Is Silymarin Hepatoprotective in Alcoholic Liver Disease?

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Silymarin is the main active complex extracted from the milk thistle (*Silybum marianum* L.), an annual plant that has been used by herbalists since antiquity. Pharmacologic evidence from numerous studies in the last few decades supports potential therapeutic benefits of milk thistle and silymarin in liver necroinflammation and fibrogenesis given its free-radical scavenging, antioxidant, anti-inflammatory, immunomodulatory, iron chelating, and membrane stabilizing properties as well as its purported ability to selectively stimulate hepatocyte proliferation.\(^1\) Current knowledge of the role of oxidative stress in the pathogenesis of alcohol liver disease (ALD), suggests that silymarin’s pharmacological properties may have potential therapeutic value in ALD.\(^2\)

Since the 1960s, milk thistle products have been prescribed by physicians in Europe for ALD as well as other liver-related conditions. Several European manufacturers have developed pharmaceutical grade milk thistle products standardized to a higher content of silymarin (70%–80%) than in non-standardized herbal preparations (=5%)\(^3\), mainly because of silymarin’s poor oral bioavailability.\(^4\) As part of pharmaceutical development, several clinical studies have been conducted in Europe to assess the efficacy of oral milk thistle products in liver diseases of diverse etiology.

Recently, a systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) selectively analyzed 16 prospective randomized placebo-controlled European trials in terms of the efficacy and safety of milk thistle products in alcohol, viral or toxin-related liver diseases.\(^5\) Six of the selected trials evaluated ALD using various doses of Legalon, a milk thistle product standardized to 80% silymarin manufactured in by Madhaus AG (Cologne, Germany). The reviewers found these trials difficult to interpret due to unclear and variable definitions of disease chronicity and severity. Some of the studies included liver diseases of various etiologies. None of the studies stratified patients by presence or absence of ongoing alcohol consumption or chronic hepatitis C infection as potential confounders. All 6 studies on silymarin and ALD found at least 1 biochemical parameter of liver function or liver histology that improved significantly with silymarin compared with placebo. The parameters that were significant varied from study to study.\(^6\)–\(^12\) Importantly, 1 of the 6 studies showed significant improvement in overall survival among cirrhotic patients treated with silymarin,\(^16\) a second study showed a non-statistical trend toward improved survival\(^9\) and yet another study showed no improvement in overall survival in silymarin compared with placebo.\(^8\) No relationship was found between duration of therapy and improvement in liver function, although 3 of the reports did not clearly describe the duration of therapy.

The previous data on silymarin in ALD along with current evidence on the potential benefit of antioxidant therapies in ALD,\(^13\) justify a more systematic assessment of silymarin in ALD. Furthermore, an evidence-based approach to the evaluation of the safety and efficacy is crucial because at least 1 multicenter survey has shown that milk thistle is the most frequently used supplement in patients with liver disease.\(^14\) In 2001, milk thistle products ranked 12th in the list of supplements sold in the US surpassing 7 million dollars.\(^15\)

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In the current issue, Lieber and colleagues report their preliminary findings on the effect of chronic treatment with a standardized silymarin extract in an experimental baboon model that has been extensively validated in ALD by the lead author. The silymarin product was provided by Madhau's AG, the manufacturer of Legalon. The primary aim is to determine whether silymarin co-administration with toxic levels of alcohol prevents development of ALD in this animal model. The authors' rationale for using an animal model was to control for alcohol intake and treatment compliance. The authors also state that their study design differs from previous clinical studies that examined the effects of silymarin in patients with established ALD and often consisted of compensated or end-stage cirrhotics. Regardless of the proven validity of the baboon model, this difference in experimental design does place a limitation on our ability to compare results from this study with previous clinical trials. Additionally, the findings of the present study would be difficult to test in humans, given the ethical issues involving the recruitment of patients with ALD who continue to consume significant amounts of alcohol.

According to the authors, silymarin dosing was calculated based on the manufacturer's previous pharmacokinetic studies in humans and on the faster metabolism of silymarin in baboons. However, it is unclear how dosing was calculated in terms of maximizing hepatoprotective effects of silymarin. It is also unclear how the sample size was determined (6 animals in the treatment and control groups) since no power calculations are given in terms of silymarin's effect size.

As in previous clinical studies in ALD, the results obtained by Lieber et al are equivocal with regard to a potential clinical benefit from silymarin as preventive therapy in chronic alcohol use or ALD, at least at the dose used in the current study (39.8 ± 5.2 mg/kg/d). The authors report that hepatic histology improved in the silymarin compared with the control group after 3 years. However, the small sample size and lack of statistical comparison limits the interpretation of these data. Nevertheless, the authors should be congratulated for attempting to study the effect of silymarin for ALD in a scientific manner. We hope that future studies would be adequately powered to compare the effect of silymarin using semi-quantitative histopathologic findings as primary endpoints.

There were, however, several favorable changes in the secondary endpoints in the silymarin treated group. Plasma levels of ALT, 4-hydroxynonenal (a marker of lipid peroxidation), procollagen type I and mRNA of α(I) procollagen (2 markers of fibrogenesis) and hepatic total triglycerides were all significantly lower in the silymarin group, thus providing indirect evidence that silymarin is hepatoprotective and may potentially retard progression in ALD. Based on the interesting findings in the current study, additional studies are warranted to determine the optimal dose of silymarin followed by carefully designed clinical trials in ALD.

REFERENCES

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