A Comprehensive Review of Ethnopharmacology and Medicinal Uses of Milk Thistle

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CHAPTER 23

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SUMMARY

Silybum marianum is an outstanding plant with rich ethnopharmacological credentials accompanied by an impressive array of health benefits. Its protective action in liver diseases, antioxidant activity with anti-inflammatory action and possible use in digestive health have been reported. Clinical trials validate its use in liver ailments as an adjunctive treatment in other long-standing ailments. By incorporating milk thistle in medicinal therapies, health care professionals can improve outcomes for their patients as well as facilitate the use of natural, nontoxic products. Due to its health benefits, milk thistle's large scale production at the farm level and its industrial prospects have to be considered. It is highly adaptable to marginal soils, making it an important crop for use in future agriculture. Future research is also needed to clarify the specific pathways through which milk thistle exerts its health benefits, maximize cultivation techniques, and identify wider applications in contemporary medicine.

INTRODUCTION

Milk thistle, *Silybum* (*S.*) *marianum*, is a flowering plant in the family Asteraceae that is native to the Mediterranean area. Though the plant is originally from the Mediterranean area but is cultivated extensively in Asia, Africa, America, and Australia (Porwal et al., 2019; Zahra, 2017). Milk thistle grows in the wild as a plant with a life cycle of two years, with the first year after germination spent in the vegetative phase. Characterized by spiny stems, distinctive purple flowers, and brilliant green leaves with white stripes, milk thistle is frequently utilized as an ornamental plant in residential settings. It is cultivated, however, primarily as an annual crop, with a cycle depending on how far in advance of spring it is planted (Young et al., 1978; Gresta et al., 2007).

Apart from being an ornamental plant, milk thistle is rich in medicinal properties. It is revealed that milk thistle contains phytochemicals with diverse health properties such as liver protection, brain health, cancer-fighting, lowering of blood pressure, and cholesterol levels (Zahra, 2017). Additionally, they had anti-inflammatory, antioxidant, and antiviral properties (Shoukheba et al., 2018; Liu et al., 2019; Aziz et al., 2020). The health-related benefits of milk thistle owe their origin to a group of compounds referred to as silymarin. The complex contains various flavonoids, including silybin A and B, isosilybin A and B, silychristin, and silydianin (Lee & Liu, 2003; Anthony & Saleh, 2012). The concentration of silymarin is highest in the achenes, also referred as seeds (Šeršen et al., 2006; Engelberth et al., 2008). The plant is utilized to treat ailments associated with the gallbladder, liver, spleen, and kidney (Schadewaldt, 1969; Flora et al., 1998).

Milk thistle has been used to treat various ailments for over 2,000 years, especially liver disorders, kidneys, rheumatism, digestion disorders, heart disease, and gallbladder disorders such as jaundice, hepatitis, and cirrhosis (Ansari et al., 2016). This plant is rich in many essential biochemical compounds. It consists of isomeric combinations of flavonolignans such as taxofillin, silychristin, silydianin, silybin, and isosilybin. Combinations of these compounds are known as silymarin (SM) (Kurkin et al., 2001).

It is eaten as a vegetable in salads, and milk production in breastfeeding women is supported by its seed in the form of a galactagogue (Bhatia et al., 2001). In traditional Iranian medicine, it is called "Harshfbari," and its use was described in the ancient book Al-Hashaish Dioscorides, where it was depicted along with its medicinal properties (Bower et al., 2014). Milk thistle has been shown to offer protection against various biological toxins, such as mycotoxins, snake venom, and bacterial toxins, as well as chemical toxins like metals, fluoride, pesticides, and toxins that harm the heart, nerves, liver, and kidneys (Brandon-Warner et al., 2012). One of its principal constituents, silymarin, reduces lipid peroxidation and exhibits antioxidant, antihypertensive, antidiabetic, and liver-preserving activities (Brantley et al., 2010; Chambers et al., 2017). Research indicates that silymarin can inhibit the

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growth, adhesion, and spread of cancer cells by promoting apoptosis and producing reactive oxygen species (ROS), while lowering levels of glutathione, Bcl-2, survivin, and cyclin D1, and raising levels of pro-apoptotic proteins like Bax (Chen et al., 2009).

Silymarin is the main active ingredient in milk thistle extract, found in the leaves, seeds, and fruit of the plant. It consists of about 70-80% flavonolignans, including silybin, isosilybin, silychristin, isosilychristin, and silydianin, as well as other flavonoids like taxifolin, quercetin, and apigenin. The remaining 20-30% is made up of a less-defined mixture of polymeric flavonoids. Among the flavonolignans, silybin has the most potent therapeutic effects. Studies suggest that silymarin can inhibit the growth of different cancer cells, including prostate (Deep & Agarwal, 2007), breast (Fanoudi et al., 2020), colon (Ferlay et al., 2021), ovary (Ferlay et al., 2010), lung (Frassová & Rudá-Kučerová, 2017), and bladder (García-Maceira & Mateo, 2009) cancers. These biological activities are mainly through cell cycle arrest at the G1/S-phase (Ansari et al., 2016), activation of cyclin-dependent kinase inhibitors like p15, p21, and p27 (Ge et al., 2011), and the inhibition of survival pathways such as nuclear factor-kappa B (NF-κB) and B-cell lymphoma-extra-large (Bcl-xL) (Goral, 2015; Girardi et al., 2018). The anti-inflammatory effects result from its ability to inhibit NF-κB-regulated genes, including cyclooxygenase-2 (COX-2), lipoxygenase (LOX), inducible nitric oxide synthase (iNOS), tumor necrosis factor (TNF), and interleukin-1 (IL-1) (Deep & Agarwal, 2007).

Milk thistle is offered to patients in multiple forms including capsules, tablets, liquid extracts (tinctures), and intravenous formulations. It interacts minimally with other drugs and does not significantly affect cytochrome P-450 enzymes (Emadi et al., 2022). Clinical trials have confirmed the safety and bioavailability of silymarin (Deep & Agarwal, 2007; Emadi et al., 2022; Hackett et al., 2013), and animal studies show no significant toxicity (Hosseini et al., 2021). In humans, silybin, silydianin, and silychristin exhibit no cytotoxic or genotoxic effects at concentrations of 100 μM (Bijak et al., 2017). Therapeutic doses of up to 700 mg taken three times daily for 24 weeks showed no adverse effects, though some patients reported mild gastrointestinal discomfort, such as nausea and diarrhea (Ansari et al., 2016).

This plant is native to various localities, such as Australia, North America, South America, Southern Europe, North Africa, and Asia (Bhatia et al., 2001). It is also widely used in salads in Europe, where its seeds are known to have galactagogue properties that facilitate milk supply in breastfeeding mothers (Parmar et al., 2022). In ancient literature, this plant is known as "Harshfbari" and is illustrated in the medicinal work Al-Hashaish Dioscorides, which is an old-time reader in traditional medicine. The qualities and synonyms of milk thistle mentioned in this work are similar to alternative sources of traditional Iranian medicine, emphasizing their ancient use in traditional medicine (Bower, 2014). *S. marianum* is also protective against several toxic chemicals, such as metals, fluoride, pesticides, as well as compounds toxic to the heart, nervous system, liver, and kidneys (Brandon-Warner et al., 2012). It also offers protection from biological toxins such as mycotoxins, snake venom, and toxins from bacteria. Silymarin, which is one of the active compounds in *S. marianum*, shows strong antioxidant activity by inhibiting lipid peroxidation. It also shows antidiabetic, liver-protective, as well as blood pressure-decreasing activities (Brantley et al., 2010; Chambers et al., 2017). Various studies have described the multifaceted curative properties of *S. marianum*. It is reported to inhibit cancer cell growth, adhesion, and migration, as well as induce apoptosis and produce reactive oxygen species (ROS) (Emadi et al., 2022).

HEALTH BENEFITS AND MECHANISMS OF ACTION

Hepatoprotective Effects

With its antioxidant properties as well as protective abilities in maintaining the liver, silymarin continues to be frequently prescribed in medicine. I is widely being used as a liver care supplement (Post-White et al., 2007; Trappoliere et al., 2009; Loguercio et al., 2011; Loguercio et al., 2012). Its efficacy in returning liver function to normal as well as in liver cell regeneration has brought about silymarin's widespread use to treat liver problems like alcoholic and non-alcoholic liver disease, viral hepatitis, liver injury from drugs, as well as mushroom poisoning cases (Abenavoli et al., 2018). It has also been attributed to having health benefits in treating steatohepatitis (Milosevic et al., 2014) as well as in treating cirrhosis (Parés et al., 1998). Because of the liver's role in detoxification, silymarin and its analogs are protective in preventing organ damage produced by toxins such as carbon tetrachloride (Lettéron et al., 1990), phalloidin (Vo et al., 2017), alpha-amanitin (Karimi et al., 2011), acetaminophen (Papackova et al., 2018), ethanol (Brandon-Warner et al., 2012), and the cancer chemotherapy drug, doxorubicin (Patel et al., 2010). The secret to silymarin's liver protective abilities is in neutralizing free radicals generated from breaking down such toxins (Trouillas et al., 2008). Secondarily, silymarin's antioxidant activity is based on various mechanisms. First, silymarin essentially prevents free radical formation by inhibiting those enzymes that are involved in their formation. Second, silymarin assists in keeping mitochondrial electron transport chains in their stable state under stressful conditions. Third, silymarin controls redox balance by activating enzymatic as well as non-enzymatic antioxidants through various factors such as transcription factors such as Nrf2 and NF-κB. Fourth, silymarin increases activity of vitagenes that are involved in generating protective molecules such as heat shock proteins (HSP), thioredoxin, and sirtuins. Lastly, silymarin increases cellular glutathione levels with decreased lipid peroxidation, thereby adding to protective action (Esmaeil et al., 2017; Surai, 2015).

In addition to serving as an antioxidant, silymarin also maintains liver health through its anti-inflammatory, antiviral, and immune-regulating properties, which act upon liver as well as immune cells (Shoukheba et al., 2018; Liu et al., 2019; Aziz et al., 2020). Recent studies have shown that silymarin is highly effective in combating the hepatitis C virus (HCV; Wagoner et al., 2010). It was also revealed in one of the studies

that silybin, which is present in silymarin, inhibits leukotriene synthesis by Kupffer cells, thus increasing its liver protective action (Dehmlow et al., 1996).

Silymarin is reported to interact with various compounds to block toxins from crossing liver cells, enhance liver cell metabolism, induce protein synthesis in liver cells by activating RNA polymerase I (Vargas-Mendoza et al., 2014), and act as an iron-binding compound (Borsari et al., 2001). Silybin is reported to significantly counteract liver toxicity caused by iron—it is clear in reduced adduct accumulation in rat silymarin-treated rats with iron-overloaded periportal hepatocytes (Pietrangelo et al., 1995).

Anti-inflammatory and Immunomodulatory Activity

Milk thistle is known for its potent antioxidant and anti-inflammatory properties, with silymarin being its primary active component. The anti-inflammatory effects of silymarin are attributed to its suppression of the 5-lipoxygenase pathway, which inhibits leukotriene synthesis, as well as its regulation of several pro-inflammatory signaling pathways and molecules, such as NF-κB, COX-2, LOX, iNOS, TNF, and IL-1 (Saller et al., 2001; Agarwal et al., 2006). Moreover, research indicates that silymarin can alleviate airway inflammation by suppressing the ERK/p38 MAPK signaling pathway in human bronchial epithelial cells exposed to cigarette smoke extract (Li et al., 2016). Beyond its anti-inflammatory actions, silymarin exhibits immunomodulatory effects by enhancing lymphocyte proliferation and cytokine secretion, including IFNγ, IL-4, and IL-10, in a dose-dependent manner (Wilasrusmee et al., 2002). Low doses of silymarin have been observed to boost neutrophil counts and spleen cell numbers in immunosuppressive mice, further highlighting its role in immune system enhancement (Karimi et al., 2018). However, higher doses appear to mitigate these effects, likely due to its reactive oxygen species (ROS) scavenging activity, which is essential for lymphocyte activation (Victor et al., 2004). Overall, these findings underscore the potential of milk thistle as both an anti-inflammatory and immune-supportive agent, making it a valuable therapeutic option in various inflammatory and immune-related conditions.

Anticancer Potential

Milk thistle, especially active constituents silymarin and silybin, exhibits impressive anti-cancer activity from in vivo as well as in vitro experiments. Silymarin is said to affect regulation of cell cycle components and apoptosis-related proteins towards maintaining the balance in cell survival versus programmed death. For instance, in oral cancer cell lines (HSC-4, YD15, and Ca9.22) studies, silymarin-induced apoptosis is said to be mediated by caspase-8 activation and death receptor 5 activation (Won et al., 2018). Silybin is also reported to regulate cancer cell proliferation, metabolic activity, inflammation, and angiogenesis (Deep & Agarwal, 2010). The antiproliferative activity of silymarin is reported in various types of cancers such as prostate cancer (Zi et al., 2000; Tyagi et al., 2002), ovarian cancer (Fan et al., 2014), breast cancer (Rastegar et al., 2013), lung cancer (Sharma et al., 2003). Silybin also reduces survivin protein levels in bladder cancer cells, which is involved in apoptosis (Tyagi et al., 2003). The compound down-regulates important gene products involved in proliferation, invasion, and angiogenesis of tumors such as cyclin D1, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF) along with anti-inflammatory activity by inhibiting NF-κB-regulated gene products such as COX-2 and TNF (Agarwal et al., 2006). The results emphasize the promising complementary role of milk thistle in cancer treatment.

Cardioprotective Effects

Cardioprotection offered by milk thistle is essentially due to reduced oxidation of low-density lipoprotein (LDL) and reduced cholesterol levels. Studies have revealed that silymarin prevents the development of atherosclerosis by inhibiting the oxidative modification of LDL, which is involved in cardiovascular disease progression (Surai et al., 2015). Apart from that, silymarin is also capable of improving the lipid profile by lowering total cholesterol as well as triglyceride levels, which in turn reduces cardiovascular risk (Ramakrishnan et al., 2008). It is also capable of enhancing high-density lipoprotein (HDL) levels, which also supports heart health (Poruba et al., 2015).

Role in Metabolic and Endocrine Health

Milk thistle, particularly its major bioactive compounds silibinin and silymarin, has been proven to have beneficial effects on metabolic as well as endocrine health. Research shows that silymarin confers many benefits to metabolic syndrome (MS), a condition characterized by increased levels of triglycerides, reduced high-density lipoprotein (HDL) levels, increased waistline, increased fasting blood glucose (FBG) and increased blood pressure (Motta et al., 2009; Alberti et al., 2009). Silymarin is capable of improving cardiovascular risk factors, which are typically bundled under the MS diagnosis, particularly increasing HDL levels and decreasing blood pressure, FBG, triglycerides, and body weight (Poruba et al., 2015; Poruba et al., 2015; Shen et al., 2020; Bouderba et al., 2014; Marková et al., 2021; Piazzini et al., 2019). Apart from that, silymarin decreases overall oxidative stress, specifically in the liver, which is one of the central organs in managing metabolic dysfunctions (Alberti et al., 2009; Shen et al., 2020; Prakash et al., 2014). This is also augmented by its hepatoprotection, which prevents inflammatory mediators associated with cardiovascular disease (CVD) development (Bouderba et al., 2014; Marková et al., 2021). Silymarin in animal experiments also demonstrated potential in treating hyperuricemia, which is an important risk factor to MS as well as to CVD, due to its ability to induce vascular inflammation as well as oxidative stress, although its impact in lowering uric acid levels is minimal in comparison to other flavonoids (Mo et al., 2007; Harris et al., 1999; Corry & Tuck, 2006). Silymarin also revealed promise in controlling diabetes, with research supporting improved glucose homeostasis, increased insulin sensitivity, and lowered oxidative stress in diabetic models (Chu et al., 2020; Gu et al., 2016). Such evidence highlights milk thistle's promise in treating metabolic as well as endocrine disorders, thus making milk thistle an important natural supplement for controlling such health issues.

Dosage, Mode of Administration and Safety

Milk thistle has been widely researched for its efficacy and safety, especially in various doses and modes of administration. In healthy subjects, clinical trials with oral silymarin doses of 175 to 420 mg/day for periods of 10 to 63 days revealed no toxic or harmful effects (Soleimani et al., 2019). In therapeutics, the standard dose for different ailments is generally 140 mg twice to three times per day for six months. This regimen is tolerated with just mild side effects, including diarrhea, headaches, and non-serious toxicity (Soleimani et al., 2019). In liver disorders, higher doses of up to 1,680 mg/day have been used, but these doses produced adverse effects in terms of headaches, abdominal pain, nausea, and respiratory infections (Parsadai et al., 2007). When silybin, one of the silymarin constituents, was combined with other compounds like Vitamin E and phosphatidylcholine, these silybin combinations produced diarrhea, pruritus, and disturbances in taste when used at 94 mg twice daily for one year (Parsadai et al., 2007). Also, in cancer of the prostate, oral silybin phytosome doses of 2.5 to 20 mg three times a day produced GI symptoms, hyperbilirubinemia, increased creatinine, calcium, and halitosis (Parsadai et al., 2007). Intravenous use of silymarin at doses of up to 1,400 mg/day and lyophilized silibinin at doses of from 5 to 20 mg/day have been used to treat hepatitis C and acute hepatotoxicity, respectively. The treatment produced transient adverse effects in terms of mild flushing and warmth sensations, which disappeared in two days (Soleimani et al., 2019). Furthermore, use of a silymarin gel with concentration of 1% applied to palms and soles for nine weeks in cancer chemotherapy recipients for cancer of the GI tract significantly reduced severity of hand-foot syndrome with no unpleasant effect (Elyasi et al., 2017). Therefore, milk thistle has good documentation of safety in all modes of use, doses, and indications, with mild, reversible adverse effects.

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