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Silybum Marianum

(Milk Thistle)

Introduction

Dietary supplements (including herbal remedies and other nutraceuticals) represent an increasingly growing market in the United States market, with \$1.8 billion in sales in 1996.¹ While an abundance of information exists supporting the safety and efficacy of conventional, allopathic products currently available in the US, this is far from the case with dietary supplements. To appropriately evaluate supplements, one must often glean information from small, poorly designed trials, usually performed outside of the United States.

Silybum marianum is the scientific name for milk thistle. There are many names associated with this dietary supplement including Marian thistle, Mary thistle, St. Mary's thistle, lady's thistle, holy thistle, sow thistle, thistle of the blessed virgin, Christ's crown, Venus thistle, heal thistle, variegated thistle, and wild artichoke. The nomenclature used to describe the dietary supplement varies depending on the researchers involved. It can be referred to as *Silybum marianum*, silymarin, silybin, or milk thistle. The majority of the trials refer to silymarin, which is the major component of milk thistle. The plant can grow to a height of ten feet and has thorny stems, dark green leaves, and white veins with a bright purple (or white) flower.²

Indications

Milk thistle extracts were used as early as the 4th century B.C., became a favored medicine for hepatobiliary diseases in the 16th century, and have been used in Europe during this century.¹ It is currently purported to have value as a liver protectant to lessen damage from potentially hepatotoxic drugs and for treating liver disorders including toxic liver damage caused by chemicals, *Amanita phalloides* mushroom poisoning, jaundice, chronic inflammatory liver disease, hepatic cirrhosis, and chronic hepatitis.³ There are also many references made to its use for food and as a coffee substitute. Germany's Commission E has approved milk thistle for use as a treatment for toxic liver disease, and as a supportive treatment for chronic inflammatory liver disease and cirrhosis of the liver.⁴

Pharmacology/pharmacokinetics

It is presumed that milk thistle has antioxidant effects in the liver, small intestine, and stomach as well as showing improvements in cytosol liver and histologic markers when exposed to a variety of hepatotoxins. According to Dehmlow et al, the mechanism of action is assumed to be an inhibition of lipid

peroxidation processes due to its free radical scavenging properties.⁵ In addition, a membrane stabilizing effect and an enhancement of protein biosynthesis have been suggested as contributing factors toward its hepatoprotective properties.

The dried seeds from the milk thistle extract contain approximately 60% silymarin.⁶ There are four isomers within silymarin consisting of: silibinin (~50 to 60%), isosilibinin (~5%), silicristin (~20%), and silidianin (~10%). The main active compound is believed to be silibinin.⁶ The bioavailability of silibinin from the extract is low and seems to depend on several factors such as the content of accompanying substances with a solubilising character such as other flavonoids, phenolderivatives, amino acids, proteins, tocopherol, fat, cholesterol, and others found in the extract, and the concentration of the extract itself.⁶ Enhancements to the bioavailability can be made by complexation with phosphatidylcholin of beta-

cyclodextrin or by adding solubilising substances to the extract. There are various methods used to determine the constituents of milk thistle including thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), colorimetry, and electrophoresis. The differences in these methods account for some of the differences in the bioavailability reports. Also, due to the fact that there are two species with different varieties, there are differences in dissolution and

oral bioavailability. For males given a single oral dose of standardized silibinin (100-360 mg), plasma silibinin C_{max} is attained within approximately two hours and ranges between 200 and 1400 mcg/L with approximately 75% in the conjugated form. An elimination half-life is estimated to be between six hours for total silibinin. Approximately 3-8% of an oral dose is excreted in the urine with approximately 20-40% being recovered from the bile in a conjugated form. The bile concentrations of silibinin are approximately 100 times those in the serum

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and bile peak concentrations are reached within 2-9 hours. The C_{max} of silibinin and the t_{max} appear to be slightly lower and delayed in cirrhotic patients as compared to healthy volunteers.⁶

Clinical studies

Buzzelli et al studied the liver protective effect of silybinphosphatidylcholine complex (IdB1016) in twenty patients with chronic active hepatitis in a randomized, double blind, placebo controlled study. These patients were randomized to receive 240 mg of silybin twice daily or placebo. In the study, the authors described the isomers as silybin (the active component), silydianin, and silychristin. In comparing the two groups, the silybin group showed statistically significant decreases in aspartate aminotransferase (AST) from 88.0 to 65.9 (a 25% decrease), alanine aminotransferase (ALT) from 115.9 to 82.5, gamma-glutamyltranspeptidase (gamma-GT) from 51.4 to 41.3, and total bilirubin from 0.76 to 0.53 ($p < 0.01$, $p < 0.01$, $p < 0.02$, and $p < 0.05$, respectively). The results were not duplicated in the placebo group. Statistical significance was not demonstrated when IdB1016 and placebo were compared for total bilirubin decreases. This study's duration was one week and showed improvement in liver function tests for patients treated with silybin over that time course.⁷

Pares and colleagues, in a randomized, double blind, placebo controlled trial, studied time to death in 125 patients with alcoholic cirrhosis. The participants were randomized to receive 150 mg silymarin three times daily or placebo over a two year study period. The five-year survival rate was 0.71 in the treated group compared to 0.76 in the placebo group with all known co-existing diseases and conditions included (p -values ranging from 0.059 to 0.99). The effects on survival are not statistically significant, however the investigators did not conduct a power calculation *a priori* and it is unclear if the sample size enrolled in this study was of sufficient size for meaningful statistical interpretation.⁸

Salmi and Sarna conducted a randomized, double blind, placebo controlled four-week study in Finland of 97 patients with elevated serum transaminase levels (serum aspartate amino-transferase (AST) and serum alanine amino-transferase (ALT)) due to acute and sub-acute alcoholic liver disease. The patients were randomized to receive either 420 mg/day of silymarin or placebo. For AST, the means in the treated group changed from 89.8 to 38.2 with the control group changing from 73.9 to 51.2 ($p < 0.001$). For ALT, the treated group changed from 152.3 to 57.5 and the control group experienced a change from 107.5 to 90.2 ($p < 0.001$). Changes in secondary outcomes involving alkaline phosphatase, serum bilirubin, sulphobromophthalein test, and serum proteins and immunoglobulins were not statistically significant. Statistical significance was shown in improvement in histological alterations proven through liver biopsies ($p = 0.0022$). These results are not generalizable to the population of liver disease patients as a whole

since all patients in the study had relatively mild liver disease due to acute and sub-acute alcoholic induced liver disease.⁹

Ferenci and colleagues designed a randomized, double blind, placebo controlled study of 105 patients with cirrhosis to determine if milk thistle improved prognosis. The patients were randomized to receive either placebo or 420 mg of silymarin daily (dosed three times daily). The mean treatment time for patients was 41 months and all were treated for at least two years. After a total of four years, the cumulative survival was greater in the treated group (58% compared to 38%, $p = 0.036$). This study involved chronic alcoholic patients who continued to consume large quantities of alcohol throughout the study thus limiting the applicability to the general population of patients with liver disease.¹⁰

In a double blind, randomized, placebo controlled study by Allain et al, 217 patients were recruited to study the effects of silymarin on serum amino-transferase levels in patients being started on tacrine for Alzheimer's disease over a 13 week period (one week with silymarin alone followed by 6 weeks of 40mg/day tacrine followed by 6 weeks of 80 mg/day tacrine). Patients were randomized to receive either placebo or silymarin in doses of 420 mg/day dosed three times daily. The main study outcome was to look at the effect of the milk thistle on the tacrine-elevated serum alanine amino-transferase levels (ALT). The study indicated that silymarin was not better than placebo in inhibiting the elevation of serum ALT ($p = 0.39$). In that group, elevation of ALT greater than 1 times the upper limit of normal (> 1 ULN) was 31.2% of placebo patients as compared to 37% for the silymarin treated group. For patients where elevation was > 3 ULN, $p = 1.0$ and where > 5 ULN, $p = 0.48$. A decrease in the rate of side effects to the tacrine was shown in the silymarin treated group, which was not statistically significant. This study indicated that silymarin was not beneficial in decreasing the effects on serum amino-transferase levels when tacrine was initiated.¹¹

Lang et al evaluated the immunomodulatory and hepatoprotective effects of silymarin for patients with alcoholic cirrhosis in a randomized, double blind, placebo controlled study that also included a third arm with the imidazol derivative 4-amino-5-imidazol-carboxamid-phosphate. The study involved 60 patients who consumed alcohol daily and examined the effects on serum transaminase levels. The silymarin group consisted of 20 patients receiving 420 mg daily in three divided doses with a one-month treatment period. For AST (55 down to 28), ALT (27 to 13), and gamma-GT (72 to 42), the silymarin group showed statistically significant improvement ($p < 0.05$, $p < 0.02$, and $p < 0.01$, respectively). In all groups, consumption of alcohol was decreased during the study period with the results being limited to patients with daily alcohol consumption and a short treatment period.¹²

Adverse effects

Milk thistle is a relatively safe compound with very few

reported adverse effects. There has been a report of a woman who developed sweating, nausea, abdominal pain, diarrhea, vomiting, and weakness at the times that she took the extract. It is not known whether the reaction was due to the extract or to other ingredients within the supplement.⁴ Also of note is a survey from 1991-1995 of the National Poison Information Service documenting over 700 cases of possible or confirmed adverse reactions relating to dietary supplement drugs.¹ Venkataramanan and colleagues examined the effect milk thistle has on the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase (UGT1A6/9). For their study, they worked with human hepatocyte cultures. Their findings indicated that using silymarin with other drugs that are conjugated by UGT1A6/9 could lead to a reduction in the clearance of certain drugs and a potential for increased toxicity due to the formation of toxic metabolite(s) from the coadministered drugs.¹³

Cost, dose and how supplied

With most of the trials focusing on the German milk thistle product called Legalon, it is important to look at the available United States version. Legalon is sold in the United States under the Nature's Way brand known as Thisilyn. The product is available in bottles of 100 capsules containing 175 mg of dried seed extract standardized to contain 80% silymarin. The suggested dosing schedule is one capsule three times daily before meals. Patients can obtain the product starting at prices around \$27.¹⁴

Conclusion

Schuppan and colleagues discussed the major problems faced when evaluating the effects of dietary supplements. These problems include differences in harvesting/preparing the herb leading to difficulties in standardization and the lack of large, multi-center, randomized, placebo-controlled trials.¹

Some trials use "milk thistle," "silymarin," and "silybin" and this leads to confusion in comparing the results of the studies due to a lack of consistency in the tested products. There are several contradictions in the available literature as to whether there are three or four flavonoids as well as agreement on what is the major compound. Still another issue is the majority of trials are done in foreign countries and we must rely on English translations, which may not be totally accurate.

The Agency for Healthcare Research and Quality (AHRQ), within the United States Department of Health and Human Services, issued an Evidence Report/Technology Assessment on milk thistle in October 2000. For this review, they examined a number of placebo-controlled studies and noted that it was difficult to interpret the data due to variability within the studies regarding such aspects as study designs, dose, and outcome measures, among others.²

For dietary supplements, it is important to consider how these products are manufactured and distributed. The Dietary Supplement Health and Education Act of 1994 provided a legal

definition for the phrase "dietary supplement" to include products containing a vitamin, mineral, herb, amino acid, or dietary substance. Because these items are considered foods, it is the manufacturer's responsibility to insure that the products are safe and properly labeled prior to marketing.¹⁵ One must consider that the United States government does not regulate standardization of the products.

The AHRQ found that milk thistle has not been proven effective.² There is an abundance of information available and taken individually, can be construed as beneficial. However, it must be noted that the products are not standardized and not governed by the FDA. Milk thistle may be effective in the treatment of liver diseases. However, as with any dietary supplement, the product consumed may or may not contain the active ingredient in a therapeutic quantity and therefore should not be considered as the appropriate treatment for patients with liver disease. ■

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