Silymarin in the Treatment of Liver Diseases: What Is the Clinical Evidence?

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Silymarin is a mixture of flavonolignans extracted from the milk thistle (Silybum marianum *Gaertneri*) and has a history as a medical plant for almost two millennia. The main component of silymarin is silibinin (in a 50:50 mixture of Silybin A and Silybin B); the remaining components are silydianin, silycristin, isosilybin A, isosilybin B, isosilycristin, and taxifolin. Silibinin has strong antioxidative and antifibrotic properties,[1,2] which make it a potentially useful drug for treatment of chronic liver diseases. Nevertheless, the role of the drug for treatment of liver diseases remains controversial. Part of this uncertainty is due to the lack of data on its pharmacokinetics and optimal dosing regimens. Because of the complexity of the absorption, metabolism, and disposition nature of various flavonoids, it is still unclear which form [i.e., the parent flavonoid or its metabolite(s)] contributes to the overall effects in the body. Although flavonoids are rapidly absorbed after oral ingestion, their plasma concentrations are very low, whereas the phase II metabolites such as glucuronides, sulfates, and methylated conjugates seem to be predominant in blood circulation. Extensive first-pass metabolism in the intestine and the liver are responsible for low oral bioavailabilities of flavonoids.

Antiviral Properties

HCV proteins activate STAT-3 via oxidative stress and Ca^{2+} signaling,[3,4] as well as lipid peroxidation products and antioxidant gene expression. Oxidative stress may contribute to fibrosis and carcinogenesis in chronic HCV and impair interferon-alpha signaling.[5] Therefore, it was explored whether the antioxidative properties of silibinin may improve the response to peginterferon/ribavirin (PegIFN/RBV) in chronic hepatitis C. Unexpectedly, potent antiviral properties of intravenous (IV) silibinin (as silibinin hemisuccinate, Legalon SIL; Madaus/Rottapharm, Modena, Italy) against the hepatitis C virus (HCV) in patients with chronic hepatitis C were documented.[6] The antiviral effect was dose dependent but was not maintained after the end of the infusion period by the oral administration of silymarin. The antiviral properties of silibinin were also demonstrated in vitro using a standardized silymarin preparation (MK-001) in the HCV replicon system.[7,8] In addition, MK-001 displayed anti-inflammatory actions via inhibition of nuclear factor kappa B–induced transcription in human liver cell cultures and inhibition of inflammatory cytokine induction in human peripheral blood mononuclear cells. Both Legalon SIL and silibinin inhibit in vitro NS5B polymerase activity.[9]

IV silibinin over 2 to 3 weeks in combination with PEG/RBV was effective in PEG/RBV nonresponders,[6,10] as well as in patients post liver transplantation.[11] In contrast, clinical studies found no effect of oral silymarin on HCV in patients with chronic hepatitis C.[12-14]

Unfortunately, silymarin is poorly water soluble; therefore, the antiviral effect of silibinin requires parenteral administration. Oral administration does not approach the levels in plasma/liver, which were tested in vitro. Similar amounts of silymarin given orally had no effect on HCV load,[15] reflecting differences in bioavailability and metabolism of silibinin resulting in far lower plasma levels.

Since interferon regimens with oral direct-acting antivirals became available, further research on the application of IV silibinin in chronic hepatitis C came to halt.

Silymarin in Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

Insulin resistance and fasting insulin levels were decreased by a 1-year treatment with silymarin.[16] These data suggest direct

Abbreviations: HCV, hepatitis C virus; IV, intravenous; NAFLD, nonalcoholic fatty liver disease; PEG/RBV, peginterferon/ribavirin

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Potential conflict of interest: P.F. holds a patent for the intravenous use of silibinin in hepatitis C.

View this article online at wileyonlinelibrary.com

doi: 10.1002/cld.522

activities of silymarin on endogenous and exogenous insulin are the basis to explore the role of the drug in nonalcoholic fatty liver disease (NAFLD). Some researchers reported that silymarin appears to reduce the biochemical, inflammatory, and ultrasonic indices of liver steatosis. A pilot study by Loguercio et al.[17] reported that Silybin + vitamin E + phospholipids for 6 months significantly improved plasma levels of liver enzymes, insulin resistance, and echographic score of liver steatosis in the NAFLD patients. Vitamin E was effective in reducing nonalcoholic steatohepatitis in the PIVENS trial.[18] More recently, a placebo-controlled, double-blind, Phase III, randomized clinical trial with the same Silybin-vitamin E complex given for 1 year showed an improvement in liver enzymes, insulin resistance, and liver histology of NAFLD.[19]

However, the standardization of silymarin formulations and dosages is still lacking. Furthermore, in most clinical trials on this topic, a better definition of the endpoints, such as the progression of fibrosis or the reduction of transaminase levels, is needed. Well-designed, double-blind, placebo-controlled studies are still required.

Silymarin in Alcoholic Liver Disease

A large, randomized, controlled trial performed in the pre–liver transplantation era and before the discovery of the HCV indicated that long-term treatment with silymarin may decrease mortality in patients with cirrhosis, mostly in those consuming ethanol.[20] In a small, randomized, controlled trial, silymarin produced a small increase in glutathione and a decrease in lipid peroxidation in peripheral blood cells in patients with alcoholic liver cirrhosis but had no impact on the clinical outcome.[21] Another trial failed to show any benefit.[22]

Hepatoprotection

The term *hepatoprotective agent* is based on data in experimental animals showing that pretreatment with silibinin prevents or mitigates hepatic injury by toxins (i.e., ethanol, galactosamine, phalloidin, and CCl_4)[23] or progression of fibrosis.[1,2,24] Translation of these observations to human disease is difficult; except for a few case reports, there is no evidence that silibinin can prevent liver disease induced by drugs or chemicals. Possibly the largest experience is the prevention of death cup (*Amanita phalloides*) intoxication by IV silibinin. Silibinin is a specific antidote of amanitin. The effect in mushroom poisoning is, in part, explained by the stimulation of nucleolar polymerase A, which increases ribosomal protein synthesis and inhibits lipid peroxidation.[25] Again, no controlled data are available.

In conclusion, silibinin is a pharmacological active compound with many properties that have the potential to improve liver diseases of various causes. Unfortunately, well-controlled prospective studies are missing to document its clinical efficacy. Furthermore, the limited bioavailability of oral silymarin limits its use in medicine. Improved preparations may bypass this problem.■

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