as prophylaxis in patients with no known liver disease who were starting potentially hepatotoxic drugs. The identified studies

addressed alcohol-related liver disease, toxin-induced liver disease, and viral liver disease. No studies were found that evaluated milk thistle for cholestatic liver disease or primary hepatic malignancy (hepatocellular carcinoma, cholangiocarcinoma).

Among six studies of milk thistle and chronic alcoholic liver disease, four reported significant improvement in at least one measurement of liver function (i.e., aminotransferases, albumin, and/or malondialdehyde) or histologic findings with milk thistle compared with placebo, but also reported no difference between groups for other outcome measures.

Three placebo-controlled studies evaluated milk thistle for viral hepatitis. The one acute viral hepatitis study reported latest outcome measures at 28 days and showed significant improvement in aspartate aminotransferase and bilirubin. The two studies of chronic viral hepatitis differed markedly in duration of therapy (7 days and 1 year). The shorter study showed improvement in aminotransferases for milk thistle compared with placebo but not other laboratory measures. In the longer study, milk thistle was associated with a nonsignificant trend toward histologic improvement, the only outcome measure reported.

Two trials included patients with alcoholic or nonalcoholic cirrhosis. The milk thistle arms showed a trend toward improved survival in one trial and significantly improved survival for subgroups with alcoholic cirrhosis or Child's Group A severity. The second study reported no significant improvement in laboratory measures and survival for other clinical subgroups, but no data were given.

Two trials specifically studied patients with alcoholic cirrhosis. Duration of therapy was unclear in the first, which reported no improvement in laboratory measures of liver function, hepatomegaly, jaundice, ascites, or survival. However, there were nonsignificant trends favoring milk thistle in incidence of encephalopathy and gastrointestinal bleeding and in survival for subjects with concomitant hepatitis C. The second study, after treatment for 30 days, reported significant improvements in aminotransferases but not bilirubin for milk thistle compared with placebo.

Three trials evaluated milk thistle in the setting of hepatotoxic drugs: one for therapeutic use and two for prophylaxis with milk thistle. Results were mixed among the three trials.

No studies were identified regarding milk thistle and cholestatic liver disease or primary hepatic malignancy [47].

CONCLUSION:

Clinical efficacy of milk thistle is not clearly established. Interpretation of the evidence is hampered by poor study methods and/or poor quality of reporting in publications. Problems in study design include heterogeneity in etiology and extent of liver disease, small sample sizes, and variation in formulation, dosing, and duration of milk thistle therapy. Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferases and liver function tests are overwhelmingly the most common outcome measure studied. Survival and other clinical outcome measures have been studied least often, with both positive and negative findings. Available evidence is not sufficient to suggest whether milk thistle may be more effective for some liver diseases than others or if effectiveness might be related to duration of therapy or chronicity and severity of liver disease. Regarding adverse effects, little evidence is available regarding causality, but available evidence does suggest that milk thistle is associated with few, and generally minor, adverse effects. Despite substantial in vitro and animal research, the mechanism of action of milk thistle is not fully defined and may be multifactorial. A systematic review of this evidence to clarify what is known and identify gaps in knowledge would be important to guide

design of future studies of the mechanisms of milk thistle and clinical trials .

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