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Clinical Endocrinology and Metabolism

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Review Article

Silymarin in Hepatology: A Historical and Contemporary Perspective on its Therapeutic Potential

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Received date: 02 April 2026 | **Accepted:** 17 April 2026 | **Published:** 24 April 2026

Citation: Aamir Jalal Al-Mosawi, (2026), Silymarin in Hepatology: A Historical and Contemporary Perspective on its Therapeutic Potential, *Clinical Endocrinology and Metabolism*, 5(2); **Doi:**10.31579/2834-8761/108

Abstract

Silymarin, a flavonolignan complex derived from Silybum marianum (milk thistle), has been extensively studied for its hepatoprotective properties since the 1960s. Early European research laid the foundation for its therapeutic application in liver diseases, including acute and chronic hepatitis, cirrhosis, and liver injury induced by toxins. Subsequent clinical studies and meta-analyses have provided robust evidence of its efficacy in improving liver enzyme levels, mitigating oxidative stress, and enhancing survival in patients with liver disorders. Notably, recent research highlights its potential in managing nonalcoholic fatty liver disease, antituberculosis drug-induced liver injury, and iron overload conditions such as β-thalassemia. Silymarin's mechanisms of action, including its antioxidant, anti-inflammatory, and iron-chelating effects, contribute to its diverse pharmacological benefits. This review chronicles the historical progression of silymarin research and its expanding applications in hepatology, underscoring its safety profile and therapeutic promise for liver disease management.

Keywords: silymarin; hepatology; liver disease

Introduction

Silymarin primarily composed of the flavonolignans silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, and silydianin, is the active compound derived from Silybum marianum (L.) Gaertn. (milk thistle). Since its initial investigation in the 1960s, with hepatoprotective effects noted as early as 1968, silymarin has been widely studied for its therapeutic potential.

Early Research and Initial Recognition

The early research conducted from the 1960s to the 1980s played a pivotal role in establishing silymarin as a potent hepatoprotective agent. Largely conducted in Europe—particularly in Germany, Romania, and Hungary. These studies laid the foundation for the therapeutic potential of silymarin in treating liver diseases, from acute viral hepatitis to cirrhosis. Today, silymarin continues to be widely studied and used in clinical settings for its hepatoprotective and other beneficial effects [1-13]. The first notable recognition of silymarin as a hepatoprotective agent came in 1969, when Vogel and Temme suggested its use for protecting the liver from toxins [3]. By 1970, Schopen and Lange proposed silymarin for the treatment of hepatitis [4]. Early experimental studies on rats confirmed that silymarin effectively protected the liver from damage induced by substances such as carbon tetrachloride, d-galactosamine, and alkyl alcohol [5, 6]. In 1971, Poser reported positive results from using silymarin to treat chronic hepatopathies [7], and by 1973, Zirm documented its therapeutic potential for treating a range of liver disorders, including subacute and chronic hepatitis as well as degenerative liver diseases [8].

Key Clinical Trials and Expanding Evidence

A landmark placebo-controlled trial in 1978 by Magliulo and colleagues provided strong evidence of silymarin's effectiveness in treating acute viral hepatitis. Among the 57 patients treated with silymarin (70 mg, three times daily), liver function markers improved more significantly than in the placebo group [9]. In 1980, Benda et al. reported that silymarin improved survival rates in patients with alcoholic cirrhosis, attributing this benefit to its protective effects against liver injury. The authors attributed this benefit to silymarin's protective effects against liver injury [10]. Notably, much of the early research on silymarin was published in German, signaling the strong influence of the German medical school on the recognition of its therapeutic potential [1-10]. Coman Tănăsescu and colleagues in Romania demonstrated in 1988 that silymarin treatment over 40 days led to beneficial outcomes with minimal toxicity in patients with chronic persistent hepatitis, chronic active hepatitis, and cirrhosis [11]. In 1989, Austrian researcher Peter Ferenci and his team in Austria highlighted the hepatoprotective effect of silymarin, the active principle of the milk thistle "Silybum marianum" which has been shown on experimental studies on animals. They confirmed silymarin's hepatoprotective effects in a placebo-controlled trial involving 73 patients with alcoholic and non-alcoholic cirrhosis. Patients who received silymarin (140 mg three times a day for an average of 41 months) showed

significantly improved survival rates and no side effects [12]. That same year, Fehér et al. conducted a a placebo-controlled study in Hungary involving 36 patients with chronic alcoholic liver disease, revealing significant improvements in liver function markers, procollagen III peptide levels, and histological liver changes after six months of silymarin treatment [13].

Mechanisms of Action and Further Studies

The hepatoprotective effects of silymarin have been attributed to several mechanisms, including its antioxidant and anti-peroxidative properties. In 1990, Müzes et al. from Hungary conducted a placebo-controlled study on patients with alcoholic liver disease, reporting that silymarin treatment (420 mg daily for six months) increased erythrocyte and lymphocyte superoxide dismutase activity, as well as serum levels of reactive -SH groups and glutathione peroxidase activity. The study also noted a decrease in serum malondialdehyde levels, supporting the idea that silymarin's hepatoprotective effects are linked to its antioxidant properties [14]. Subsequent studies have further validated silymarin's beneficial effects in various liver conditions. For instance, in 2009, a placebo-controlled trial by Samer Said El-Kamary in Egypt demonstrated that silymarin (140 mg daily for four months) led to more rapid symptomatic improvement in patients with acute hepatitis without any side effects [15]. In 2017, Zhang et al. from China conducted an analysis of eight controlled studies with 587 patients, showing that silymarin significantly reduced transaminase (AST and ALT) levels [16]. In 2019, Tao et al. conducted a meta-analytic study involving five randomized controlled studies which included 1198 patients; 585 patients received prophylactic silymarin to prevent antituberculosis drug-induced liver injury and 613 received placebo. The use of silymarin markedly decreases the development of antituberculosis drug-induced liver injury [17]. In 2021, Kalopitas and colleagues conducted a systematic review and meta-analysis involving eight controlled studies, demonstrating that silymarin significantly lowered transaminase levels in nonalcoholic fatty liver disease patients [18]. Similarly, a 2023 systematic review by Calderon Martinez et al. involving 3,846 patients from 29 controlled studies confirmed that silymarin supplementation (ranging from 140 mg to 420 mg) can effectively lower liver enzyme levels in patients with nonalcoholic fatty liver disease [19].

Recent Studies and Emerging Applications

Recent research continues to highlight the broad potential of silymarin in liver diseases. Furthermore, a 2024 systematic review by Rahimi-Dehkordi et al. reported that silymarin can decrease liver siderosis, improve liver function tests, and normalize abnormal enzyme levels, including aspartate transaminase, alanine transaminase, alkaline phosphatase, serum bilirubin, and protein levels. Additionally, silymarin's iron-chelating effect was found to decrease reactive oxygen species production while increasing intracellular antioxidant enzymes such as glutathione, thus exerting potent antioxidant effects. Silymarin can reduce iron overload, inhibit red blood cell hemolysis, increase RBC count, and reduce the need for a transfusion. In patients with β-thalassemia, silymarin was found to be safe, with no serious side effects observed [20]. A recent systematic review and a meta-analytic study conducted by Malik et al. (2024) further supported silymarin's beneficial effects on liver enzymes and lipid metabolism in patients with metabolic dysfunction-associated steatotic liver disease. They found that silymarin can improve liver enzymes (Alanine aminotransferase and aspartate aminotransferase), and lipid abnormalities (Triglyceride and high-density lipoprotein) in metabolic dysfunction-associated steatotic liver disease [21].

Conclusion

Silymarin has emerged as a well-established hepatoprotective agent with diverse therapeutic effects across a variety of liver diseases. From early studies demonstrating its protective role against hepatotoxic substances to contemporary meta-analyses confirming its ability to improve liver function in conditions such as nonalcoholic fatty liver disease, cirrhosis, and hepatitis, silymarin continues to demonstrate promise. Given its established safety profile, silymarin remains a valuable tool in hepatology.

Conflict of interest: None.

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