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File: ■ Milk Thistle (*Silybum marianum*)
■ Silymarin
■ Desferrioxamine
■ β-Thalassemia Major

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RE: Oral Silymarin Is Proven Effective in β-Thalassemic Major Patients under Conventional Chelation Therapy

Gharagozloo M, Moayedi B, Zakerinia M, et al. Combined therapy of silymarin and desferrioxamine in patients with β-thalassemia major: a randomized double-blind clinical trial. *Fundam Clin Pharmacol*. 2009;23:359-365.

Silymarin is a flavonolignan complex isolated from the fruits of milk thistle (*Silybum marianum*) endowed with strong antioxidant, hepatoprotective, and iron-chelating properties. Silymarin is clinically used for the treatment of liver diseases with degenerative necrosis and functional impairment.[1] One of its active components, silybin, shows strong iron-chelating properties: oral administration of silybin protects against iron-induced hepatic toxicity in vivo, suggesting its possible use in the chelation therapy of chronic iron overload disorders, such as β-thalassemia major. [2,3]

β-Thalassemia is a single gene disorder characterized by absence or decreased production of the β chain of hemoglobin, resulting in anemia and requiring regular blood transfusions. The excess transfusional iron builds up in different organs leading to functional disruption and organ failure.[4] Iron chelation with subcutaneous (s.c.) or intravenous desferrioxamine is widely used to overcome body iron over-storage, prevent iron-induced cardiac disease, and improve survival in chronically transfused patients. As reactive oxygen species and iron overload play an important role in the pathophysiology of thalassemia, co-administration of desferrioxamine with silymarin may be an effective therapy given silymarin's antioxidant, cytoprotective, and iron-chelating properties.

This randomized, double-blind, placebo-controlled, 3-month trial was designed to investigate the therapeutic activity of orally administered silymarin in patients with β-thalassemia major under conventional iron chelation therapy. Sixty β-thalassemia major patients aged 12 years or older (mean 19.5 ± 5.4 years) with serum ferritin levels above 1000 µg/L over the previous 6 months were selected from referrals to Dastgheib Clinic of Thalassemia (Shiraz University of Medical Sciences; Iran). All patients had homozygous β-thalassemia major, were regularly transfused to maintain hemoglobin levels above 9.5 g/dL at a mean transfusional interval of 17 days, and chelated with s.c. desferrioxamine

(mean dose 40-50 mg/kg per infusion over 8-12 h, 5-6 days per week). Patients were randomized to receive either placebo or a 140 mg silymarin tablet (Legalon®; Madaus Pharma; Padova, Italy) at least an hour before food, 3 times daily, in addition to conventional desferrioxamine (Novartis Pharma AG; Basel, Switzerland) therapy.

Chelators' efficacy was assessed by serum ferritin measurements. Patients were evaluated at the beginning, middle, and end of each treatment period for clinical laboratory parameters: regular laboratory tests were performed including full blood count and liver and renal function. The mean of difference values in the silymarin group was compared with placebo using t-test of 2 independent samples. ANOVA repeated measure analysis was used to examine the changes of serum ferritin level between baseline, end of 1.5 months, and 3 months. Results were expressed as the mean ± SD. All tests were two-tailed and a significance level of 0.05 was applied.

Fifty-nine patients completed the study (silymarin, n = 29; placebo, n = 30). There were no significant differences between groups in initial serum ferritin levels, age, sex distribution, desferrioxamine dose, or amount of blood transfused. There were no significant differences in hemoglobin, hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) levels, as well as red blood cells (RBC), platelet, lymphocyte, monocyte, eosinophil, and neutrophil counts at baseline and end of the treatments in both groups. No significant variations were registered in serum chemicals (calcium, phosphorus, and fasting blood sugar) and electrolytes (blood urea nitrogen, creatinine, sodium, and potassium) after 3 months of silymarin or placebo treatment.

However, a significant decrease in serum alkaline phosphatase (ALP) was observed in patients receiving silymarin. Reduced glutathione (GSH) concentration of RBC was significantly greater in silymarin-treated patients compared to the placebo group. An ANOVA repeated measure analysis demonstrated a significant decrease in serum ferritin levels at baseline, 45, and 90 days of silymarin therapy using Wilks' Lambda test [F = 4.69, d.f. (degrees of freedom) = (2; 55), P = 0.014]. A fall in serum ferritin was noted in 22/29 patients (75.8%) after 45 days, and in 25/29 (86.2%) after 90 days of silymarin therapy. However, the serum ferritin levels of 20/30 patients (66.6%) decreased after 45 days, and 21/30 (70.0%) patients after 90 days of desferrioxamine treatment. The decrease in serum ferritin levels was not significant in the placebo group. On the other hand, ANOVA repeated measure analysis demonstrated no significant difference in serum ferritin levels between silymarin and placebo groups after 45 and 90 days of treatment, as evidenced by the Wilks' Lambda [F = 0.53, d.f. = (1; 56), P = 0.82] with the observed power of 0.06.

The significant decrease in ALP levels in silymarin-treated patients highlights silymarin's hepatoprotective activity: ALP is a liver enzyme whose concentration is abnormally elevated in chronic liver diseases affecting thalassemic patients as a consequence of iron overload caused by the regular transfusion regimen.[5,6] The key mechanisms that ensure hepatoprotection appear to be free radical scavenging, reduction of oxidative stress via restoration of intracellular GSH deficiency of RBC, and increased synthesis of ribosomal RNA resulting in inducing liver regeneration.[7]

Concomitant administration of silymarin and desferrioxamine can be safely used in treatment of iron-loaded patients. In patients taking combined therapy (silymarin plus desferrioxamine), the mean drop in serum ferritin was higher than in desferrioxamine-

treated patients, indicating that the combined therapy was more effective than desferrioxamine in reducing serum iron overload. No significant difference in serum ferritin levels was detected between silymarin and placebo groups, probably due to the low observation power of the study (about 6%), caused by a sample size insufficient to detect subtle changes in ferritin levels. Silymarin was effective in reducing adverse side effects of conventional iron chelator desferrioxamine and showed remarkable antioxidant, hepatoprotective activities, and no sign of toxicity. The improvement in iron status resulting from the combined therapy needs to be confirmed in larger studies with a longer follow-up period.

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References

[1]Gazak R, Walterova D, Kren V. Silybin and silymarin - new and emerging applications in medicine. *Curr. Med. Chem*. 2007;14:315-338.

[2]Borsari M, Gabbi C, Ghelfi F, et al. Silybin, a new iron-chelating agent. *J Inorg. Biochem*. 2001;85:123-129.

[3]Pietrangelo A, Borella F, Casalgrandi G, et al. Antioxidant activity of silybin in vivo during long-term iron overload in rats. *Gastroenterology.* 1995;109:1941-1949.

[4]Rund D, Rachmilewitz E. Beta-thalassemia. *N Engl J Med*. 2005;353:1135-1146.

[5]Prati D, Maggioni M, Milani S, et al. Clinical and histological characterization of liver disease in patients with transfusion-dependent beta-thalassemia. A multicenter study of 117 cases. *Haematologica*. 2004;89:1179-1186.

[6]Li CK, Chik KW, Lam CW, et al. Liver disease in transfusion dependent thalassaemia major. *Arch Dis Child*. 2002;86;344-347.

[7]Valenzuela A, Garrido A. Biochemical bases of the pharmacological action of the flavonoid silymarin and of its structural isomer silibinin. *Biol Res.* 1994;27:105-112.

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