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Silymarin: A Novel Drug: A Game Changer

Bhagyashali Janardan Pawar*, Shruti G. Dake, Mrunali D. Kathar

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ABSTRACT:
Silymarin, a flavonolignan derived from "milk thistle" (Silybum marianum) seeds, has been utilised for hepatoprotection since ancient times. It mostly consists of three flavonolignans, silybin being the most active. These flavonolignans are silidianin, silychristine, and silybin. Toxin/drug-induced hepatitis, acute and chronic viral hepatitis, cirrhosis, and alcoholic liver illnesses have all been treated medically using silymarin. Additionally, some malignancies have been said to respond well to it.
Its mode of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane, reduction of glutathione oxidation to increase liver and intestine levels, antioxidant activity, stimulation of ribosomal RNA polymerase and subsequent protein synthesis, and enhanced hepatocyte regeneration. Because it is poorly soluble in water, it is absorbed orally but has very low bioavailability. This review concentrates on the pharmacokinetics, pharmacodynamics, and toxicity of silymarin. Silymarin's novel application as a method of organ protection for organs other than the liver may prove to be a game-changer.
Keywords : Silymarin, Cytoprotective, Herbal drug, Hepatoprotection, MilkThistle

I. INTRODUCTION:

The benzo gamma-pyrone family includes flavonoids. There are already more than 4000 different types of flavonoids, and they are found all throughout the world, not just in plants. Particularly prevalent in the animal kingdom as well as the photosynthetic cells of higher plants. They have been given many therapeutic characteristics over the years, and several have been utilized as well-known therapeutic treatments.

Activating ingredients have included substances like quercetin, taxifolin, and silymarin, both on their own and as parts of elaborate chemical formulations. A flavonolignan called silymarin has only lately been made available as a hepatoprotective medication. It is derived from the seeds and fruit of the composite plant Silybum marianum, and it actually combines the structural elements silibinin, silydianine, and silychristine. From a medical point of view, silymarin and silibinin have been found to provide cytoprotection and above all,hepatoprotection (2, 5). Silymarin is used for the treatment of numerous liver disorders characterised by degenerative necrosis and functional impairment (3) Furthermore, it is able to antagonise the toxin of Amanita phalloides (6,7) and provides hepatoprotection against poisoning by phalloidin (8) galactosamine (9) thioacetamide (10) halothane (11) and carbon tetrachloride (12). The compound also protects hepatocytes from injury caused by ischaemia, radiation, iron overload and viral hepatitis (13).silymarin is included in the pharmacopoeia of many countries under the trademark LegalonTM or HepatronTM and is often used as supportive therapy in food poisoning due to fungi and in chronic liver disorders, such as steatosis (14) and alcohol-related liverdisease (15).

CHEMISTRY OF SILYMARIN

Silymarin is isolated from dried milk thistle seeds since it is concentrated there more than in other plant components (16). The active principle was first isolated and chemically characterized during 1968-1974. Later the biochemical effects of silymarin on RNA, protein and DNA synthesis was reported by Sonnenbichler and Zetl(17).

Silymarin has the empirical formula C25H22O10 and is a complex combination of the flavonolignan isomers silybin, isosilybin, silydianin, and silychristin. It is thought that silymarin's facilitative effects on protein synthesis are caused by its structural resemblance to steroid hormones. Among the isomers silybin is the major and most active component and represents about 60-70 %, followed by silychristin (20%),silydianin (10%), and isosilybin (5%) (18). Silipide (IdB1016) isthe silybin - phosphatidylcholine complex which ensures a
large increase in the bioavailability of silybin (19).

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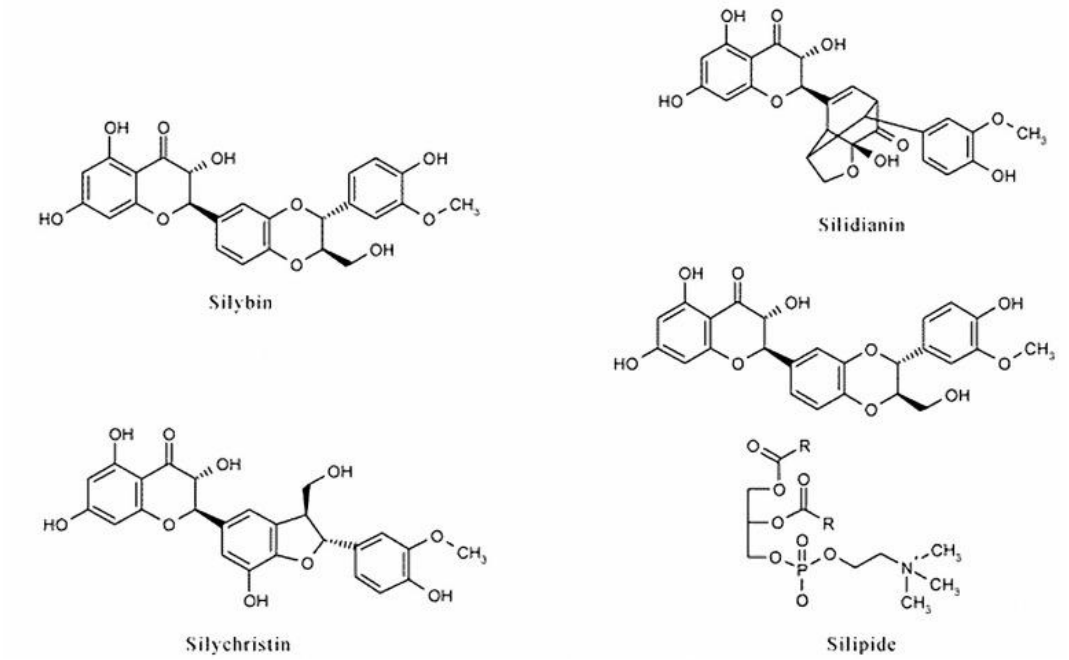

Chemical structure of some Silymarin compounds

PHARMACOKINETICS

Since silymarin is not soluble in water, it is often taken as a standard extract in capsule form (70 to 80% silymarin).Recovery in the bile of rats following oral treatment ranges from 2 to 3%, indicating rather limited absorption. Peak plasma concentrations are reached in both humans and animals in 4 to 6 hours. The main excretion channels for silymarin are the bile and, to a lesser extent, the urine. Its half-life for elimination is 6 to 8 hours. (20-22). However, other authors (23) reported plasma levels of 500 mg/L (as silibinin) 90 minutes after oral administration of 200 mg/kg of silymarin or of purified S. marianum extract in mice. In the liver, silibinin and other silymarin constituents quickly conjugate with glucuronic acid and sulphate. The conjugates are absorbed into the plasma and bile, where they are detected in concentrations equal to 80% of the total dose. Only a small amount is excreted in the urine.

These results point to the occurrence of intestinal absorption, conjugation in the liver, excretion in the bile, hydrolysis by the intestinal flora, and reuptake in the gut (24).

PHARMACODYNAMIC PROPERTIES

1) Antioxidant properties:

In general, flavonoids have good antioxidant action. A potent inhibitor of the oxidation of the linoleic acid-water emulsion caused by Fe2+ salts is the silibinin dehydrosuccinate sodium salt, which is water soluble. (25). Additionally, it suppresses the well-known experimental system for the production of hydroxy radicals, NADPH-Fe2+-ADP-induced microsomal peroxidation, in a concentration-dependent manner. (26). Studies in rat hepatic microsomes have shown that silibinin dihemisuccinate inhibits lipid peroxidation caused by Fe(III)/ascorbate; the inhibition is concentration-dependent (27, 28). It has been demonstrated that silymarin exhibits antiperoxidant action comparable to quercetin, dihydroquercetin, and quercitrin, regardless of the experimental model employed to create peroxidation. (29). According to a recent study, silymarin enhances oxygen consumption, decreases lipid peroxide generation, reduces lactate dehydrogenase loss, and boosts urea synthesis in the perfusion medium in rat hepatocytes treated with tert-butyl hydroperoxide (TBH). Additionally, silymarin can counteract the rise in Ca2+ caused by TBH, bringing ion levels below 300 nmol/L. The suppression of lipid peroxidation, which is how silymarin exerts its protective effects, and the modification of hepatocyte Ca2+ level appear to be key factors in this process (30).

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2) Activity against Lipid Peroxidation:

Lipid peroxidation is a result of interactions between free radicals from numerous sources and the unsaturated fatty acids found in lipids. Numerous changes are brought about by lipid peroxidation, and the degeneration of cell membranes that results may contribute to the emergence of additional disorders of lipoprotein metabolism in the liver and in peripheral organs. Silymarin appears to act as an antioxidant due to its effects on the glutathione and superoxide dismutase enzyme systems (32), in addition to the fact that it scavenges the free radicals that induce lipid peroxidation (27, 33). All silymarin components have been shown to prevent the lipoxygenase-catalyzed oxidation of linoleic acid (34), and silymarin has been shown to shield rat liver mitochondria and microsomes against lipid peroxide production in vitro (35).

3) Effects on Liver Lipids:

The effects of silymarin on cellular permeability are strongly related to changes in the membrane lipids (both cholesterol and phospholipids) on both a qualitative and quantitative level (31, 36, 37). This shows that silymarin may also affect other lipid storage areas in the liver, which could affect the release and uptake of lipoproteins. It has been demonstrated that silymarin and silibinin decrease phospholipid production and turnover in rat liver. The inhibition of phospholipid production and the decrease in the incorporation of labelled glycerol into the lipids of isolated hepatocytes are two additional effects of ethanol in rats that can be countered by silibinin (38) 61). In addition, silibinin stimulates phosphatidylcholine synthesis and increases the activity of cholinephosphate cytidyltransferase in rat liver both in normal conditions and after intoxication by galactosamine (39). Data on the influence of silymarin on triglyceride metabolism in the liver are scanty. It is known that in rats silibinin is able to partly antagonise the increase in total lipids and triglycerides produced in the liver by carbon tetrachloride (40) and probably, to activate fatty acid ßoxidation.It has also been suggested that silymarin may diminish triglyceride synthesis in the liver (38). Letteron et al(27) studied the mechanisms of action of silymarin that provide protection against lipid peroxidation and the hepatotoxicity of carbon tetrachloride in mice and came to the conclusion that silymarin works by reducing metabolic activation by carbon tetrachloride and by acting as an antioxidant that prevents chain rupture authors have shown that silymarin affords hepatoprotection against specific injury induced by microcystin (a hepatotoxin), paracetamol, halothane and alloxan in several experimental models (43-44).

4) Effects on Plasma Lipids and Lipoproteins:

The administration of silymarin reduces plasma levels of cholesterol and low-density lipoprotein (LDL) cholesterol in hyperlipidaemic rats, whereas silibinin does not reduce plasma levels of cholesterol in normal rats; however, it does reduce phospholipid levels, especially those transported in LDL (38). Data obtained in experimental models of hepatic injury have shown that silymarin is able to normalise the increase in plasma lipids observed after administration of carbon tetrachloride and to antagonise the reduction in serum free fatty acids induced by thioacetamide. In the experimental model of hepatic injury produced by thioacetamide, silymarin did not appear to be able to normalise the reduction in triglycerides in serum. In the experimental model of hepatic injury produced by paracetamol in rats, it was evident that silymarin improves LDL binding to hepatocytes, an important factor for the reduction of LDL in plasma (38).

5) Stimulation of Liver Regeneration:

Increased protein synthesis in the wounded liver is one of the methods that silymarin can use to encourage the regeneration of liver tissue. Silibinin significantly increased the creation of ribosomes, DNA synthesis, and protein synthesis in in vivo and in vitro tests carried out in the livers of rats from which a portion of the organ had been excised (45). It's interesting to note that silibinin only increased protein synthesis in damaged livers; it had no effect on healthy controls (46). Silibinin increases the production of ribosomes in the liver through an unidentified mechanism that may be related to the physiological regulation of RNA polymerase I at particular binding sites (47). Treatment with intraperitoneal silymarin 140 mg/kg for 4 days totally eliminated the inhibitory impact of galactosamine on the production of liver proteins and glycoproteins in rats with experimental hepatitis brought on by galactosamine (48). These findings are consistent with earlier research in a rat model of acute hepatitis, where silymarin protected liver glucose reserves, enzyme activity, and hepatic structures against damage brought on by galactosamine in vivo (49).

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Silymarin's ability to promote protein synthesis in neoplastic cell lines has also been investigated.

6) Anti-Inflammatory and Anticarcinogenic Properties:

Silymarin has been shown to significantly reduce inflammation in liver tissue. According to studies, silymarin inhibits the migration of neutrophils, Kupffer cells, leukotriene synthesis, the production of prostaglandins, and neutrophil migration (47, 50–52). In numerous experimental animal models, the protection offered by silymarin against carcinogenic substances has been investigated. In order to explore the initiation, promotion, and full carcinogenesis of nonmelanoma skin cancer caused by UVB radiation, a number of tests were carried out on naked mice. The incidence, multiplicity, and volume of tumours per animal appeared to be significantly reduced in all stages of the study when silymarin was administered topically in various doses. Furthermore, in a short-term experiment (using the same experimental model), the application of silymarin significantly reduced apoptosis, skin oedema, depletion of catalase activity and induction of cyclo-oxygenase and ornithine decarboxylase activity. This effect provides protection against photocarcinogenesis (53). Similar results were also obtained in the model of skin carcinogenesis produced by chemical carcinogenic agents in carcinogenesis-sensitive (SENCAR) mice (54, 55). The molecular bases of the anti-inflammatory and anticarcinogenic effects of silymarin are not yet known; they might be related to the inhibition of the transcription factor NF-kB, which regulates the expression of various genes involved in the inflammatory process, in cytoprotection and carcinogenesis (56-58). It has also been hypothesised that silymarin may act by modulating the activation of regulating substances of the cellular cycle and of mitogen-activated protein kinase (59).

TOXICITY

After intravenous infusion, the acute toxicity of silymarin has been investigated in mice, rats, rabbits, and dogs. For mice, rats, and dogs, the 50% fatal dosage (LD50) values are 400 mg/kg, 385 mg/kg, and 140 mg/kg, respectively. These figures, however, are simply approximations because they are based on the infusion rate. Rats may respond at levels of 2 g/kg when the drug is slowly infused (over 2 to 3 hours). Tolerance is even higher after oral treatment, with levels exceeding 10g/kg. Cardiovascular failure appears to be the cause of death in cases of acute intoxication (60). Vogel et al. (61) also achieved similar outcomes. Other experiments to assess the acute toxicity of silymarin were performed in beagle dogs, rabbits, Wistar rats and NMRI mice after an intravenous bolus dose. Silymarin was used as the hemisuccinate sodium salt and the animals were kept under observation for 14 days.

The LD50 was 825 and 920 mg/kg for male and female rats, respectively, and 1050 and 970 mg/kg for male and female mice, respectively. The maximum tolerated dose in dogs and the mean lethal dose in rabbits, respectively, were both determined to be around 300 mg/kg (50). These findings show that silymarin has a very low acute toxicity. Additionally, the chemical has very low subacute and chronic toxicity and no potential for embryotoxicity (62).

II. CONCLUSION

Silymarin is a very promising medication of natural origin due to its remarkable hepatoprotective efficacy as well as its immunomodulatory, antioxidant, and anti-inflammatory properties, which are demonstrated by a number of the research described above. Additional benefits include its affordable price, simple availability, and high level of safety. Its effectiveness in regenerating liver cells and restoring liver function has been demonstrated. Due to greater standardization, quality control, and lack of microbial and metal contamination, it may soon prove to be superior to polyherbal formulations. Silymarin might become a game-changer as a novel strategy to safeguard organs other than the liver.

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