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File: ■ Milk Thistle (*Silybum marianum*)
■ Silymarin
■ Acute Hepatitis

HC 070591-382

Date: August 14, 2009

RE: Silymarin Enhances Symptomatic Improvements in Acute Hepatitis

El-Kamary SS, Shardell MD, Abdel-Hamid M, et al. A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis. *Phytomed*. 2009;16:391-400.

Acute hepatitis (liver inflammation) can be caused by viruses, alcohol, drugs, etc. Viral hepatitis is the most common cause of acute hepatitis. Symptoms of acute hepatitis can range from flu-like to liver failure. There is no standard medical treatment for acute viral hepatitis. Silymarin is the main active constituent of milk thistle (*Silybum marianum*). Milk thistle and silymarin are used for liver support; however, the results from randomized controlled trials on alcoholic liver disease and chronic viral hepatitis (n = 6 trials published) are inconclusive. The purpose of this study was to evaluate the safety and efficacy of silymarin for acute hepatitis.

Symptomatic patients with acute manifestations of hepatitis (n = 105, ≥ 13 years) and aminotransferase (ALT) levels > 2.5 times the upper limit of normal were enrolled from Tanta and Banha Fever Hospitals in the Nile Delta, Egypt to participate in this randomized, double-blind, placebo-controlled study. Patients received standard recommended 140 mg silymarin (Legalon®; Madaus GmbH; Cologne, Germany) or the recommended daily allowance of multivitamin/mineral capsule as placebo 3x/day for 4 weeks. Assessments were made through 6 visits in an 8-week follow-up. Primary outcome measures were normalization of bilirubin and hepatic enzymes within 8 weeks, defined as: alanine transaminase (ALT) ≤ 40 IU/L, aspartate aminotransferase (AST) ≤ 42 IU/L, total bilirubin ≤ 1.0 mg/dL and direct bilirubin ≤ 0.3 mg/dL. Other primary outcomes were signs and symptoms of acute hepatitis, while adverse effects and tolerability of silymarin were also monitored.

The patients had acute hepatitis from a variety of etiologies: n = 16 (15.2%) with acute hepatitis A (HAV), n = 35 (33.3%) with acute hepatitis B (HBV), n = 3 with acute

hepatitis C (HCV), n = 3 with acute hepatitis E (HEV), n = 2 with acute Epstein-Barr virus (EBV), and n = 1 with acute cytomegalovirus (CMV), n = 1 with chronic HBV with acute manifestations, and n = 18 (17.1%) with chronic HCV infection with acute manifestations. Compared with the placebo group, patients in the silymarin group had a significantly faster resolution of the mean number of symptoms of impaired biliary excretion (P = 0.042). Specifically, silymarin-treated patients had a significant improvement in dark urine (P = 0.013), jaundice (P = 0.02), and scleral icterus (P = 0.043). There was no significant difference between groups in the improvement in the mean number of symptoms of hepatocellular damage, except for indirect bilirubin at day 56 (P = 0.012). The decline in the mean levels of ALT and AST did not differ between the groups. Likewise, there was no significant difference between groups in the improvement in the mean number of symptoms of liver inflammation, although subjective indicators showed that patients treated with silymarin had faster resolution in fatigue (P = 0.06), malaise (P = 0.045), and anorexia (P = 0.061) at 8 weeks post-randomization.

Adverse events (AEs) were similar in frequency and uncommon in both groups. There were no serious AEs. Diarrhea is an AE that has been previously reported with silymarin treatment. In this study, diarrhea was reported infrequently and was not significantly different between groups.

The authors conclude that silymarin is safe and well-tolerated by patients with acute clinical hepatitis. The study showed a trend towards improvement that was mostly subjective and clinical without a corresponding decline in biomarkers of inflammation. Since the benefits appear to be mostly subjective, the authors speculate that the potential beneficial effects of silymarin may not be captured by traditional laboratory biomarkers (liver enzymes and viral loads). Although the authors used a mixed population so that the results could be more generalizable, this study design is a limitation. It is possible that silymarin is more effective for specific types of acute hepatitis. In addition, animal studies show silymarin to be beneficial at much higher doses. Larger studies and higher doses of silymarin should be evaluated. Currently there is no treatment for acute hepatitis, so even though silymarin did not improve the underlying inflammatory process it may still help the patient. The authors suggest that hepatocyte membrane stabilization by silymarin and its scavenging of free radicals released from damaged cells provide a plausible rationale for its beneficial influence.

—Heather S. Oliff, PhD

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