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Milk Thistle

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Continuing Education Activity

Herbal products have become increasingly popular, especially among those with chronic diseases. Herbalists and clinicians alike used the milk thistle for hundreds of years to treat a wide range of liver pathology, including fatty liver disease, hepatitis, cirrhosis, and to protect the liver from environmental toxins. Today, millions of people consume milk thistle to support healthy liver function. Researchers have focused their efforts on studying silymarin, a mixture of flavonolignans extracted from milk thistle, and the most active ingredient of this extract, silybin. This activity will highlight the mechanism of action, adverse event profile, pharmacology, monitoring, and relevant interactions of milk thistle, pertinent for interprofessional team members in the treatment of patients with conditions where it might be of clinical value.

Objectives:

- Summarize the mechanisms of action of milk thistle.
- Describe the reported indications for using milk thistle as a supplement.
- Review the potential adverse effects and necessary monitoring when a patient is taking milk thistle.
- Outline the importance of collaboration and communication among interprofessional team members to improve outcomes and treatment efficacy for patients who might benefit or already be taking milk thistle.

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Indications

Herbal products have become increasingly popular, especially among those with chronic diseases. Herbalists and physicians alike used the milk thistle for hundreds of years to treat a wide range of liver pathology, including fatty liver disease, hepatitis, cirrhosis, and to protect the liver from environmental toxins. Today, millions of people consume milk thistle to support healthy liver function. Researchers have focused their efforts on studying silymarin, a mixture of flavonolignans extracted from milk thistle, and the most active ingredient of this extract, silybin.[1] Silymarin and silybin have become some of the most prescribed natural compounds, and the two names are often interchangeable. However, each has a different clinical purpose, but there are no definitive results in terms of clinical efficacy. Currently, there is no regulation of herbal products such as milk thistle in the United States as they are not considered drugs and are not under the supervision of the US Food and Drug Administration. Like most herbal products, the FDA does not approve or recommend milk thistle as a treatment for any medical condition.

Recent studies have focused on the role of milk thistle in treating nonalcoholic fatty liver disease, a common hepatic manifestation of metabolic syndrome. The prevalence of NAFLD in western countries is approximately 20% to 30%.[2][3] Currently, there is no consensus approach when it comes to the treatment of NAFLD. Most clinicians approach the disease by emphasizing lifestyle modification, including diet, weight loss, and limiting alcohol intake. However, studies suggest milk thistle can exert beneficial effects in patients with NAFLD. Data indicate that silymarin treatment correlated with a reduction in insulin resistance and a significant decrease in fasting insulin levels. Patients treated with 600mg/day of silymarin for 12 months demonstrated lower fasting insulin levels.[4] A separate clinical trial evaluated the effectiveness of silymarin compared to metformin and pioglitazone in NAFLD patients. Research showed that patients treated with silymarin had significantly lower transaminase levels compared to those treated with metformin or pioglitazone.[5] In a sample of 25 patients, treated for four months with 200 mg silymarin three times a day before meals, there was a significant reduction in blood glucose levels (from 156 +/- 46 mg/dl to 133 +/- 39 mg/dl), compared to an increase in the placebo-treated group. In the same period, their HbA1c levels also dropped by an average of 1 point. The same group of patients also demonstrated significantly reduced levels of total cholesterol, triglycerides, and LDL.[6][7] Another study aimed to evaluate the efficacy of combined treatment, which includes vitamin E, silybin, and phospholipids, demonstrated that this complex improves liver damage, especially plasma markers of liver fibrosis, as well as insulin resistance.[8]

Mechanism of Action

Milk thistle exhibits its hepatoprotective properties by three major mechanisms: 1) serving as an antioxidant, 2) an anti-inflammatory, and 3) an antifibrotic substance.[9] The anti-inflammatory properties of milk thistle are attributable to its ability to regulate cytokines responsible for inducing inflammation. Milk thistle has been shown to down-regulate and inhibits the expression of COX-2, a key mediator of inflammatory pathways.[9][10] Silymarin also inhibits the transduction cascade controlled by Nf-kb, a protein complex that induces the expression of pro-inflammatory genes responsible for encoding cytokines directly involved in the inflammatory process. NF-kB also regulates the survival of inflammatory T cells. Studies done on mice showed silybin reduced liver and plasma content of pro-inflammatory cytokines while increasing IL-10, a cytokine whose function is to decrease and regulate the inflammatory response.[11]

Milk thistle has also shown antioxidant properties on hepatocytes. It can inhibit free radicals derived from the metabolism of toxic substances such as ethanol, acetaminophen, and carbon tetrachloride. It stimulates protein synthesis by protecting cell membranes from free radical-induced damage and directly inhibiting radical formation. It can also act as a free radical scavenger and increase the intracellular content of scavengers.[12] Studies have shown that silymarin increases the activity of superoxide dismutase and serum levels of glutathione and glutathione peroxidase.[13][14] Silybin can also act as an iron chelator, further strengthening its antioxidant properties.[15]

In addition to its anti-inflammatory and antioxidant properties, silybin also shows promise as an antifibrotic agent, which is attributable to its ability to decrease platelet-derived growth factor (PDGF) induced DNA synthesis in cells, which inhibits the transformation of stellate hepatocytes into myofibroblasts. By decreasing myofibroblasts, silybin indirectly prevents the deposition of collagen fibers that lead to liver injury progression.[9] Finally, silybin has demonstrated an association with a significant reduction of TGF-B, a key regulator in the pathogenesis of liver fibrosis.[16]

Administration

Like most herbal supplements, milk thistle administration is oral. It is available in capsule form, tablet, or as a liquid extract. In Europe, silybin has also been used intravenously as an antidote to *Amanita phalloides*, a mushroom toxin that causes severe liver damage.[17]

Adverse Effects

According to pharmacological studies, silymarin has recognition as a safe herbal product since taking it at therapeutic doses is not toxic. Although rare, some of the adverse effects of milk thistle include[9]:

- Gastroenteritis
- Diarrhea
- Headache
- Dermatological symptoms (hives, rash, pruritus)

Contraindications

There are currently no documented contraindications to using milk thistle. However, little information is available regarding interactions with cancer drugs, radiation therapy, or other medications.

Monitoring

Like with most herbal products, there is no concrete way to monitor blood levels of milk thistle or its compounds, and little data is available on the therapeutic index of the supplement. However, silymarin has been shown to decrease the activity of cytochrome P-450 enzymes and UDP-glucuronosyltransferase (UGT) enzymes, prompting health care providers to caution patients against co-administration of milk thistle and pharmaceutical drugs.[18]

Toxicity

Reports exist of asymptomatic liver toxicity in clinical trials performed on cancer patients, in whom researchers observed an increase in ALT and bilirubin levels. However, this observation was at extremely high doses of silybin (between 10 to 20g/day).[9]

Enhancing Healthcare Team Outcomes

Data has indicated that milk thistle has great potential in reducing biochemical changes seen in patients with NAFLD, and multiple pharmacological studies have demonstrated why many consider the plant to be a hepatoprotective substance. Based on the data available today, many believe that milk thistle represents a viable alternative for patients with acute and chronic liver disease, especially those in whom standard therapy has failed. However, despite this current data, more evidence is needed to establish the short-term and long-term effects of milk thistle.

Healthcare workers, including physicians, nurse practitioners, nursing staff, and pharmacists, should be aware that currently, there is no firm clinical evidence to recommend the use of silybin or silymarin in the clinical setting.[19] In addressing patient needs, these providers need to function as an interprofessional team to ensure that all care team members are aware of what drugs and supplements the patient might be taking. Physicians, nurses, and pharmacists need to inquire about non-prescription agents that the patient may be taking, and milk thistle would be in this query as an over-the-counter substance. The pharmacist should include milk thistle and other OTC substances in their medication reconciliation and alert the rest of the team as to its presence in the patient's regimen and any potential interactions. Nursing should be aware of the pharmacology of milk thistle and document it in the patient's chart so all other healthcare team members can be informed. All healthcare team members need to make the patient understand that just because milk thistle is available over the counter does not make it a benign substance. This type of collaboration on the interprofessional team is crucial to managing patient outcomes effectively. [Level 5]

At this time, using milk thistle is not consistent with the standard of care. There have been thousands of papers published on milk thistle to date, and the high publication volume suggests that interest among the research community remains high. Future research should continue to assess the mechanisms for preventing inflammatory sequelae and the cytoprotective effects of milk thistle, including silymarin and silybin. This research will allow for better recognition of cellular targets of milk thistle, leading to a more potent and selective compound that could prove clinically useful in treating a wide variety of liver pathology.

Review Questions

- Access free multiple choice questions on this topic.

- Comment on this article.

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