HERBAL PREPARATIONS FROM MILK THISTLE: MECHANISMS OF ACTION AND APPLICATION IN LIVER DISEASES

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✓ **Abstract**

Herbal preparations from Milk Thistle possess documented hepatoprotective properties. Nowadays the increase of interest to this herbal drug is connected with the prevalence of different forms of liver pathology and with the discovery of new properties of its active components. This review contains information on pharmacology, mechanism of action, efficiency of Milk Thistle preparations applications in liver diseases and demonstrates possibilities of their using in other pathological states.

Key words: *Milk Thistle, silymarin, hepatoprotective properties, hepatitis, liver cirrhosis.*

Introduction

Milk thistle (Silybum marianum-L.) has been used since ancient times to treat various liver diseases. The first mention of the use of an extract of this medicinal plant is contained in the works of the ancient Greek physician Theophrastus (4th century BC). The research of the 18th century Swiss naturalist Albrecht von Haller formed the basis for the practical use of milk thistle in modern medicine [1, 2]. In the 60s of the last century, the chemical structure of the main active components of milk thistle, known as silymarin, was established. Silymarin has experimentally and clinically proven hepatoprotective properties, which allows its use in the treatment of such nosological forms of liver pathology as alcoholic liver disease, cirrhosis, viral and toxic hepatitis. Currently, new properties and possibilities for using this drug are being actively studied, in particular, its antitumor effect. This review contains information on the pharmacology, mechanism of action, and effectiveness of milk thistle preparations for liver pathology and demonstrates the possibilities of their use in other pathological conditions.

Chemical and pharmacokinetic properties of silymarin The active component of milk thistle is silymarin - a standardized extract obtained from the fruits of this plant and containing approximately 70-80% flavonolignans, among which the main and most active component is silybin (synonym - silibinin). Silybin is a mixture of two diastereomers A and B in approximately equal proportions. The extract also contains other flavonolignans: isosilybin, dehybrosilibin, silydianin, silicristin and several flavonoids, mainly taxifolin [2, 3]. Since silymarin has a low absorption capacity in the

intestine, methods are used to increase its bioavailability by combining the active component silibinin with phosphatidylcholine (the drug “Silipid”) or liposomes. After oral administration of silymarin, peak plasma concentrations are reached within 1–2 hours, with an elimination half-life of 6–8 hours [4, 5]. Silymarin is metabolized in the liver by conjugation with glucuronic and sulfuric acids, and is excreted mainly in bile and to a lesser extent in urine. The presence of enterohepatic circulation makes it difficult to study the absorption of silymarin.

Side effects (laxative effects, allergic reactions) when using milk thistle preparations are rare [1, 5]. Milk thistle preparations belong to the category of low-toxic substances. In animal experiments, the LD50 for intravenous infusion was 400 mg/kg for mice, 385 mg/kg for rats, and 140 mg/kg for rabbits and dogs. The LD50 value increased with slowing down the infusion rate, and with oral administration of the drug reached 10 g/kg. In acute intoxication, death occurred from cardiovascular failure [1].

Antioxidant action. One of the main pathogenetic mechanisms of damage to hepatocytes when exposed to toxins is the excessive accumulation of free radicals, which is accompanied by damage to cellular organelles and macromolecules. The antioxidant effect of silymarin is due to the presence of a phenolic structure in the molecule of its active substance, due to which it interacts with reactive oxygen species and other free radicals. Silymarin prevents cell damage by inhibiting lipid peroxidation (LPO) not only by direct binding of radicals, but also by increasing the concentration of glutathione and increasing the activity of superoxide dismutase [6, 7]. Moreover, by interacting directly with the components of cell membranes, silymarin prevents disturbances in the composition of lipid fractions responsible for maintaining normal membrane fluidity, which is a necessary condition for the normal functioning of cells [5]. The antioxidant effect of silymarin has been clearly demonstrated in vitro and in models of oxidative stress [1, 5]. Thus, when CCl4 exposed the liver of rats, the use of silymarin led to complete normalization of the increased activity of transaminases. In experiments on rats, silymarin prevented paracetamol-induced necrosis of hepatocytes in 87.5% of animals [5], and during acute intoxication with acetaminophen, silybin digemisuccinate exhibited protective properties by reducing lipid peroxidation and influencing the glutathione system, preventing an increase in serum transaminases [7]. Stimulation of protein synthesis. Silymarin is able to accelerate the regeneration of liver cells by increasing protein synthesis in damaged liver tissue. Experiments on laboratory animals have shown that silibinin causes a significant increase in the formation of ribosomes in hepatocytes, and, as a result, an increase in the synthesis of structural and functional proteins, which is a condition for the restoration of damaged hepatocytes and the normalization of liver function. Recent studies suggest that silibinin may be used to treat type 2 diabetes due to its antihyperglycemic properties.

In an experiment on perfused rat hepatocytes, it was shown that silibinin inhibits hepatic glucose-6-phosphatase and suppresses gluconeogenesis [17]. Silymarin has an immunomodulatory effect and increases the secretion of IFN-γ, IL-4 and IL-10 in a mixed culture of lymphocytes, and also inhibits the production of nitric oxide in macrophages [2]. Administration of silymarin reduces the concentration of low-density lipoprotein cholesterol in rats with hyperlipidemia, which suggests its use as a potential hypocholesterolemic agent [18]. Silymarin may be effective in treating and preventing certain neurodegenerative and neurotoxic processes. Wang et al. demonstrated that silymarin was able to effectively protect dopaminergic neurons during lipopolysaccharide-induced neurotoxicity by inhibiting microglial activation [19]. Interesting data were obtained by Jung et al. when studying the effects of silybin on microorganisms. The authors found that silybin has an antibacterial effect on methicillin-resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa in combination with some antibacterial agents, which opens up the prospect of its use in combination antibacterial therapy for infections caused by antibiotic-resistant microorganisms [20]. De F. Monbrison et al. demonstrated the antimalarial activity of dehydrosilybin in in vitro experiments, which opens up prospects for its use during infection with drug-resistant strains of Plasmodium falciparum [21].

Clinical use of silymarin The pronounced hepatoprotective properties of silymarin, known from traditional medicine and proven, have prompted many researchers to conduct clinical trials of this drug for diseases such as alcoholic liver disease, cirrhosis of the liver, acute and chronic viral hepatitis, toxic and drug-induced liver damage. Alcoholic liver disease. Conducted clinical studies on the effectiveness of the use of milk thistle preparations for chronic alcoholic liver damage have revealed a beneficial effect on clinical symptoms, biochemical parameters and partly on histological changes in the liver. At the same time, silymarin does not have a direct effect on the metabolism of ethanol and does not affect the rate of its removal from the body [22]. According to Feher et al., who used silymarin to treat patients with chronic alcoholic liver disease (ALD) for 6 months, exposure to the drug led to normalization of the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGTP), concentration total bilirubin and improvement of the histological picture of the liver [23]. Salmi et al. evaluated the effect of using silymarin in patients with ALD for 4 weeks. At the end of the study period, the authors observed a significant decrease in AST and ALS activity by 30.1 and 40.8%, respectively, in patients receiving silymarin compared with the group of patients receiving placebo. However, no significant differences in the content of total and conjugated bilirubin in the serum were noted [24]. However, the results of individual clinical trials are conflicting, which may be due to differences in the amount of alcohol consumed during the study and the complexity of the pathogenesis of the disease, as well as differences

in the composition of the silymarin preparations used depending on the cultivation conditions and extraction process [3]. Thus, according to Lucena et al., in patients with ALD, in whom other causes of liver disease, including hepatitis C, were excluded, after 6 months of treatment with silymarin, no significant changes were detected in the activity of ALT, AST, alkaline phosphatase (ALP), GGTP, albumin content, prothrombin time, platelet count [25]. Cirrhosis of the liver. A number of clinical trials have demonstrated the possibility of slowing the progression of liver cirrhosis under the influence of milk thistle therapy. Ferenci et al. investigated the effectiveness of silymarin in patients with histologically confirmed cirrhosis. Average survival after 4 years of use of this drug was significantly higher in patients receiving silymarin compared with the control group using placebo (58 and 39%, respectively), but no significant differences were found in biochemical markers [26]. However, a study of patients with histologically confirmed alcoholic cirrhosis conducted by Pares A. et al. did not reveal a significant positive effect on survival after 2 years of treatment with silymarin compared with the placebo group [27].

Drug-induced and toxic liver damage. It is known that the use of many drugs, such as rifampicin, isoniazid and others, can lead to liver damage, especially with long-term use. Clinical trial results indicate that the combination of silymarin with potentially hepatotoxic drugs may reduce or completely prevent their side effects [5]. The therapeutic effect of silymarin in case of poisoning with toadstool (Amanita phalloides) deserves special attention. When studying the protective effect of silymarin on laboratory animals, it was found that the more time passed after the administration of the toxin, the less effective the use of this drug. In experiments on mice, silymarin administered intravenously before or within 10 minutes after intoxication showed 100% effectiveness [1]. When LD50 Amanita phalloides was administered orally to dogs, not a single animal died that received silymarin 5 and 24 hours after intoxication, and the drug reduced the degree of liver necrosis and changes in biochemical parameters [28]. The results of retrospective studies of the treatment of toadstool poisoning demonstrated a positive effect from the use of silymarin. Enjalbert et al. conducted a retrospective study of clinical data of 2108 patients hospitalized over 20 years in North America and Europe with amatoxin poisoning, and a statistical comparison of the number of survivors and deaths confirmed the positive effect when using silybin in mono- and combination therapy [29]. Hruby et al. found that the severity of liver damage was less the earlier from the moment of toxin consumption, treatment with silibinin began. However, administration of silibinin even 48 hours after poisoning was able to effectively prevent damage to liver tissue [30]. These studies confirm the possibility of using silymarin as an antidote for poisoning with toadstool. Viral hepatitis. Silymarin does not have a direct effect on the replication of the hepatitis virus, however, due to its inhibitory effect on inflammatory and cytotoxic processes

caused by viral infection, as well as its stimulating effect on liver regeneration, this drug can have a positive effect in viral liver damage. In viral hepatitis C, the antioxidant effect of therapy helps reduce the risk of malignant transformation of hepatocytes [5]. Magliulo et al. [31] showed that significantly more patients with acute hepatitis A or B experienced normalization of AST and bilirubin after 21 days of treatment with silymarin compared with patients receiving placebo. The differences in the dynamics between ALT and ALP between the two groups were insignificant. When using silybin for hepatitis C, Buzzelli et al found a statistically significant decrease in transaminase activity in patients receiving silybin compared with the placebo group, as well as a decrease in AST activity compared to baseline in the silybin group. However, no significant changes in ALT, alkaline phosphatase, GGTP, and bilirubin were observed [32]. In the group of patients with chronic hepatitis B and C who received silipid, a statistically significant decrease in transaminases and GGTP was detected compared with the baseline and the placebo group [33]. Similar data were obtained by Vailati et al. when studying chronic hepatitis of both viral and alcoholic origin [34]. When assessing the effect of the silybin-vitamin E-phospholipid complex in patients with hepatitis C virus who received this drug, a significant and stable decrease in ALT and AST in the blood serum was observed compared to controls [35].

Evaluation of the results of studies of silymarin in patients with hepatitis B or C is complicated by the small number of patients, the lack of placebo control in some studies, and the grouping of hepatitis of different etiologies into one category [2]. However, most clinical trials have shown that in patients with viral hepatitis, the use of silymarin leads to a decrease in transaminase activity, but its effect on the progression and outcome of the disease is still unclear, which requires further study.

Conclusion

Flavonoids from milk thistle: silymarin and its structural component, silibinin, have pronounced hepatoprotective properties and are capable of exerting a therapeutic effect through four main mechanisms: 1) as antioxidants and regulators of intracellular glutathione content; 2) as stabilizers and regulators of permeability, preventing the entry of hepatotoxic substances into hepatocytes; 3) as activators of ribosomal RNA synthesis, stimulating regenerative processes in the liver; 4) as inhibitors of the transformation of stellate hepatocytes into myofibroblasts, a process leading to liver cirrhosis. Experimental studies have shown that milk thistle preparations provide liver protection when exposed to various hepatotoxic agents. There are reports that silymarin not only has a hepatoprotective effect, but is also effective in the treatment of a number of other diseases. The mechanisms of the antitumor effect of this drug are being actively studied. It is assumed that silymarin can have a therapeutic effect in diabetes mellitus, kidney disease, malaria, atherosclerosis, and some neurodegenerative and neurotoxic processes. Currently, silymarin is included in the list of drugs used for toxic

liver damage (alcoholism; intoxication with halogenated hydrocarbons, heavy metal compounds; drug-induced liver damage), chronic hepatitis, and cirrhosis of the liver. Silymarin also has a pronounced therapeutic effect in case of poisoning with toadstool. Most of the clinical trials conducted have demonstrated an improvement in biochemical parameters of liver function with the use of this drug. However, the results obtained in the studies dictate the need for further study of the effect of milk thistle preparations on the course and long-term results of treatment of diseases of various etiologies.

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