ejpmr, 2018,5(7), 193-195

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SILYMARIN: IS IT A TRITON AMONG THE MINNOWS?

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Article Received on 24/04/2018 **Article Revised on 14/05/2018** **Article Accepted on 04/06/2018**

ABSTRACT

The flavonoid silymarin has documented hepatoprotective properties. The mechanisms of action are still poorly understood. However, the data in the literature indicate that silymarin acts in four different ways: as antioxidants, scavengers and regulators of the intracellular content of glutathione; as cell membrane stabilisers and permeability regulators that prevent hepatotoxic agents from entering hepatocytes; as promoters of ribosomal RNA synthesis, stimulating liver regeneration; and as inhibitors of the transformation of stellate hepatocytes into myofibroblasts. The key mechanism that ensures hepatoprotection appears to be free radical scavenging. Anti-inflammatory and anticarcinogenic properties have also been documented. Silymarin is able to neutralise the hepatotoxicity of several agents, including *Amanita phalloides*, ethanol, paracetamol (acetaminophen) and carbon tetrachloride in animal models. Hepatoprotection has been documented by improvement in liver function tests; moreover, treatment with silymarin was associated with an increase in survival in a placebo-controlled clinical trial in alcoholic liver disease. Pharmacokinetic studies have shown that silymarin is absorbed by the oral route and that it distributes into the liver, stomach, intestine, and pancreas. It is mainly excreted as metabolites in the bile, and, is subject to enterohepatic circulation. Toxicity is very low, the oral 50% lethal dose being 10,000 mg/kg in rats and the maximum tolerated dose being 300 mg/kg in dogs. Moreover, silymarin is devoid of embryotoxic potential. In conclusion, silymarin is a well-tolerated and effective antidote for use in hepatotoxicity produced by a number of toxins. Numerous experimental studies suggest that it acts as a free radical scavenger, with other liver-specific properties that make it a unique hepatoprotective agent.

KEYWORDS: Silymarin, Hepatoprotective, Carbon tetrachloride.

BACKGROUND

Silymarin is the standardized extract of seeds of milk thistle (*Silybum marianum*), containing a mixture of flavonolignans consisting of silybin, isosilybin, silychristine and silidianin (Khan et al., 2017; Pradhan et al., 2006). Silybin component is the major active phytoconstituent and comprises about 50% to 70% of silymarin. Silybin itself is a mixture of two diastereomers, silybin A and silybin B, in approximately equimolar ratio. Silymarin is found in the entire plant, but it is concentrated in the fruits and seeds (Freitag et al., 2015). Silymarin has been used to treat liver disorders, including acute and chronic viral hepatitis, alcoholic liver disease, drug and toxin-induced liver disease (Wen et al., 2008).

Silybum marianum plant has been used for centuries in the treatment of liver related disorders (Hellerbrand et al., 2016). This plant is native to the Mediterranean region and grows throughout Europe and North America. It also grows in India, China, South America, Africa and Australia. It is an annual or bi-annual plant up to 2 meters in height. It has large bright leaves with wavy margins and characteristic white stains. The leaves are characterized by milky veins from which the plant derives its name (Karimi et al., 2011).

The precise mechanism of hepatoprotective action of silymarin is still unclear, but its hepatoprotective action may include inhibition of binding of hepatotoxin to receptor sites on the membrane of hepatocytes, the reduction of glutathione degradation, increase in the level of glutathione, antioxidant activity, stimulation of ribosomal RNA polymerase and hence protein synthesis which is essential for the regeneration of hepatocytes (Gharagozloo et al., 2013).

Pharmacokinetics: Silymarin is poorly soluble in water. It is available in different formulations as tablets, capsules, and syrups. The oral absorption of silymarin is only about 23-47%, leading to the low oral bioavailability of the compound (Calani et al., 2012). Peak plasma concentration is achieved in 6-8 hours. Silybin and other constituents of silymarin are rapidly conjugated with sulfate and glucuronic acid in the liver and excreted through the bile (Fraschini et al., 2002). Poor water solubility and low oral bioavailability have

led to the development of enhanced formulations of silymarin (Dixit et al., 2007).

Silipide, a complex of silymarin and phosphatidylcholine is approximately ten times more bioavailable than silymarin (Ghosh et al., 2010). Another formulation containing inclusion complex formed between silymarin and β-cyclodextrin has been shown to improve the solubility and dissolution rate of silymarin, which in turn enhances its hepatoprotective activity (Ferenci, 2016).

Toxicity studies: Acute toxicity studies of silymarin after intravenous infusion have been carried out in mice, rats, rabbits, and dogs. With slow intravenous infusion (over 2-3 h) LD50 was 2g/kg in rats and after oral administration, LD50 was 10g/kg in rats. LD50 values were 400mg/kg in mice, 385mg/kg in rats, 140mg/kg in rabbits and dogs after intravenous infusion. Acute toxicity studies have also been carried out in NMRI mice, Wistar rats, rabbits and dogs using Hemisuccinate sodium salt as intravenous bolus dose. LD50 was 1050mg/kg in male mice, 970mg/kg in female mice, 825mg/kg in male rats, 920mg/kg in female rats and 300mg/kg for both the rabbits and dogs. Acute as well as subacute and chronic toxicity of silymarin are very low as reported by multiple studies (Polyak et al., 2013).

Hepatoprotective activity: Silymarin has been shown to demonstrate hepatoprotective activity in various models of hepatotoxicity (Khan et al., 2017). Silymarin has been reported to protect against CCl_4 induced lipid peroxidation and hepatotoxicity (Salam et al., 2007). Silymarin normalizes serum transaminase levels and membrane ratios of cholesterol: phospholipids and sphingomyelin: phosphatidylcholine (Vargas-Mendoza et al., 2014). Administration of ethanol produces a decrease in hepatic glutathione content and an increase in serum transaminase levels. Silymarin has been demonstrated to protect against ethanol-induced liver damage (Ghosh et al., 2010).

Silymarin has also been shown to provide hepatoprotection against Thioacetamide-induced liver damage (Chen et al., 2012). Administration of Galactosamine causes cholestasis and impairment in the synthesis of bile acids, as well as their conjugation with proteins, gets disrupted. Silymarin has been found to reduce cholestasis and normalize the level of serum transaminases in animal studies (Ferenci, 2016). Silymarin, by its stabilizing action on the plasma membrane, has been shown to normalize paracetamol induced elevated biochemical parameters in the liver and serum (Freitag et al., 2015).

Amanita phalloides toxin produces acute toxicity in mice, rats, rabbits, and dogs. The elevation of hepatic transaminases and reduction in coagulation factors seen with sublethal doses of Amanita phalloides can be prevented with silymarin. Silymarin has been found to provide protection against ischemia-induced hepatic injury, viral hepatitis and radiation mediated injury to hepatocytes (Mansour et al., 2006). Silymarin has also been reported to possess anti-inflammatory, antiarthritic, antifibrotic, antioxidant and anticancer properties (Chhabra et al., 2013).

Mechanisms of hepatoprotective action of silymarin:

- Activity against lipid peroxidation as a result of free radical scavenging effect and the ability to increase cellular content of glutathione (Anthony et al., 2013)
- Enhanced hepatocyte regeneration by stimulation of ribosomal RNA polymerase and protein synthesis (Hellerbrand et al., 2016)
- Improvement in detoxification function of liver via inhibition of phase I detoxification (Karimi et al., 2011)
- Inhibition of transformation of stellate hepatocytes into myofibroblasts which are responsible for the deposition of collagen fibres leading to cirrhosis (Maiti et al., 2008)
- Improvement in glucuronidation function of liver (Polyak et al., 2013)
- Immunomodulatory effects on liver (Gharagozloo et al., 2013)
- Anti-inflammatory effects which include inhibition of leukotriene and prostaglandin synthesis, inhibition of kupffer cells, stabilization of mast cells and neutrophil migration (Wen et al., 2008)
- Antineoplastic activity due to inhibition of cyclin-dependent kinases and impairment of growth of cancer cells (Miranda et al., 2008)

Adverse effects: Silymarin is very well tolerated and has a very low toxicity profile. However, at high doses, a laxative effect has been reported due to increased biliary secretion. Most of the reported side effects are related to gastrointestinal tract, such as nausea, abdominal discomfort, bloating and dyspepsia. Loose stools have been reported in approximately 2-10% of patients (Ferenci et al., 2013).

Therapeutic indications: Amanita mushroom poisoning, acute and chronic viral hepatitis, alcoholic liver disease, drug-induced and toxin-induced liver disease, hypercholesterolemia and psoriasis (Freedman et al., 2011).

Dosage: The daily oral dose of silymarin is from 280 to 800mg. This is equivalent to 400 to 1140mg of an extract containing 70% silymarin. The recommended dose for the active liver disease is 140mg of silymarin (200mg of extract) three times daily. Silipide (silymarin-phosphatidylcholine) is given in a dose of 100mg three times daily (Miranda et al., 2008).

CONCLUSION

Silymarin is a well-tolerated and effective antidote for use in hepatotoxicity produced by a number of toxins. Numerous experimental studies suggest that it acts as a

free radical scavenger, with other liver-specific properties that make it a unique hepatoprotective agent.

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