IJBPAS, May, 2023, 12(5): 2003-2016

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

SILYMARIN: AN INSIGHT TO ITS PHYSIOLOGY TO FORMULATION AND VALUABLE PROSPECTS

KOTAME R*[1] AND DANIEL K[2]

1: Research Scholar, Oriental University, Indore

2: Professor, Oriental University, Indore

***Corresponding Author: Radhika Kotame: E Mail:**

Received 10th June 2022; Revised 15th July 2022; Accepted 19th Sept. 2022; Available online 1st May 2023

https://doi.org/10.31032/IJBPAS/2023/12.5.7104

ABSTRACT

Background- Silymarin, a flavonolignan resultant since the kernels of the'milk thistle' (Silybum marianum).It is mainly collected of three flavonolignans: silidianin, silychristine, silybin, the greatest active of which is silybin., widely used aimed at its hepatoprotective belongings subsequently antique times. Silymarin has been used to treat a diversity of liver circumstances, poison/drug-related hepatitis, cirrhosis, and alcoholic liver disease.

plus acute and chronic virus-related hepatitis.

Main text-Silymarin, a flavonolignan has been exploited as a hepatoprotective drug other activities include antioxidant, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulatory, and liver regeneration derived from the 'milk thistle' plant, since ancient times..In addition to hepatoprotective function, Silymarin is used in the treatment of alcoholic viral hepatitis, liver disease, liver cirrhosis, Amanita mushroom poisoning, toxic and drug-induced liver illnesses, psoriasis, and other skin conditions, neuroprotective and neurotropic properties.

Conclusion- Silymarin is a self-same auspicious likely drug because of its amazing hepatoprotective act, with its antioxidant, immunomodulatory, and anti-inflammatory actions, as showed by a number of research described above.

Keywords: Silymarin, hepatoprotection, anti-inflammatory, liver, neuroprotective

1. INTRODUCTION

Wide laboratory investigation by the use of therapeutic plants to fortify the immune system of research laboratory wildlife undertaken in new decades, showing the positive effect of countless of them in wildlife resistant system

improvement. The usage of such floras to luxury and contest microbial and fungiform contagions elucidated a pharmacological tactic to those residents. Since of their antioxidant, antibacterial potentials, therapeutic plant quotations is now have been extended remained rummage-sale to extravagance and switch a variety of diseases. Fruits, medicinal plants, vegetables, are the most important sources of antioxidants in nature **[1]**.

These florae have optimistic welfares by levitation the action of peptic enzymes in duodenal mucosal cells and motivating the amplified action of pancreatic enzymes (protease, lipase, amylase). Their phenolic apparatuses lesser the quantity of damaging microbes in the instestinal flora and stop nutrient damage, improving colonic well-being, nutrient absorption, and production efficacy. The custom of such florae in muesli grain-based foods has been shown to surge the relief of peptic enzymes, progress nourishing digestibility, and subordinate the viscidness of gastric insides and the quantity of tacky or slushy faces in chickens. The usage of medicinal plants and their essential oils has an impact on the flora and arrangement of the environment. Broiler gastrointestinal system develops immune system, diminutions blood cholesterol hence advances body function. Antibiotics may be second-hand less regularly in rooster diet as a result of these reactions, resulting in fewer adverse effects and perilous remainders in hen products **[2, 3]**.

1.1. Silymarin: Source and Physicochemical Properties

It is a chemical of flavonoid inaccessible after the slight firm fruits (kenguil kernels) of the Silybum marianum, which produces broadly in Asia and Europe, including India. The medicine is a flavonolignan, a kind of particle complete in the herbal by fundamental link of flavonoids and coniferyl alcohol. The mechanisms of a orientation arrangement are silibinin /silybin (32.4%), silychristin (13.9%), silydianin (3.8%), and isosilybin (9.35%), which are believed to be accountable for the herbal citation therapeutic liver-protective result. Various products of profitable consistent milk thistle excerpts might be unlike silymarin structures and relations of particular components **[4, 5]**.

1.2 CHEMISTRY OF SILYMARIN

SL is derived from the dry seeds of plant of the milk thistle, anywhere it can be originate in superior attentions than in other shares of the herbal. In 1968, the active value was mined and chemically defined for the first time **(Figure 1) [6]**.

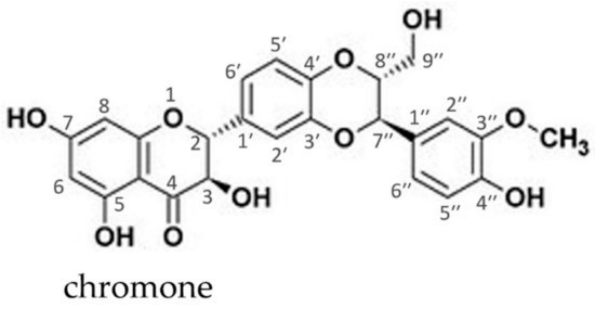

Figure 1

1.3 MECHANISM OF ACTION

(i) Incentive of protein fusion:

SL having the capability to arrive the centre and work on RNA polymerase enzymes, subsequent in improved ribosome invention. As a consequence, protein and DNA amalgamation is enhanced. This exploit has noteworthy beneficial insinuations for the reparation of injured hepatocytes and the refurbishment of usual liver operative **[9]**.

(ii) Antioxidant possessions:

Free radicals linked to liver infections, plus the hydroxyl radical (OH), superoxide radical, lipid peroxide radicals, hydrogen peroxide (H2O2). The manufacture of responsive oxygen type is a ordinary by-product of metabolic progressions **[8]**.

(iii) Antifibrotic activity:

Hepatic inadequacy, portal hypertension, and hepatic encephalopathy produced via liver fibrosis, which sources adjustment of the liver construction. These courses need a difficult communication amid cells and intermediaries. Propagation of hepatic parenchymal cells will occur in the early stages. The conversion of hepatic stellate cells into myofibroblast is thought to be the most noteworthy stage in fibrogenesis **[11]**.

(iv) Anti-inflammatory actions:

A important pharmacological piece of silymarin is its inhibitory act on the 5-lipoxygenase pathway, which fallouts in leukotriene manufacture conquest. At cumulative amounts of silibinin, leukotriene (B4) mixture was reserved while prostaglandin (E2) mixture was genuine **[10]**.

1.4 PHARMACOKINETICS

1) insoluble in water

2) peak plasma concentrations are reached in 4 to 6 hours.

3)eliminated in the bile.

4)elimination half-life 6 and 8 hours.

5)plasma levels of 500 mg/L in mice 90 minutes(oral administration of 200 mg/kg silymarin or pure S. marianum extract) **[12, 13]**.

1.5 PHARMACODYNAMICS

1) Antioxidant possessions:

Antioxidant action is regularly elevated in flavonoids. The water-soluble dehydrosuccinate sodium salt of silibinin is an current inhibitor of Fe2+ salt-catalyzed oxidation of linoleic acid-water emulsions. It too overpowers the microsomal peroxidation instigated by NADPH - Fe2+ - ADP in a concentration-dependent manner **[15]**.

2) Oxidative Stress:

The unrestrained group of pro-oxidant free radicals sources oxidative stress, which roots physical and/or purposeful damage in tissues. When the pro-oxidant effect of an inducer surpasses the anti-oxidant ability of the cell defence scheme, oxidative stress happens, disrupting the cell's homeostatic ability. Oxidative stress is produced by a diversity of compounds, with carbon tetrachloride, TBH, ethanol, paracetamol (acetaminophen), and phenylhydrazine. Silibinin has been confirmed to protect newborn hepatocytes in contradiction of cell damage instigated by amitriptyline, erythromycin, nortriptyline, in rats **[16, 17]**.

3) Activity against Lipid Peroxidation:

Lipid peroxidation is instigated by the interface of free extremists from several sources with unsaturated fatty acids in lipids. Lipid peroxidation roots a wide range of changes, and the resulting deficiency of cell membranes might chief to the advance of several lipoprotein metabolic illnesses in the liver and peripheral tissues **[18]**.

4) Effects on Liver Lipids:

The result of silymarin on cellular penetrability is connected to variations in membrane lipids (both cholesterol and phospholipids) in both qualitative and quantitative terms. This shows that silymarin could possibly alter lipoprotein production and fascination by acting on additional lipid compartments in the liver. The phospholipid production and revenue in the liver of rats has been found to be reduced by silymarin and silibinin **[19]**.

5) Belongings on Plasma Lipids and Lipoproteins:

In hyperlipidaemic rats, silymarin lessens plasma cholesterol and low-density lipoprotein cholesterol levels, while silibinin does not diminish plasma cholesterol stages in normal rats; however, it does decrease phospholipid levels, particularly those carried in LDL. Silymarin can regularize the upsurge in plasma lipids pragmatic succeeding injection of carbon tetrachloride and irritate the lessening in serum free fatty acids produced by thioacetamide, rendering to informations composed in animal replicas of hepatic injury **[20]**.

6) Incentive of Liver Regeneration:

One of the devices that enlightens silymarin's ability to arouse liver tissue revival is an surge in protein synthesis. In

incapacitated rats' livers, silibinin instigated a noteworthy surge in the development of ribosomes and DNA synthesis and an rise in protein synthesis. Surprisingly, silibinin created an escalation in protein synthesis solitary in injured livers not in healthy controls **[21]**.

7) Effects during Experimental Intoxication with Amanita phalloides:

The relaxing probable of silymarin in the behaviour of mushroom poisoning is chiefly noteworthy. Silymarin's hepatoprotective potentials have been intentional in rabbits, dogs, mice, rats. A dose of 16mg/kg of silymarin was given intravenously 1hour before a deadly dose of phalloidin was given intraperitoneally, and it was found to guard every animal species tested against the toxin's belongings **[22]**.

9) Antifibrotic effects:

In the process of hepatic fibrogenesis, stellate hepatocytes play a critical role. They multiply and alteration into myofibroblasts, which are accountable for the statement of collagen grits in the liver, in reply to fibrogenic factors (prolonged exposure to carbon tetrachloride or ethanol) **[23]**.

10) Reticence of Cytochrome:

SL inhibits the cytochrome P450 (CYP) detoxification trail in the liver (phase I metabolism). The capability of silibinin to overpower a diversity of hepatic CYP enzyme wave has recently been demonstrated in mice **[24]**.

11) Overview of Mechanisms of Action:

The hepatoprotection provided by silymarin appears to be based on four properties:

• Activity in contradiction of lipid peroxidation via free radical scavenging and the skill to upsurge cellular GSH content;

• Capability to control membrane penetrability and rise membrane firmness in the presence of xenobiotic harm;

• Capacity to order nuclear countenance via a steroid-like effect;

• Inhibition of the transformation

1.6 Representative of flavonoids in milk thistle

Milk thistle fruits harvest and stock a diversity of flavonoids, the quantity of which varies dependent on environment, region and plant type. The plant's foremost constituent is a blend of flavonolignans known as silymarin, which has strong antioxidant belongings. Silybin is the most plentiful flavonolignan in silymarin, secretarial for 50% of the total, followed by sily chrysanthemum (21%), silydianin (11%), and isosilibine (4%) **[26]**.

1.7 Science-Based Benefits of Milk Thistle

Milk thistle, usually recognised as Silybum marianum, is a herbal behaviour derivative from the milk thistle plant. The purple blossoms and white veins on this

prickly herbal are said to have been shaped by a drop of the Virgin Mary's milk dropping upon its shrubberies, Milk thistle mine is the herbal therapy for it. Milk thistle mine has a high percentage of silymarin (66–70%), which has been mined from the milk thistle herbal. Milk thistle silymarin has been shown to have antioxidant, antiviral, and anti-inflammatory effects **[27]**.

Is Milk Thistle Safe?

When consumed by orally, milk thistle is normally viewed safe.

In detail, only almost 2% of publics testified adverse things in lessons when large doses stood directed for prolonged periods of time.

When milk thistle side effects are verified, they are typically stomach conflicts such as nausea, bloating, Diarrhoea.

• Pregnant women: Because there is no study on its security in pregnant women, this extra is normally avoided **[28]**.

• Those exaggerated to the herbal: People who are affected to the Asteraceae/ Compositae family of plants may experience an hypersensitive reaction to milk thistle.

• Diabetic patients: Milk thistle's blood sugar-lowering belongings could put diabetics at hazard of low blood sugar **[29]**.

• Those with certain infections: Milk thistle has estrogenic belongings, which force worsen hormone-sensitive conditions including breast cancer **[30]**.

Benefits of Milk Thistle

1. **Milk Thistle Defends Your Liver**

Milk thistle is famous for its liver-protective chattels. People with liver harm from hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease often exploit it as a incremental analysis. It's also exploited to defend the liver from poisons such as amatoxin, a toxin produced by the death cap mushroom that can be fatal if expended. Milk thistle supplementation has been established to improvement liver function in persons with liver disorders, signifying that it may help diminish liver irritation and damage **[31]**.

2. **Help to Prevent Age-Related Decline in Brain Function**

For over two thousand years, milk thistle has been cast-off as a outmoded linctus for nerve diseases such as Alzheimer's and Parkinson's disease.

Its anti-inflammatory and antioxidant assets recommend that it may be neuroprotective, avoiding the harm in brain function that arises as people age.

Milk thistle is institute in large amounts in the brains of persons with Alzheimer's disease, telling that it

could be exploited to treat this interesting complaint **[32]**.

3. **Milk Thistle Could Protect Your Bones**

Osteoporosis is a ailment that sources reformist bone loss. It origins weak and flimsy bones that discontinuity simply, even after minor falls. Milk thistle has been shown to stimulate bone mineralization and hypothetically keep against bone loss in untried test-tube and visceral studies. As a result, scholars suggest that milk thistle may be a useful therapy for averting or delaying bone loss in postmenopausal women **[33]**.

4. **It May Improve Cancer Treatment**

It's been planned that silymarin's antioxidant belongings may have anticancer possessions, which could be valuable to cancer patients. Milk thistle has been found in animal trials to help diminish the adverse effects of cancer treatments **[34]**.

5. **It Can Boost Breast Milk Production**

Milk thistle has been stated to surge breast milk making in breastfeeding females. It everything by cumulative the invention of the milk-producing hormone prolactin. While the indication is scarce, one randomised controlled trial found that moms who took 421 mg of silymarin for 60 days made 66% more milk than those who took a placebo **[35]**.

6. **It Could Help Treat Acne**

Acne is an provocative skin condition that lasts for a extended time. While it is not harmful, it can consent scars. It may also be aching, and people may be troubled about the significances on their appearances. It's been planned that oxidative strain in the body has a role in acne development. Milk thistle may be a advantageous extra for acne losses due to its antioxidant and anti-inflammatory properties **[36]**.

7. **Milk Thistle Can Lower Blood Sugar Levels for People With Diabetes**

Milk thistle may be an real additional remedy for management of type 2 diabetes. One of the chemicals in milk thistle has been exposed to operate in a alike technique to some diabetes actions, refining insulin sensitivity and lowering blood sugar levels **[37]**.

1.8 The mechanism of action of Silymarin on some laboratory animals

In the Alzheimer's model fashioned by amyloid beta injection

in animals, silymarin management was demonstrated to greatly lessen the buildup of amyloid beta plaques and advance memory recital. In Alzheimer's disease, silymarin at absorptions of 15 and 50 g/ml enlarged Bcl-2 levels and diminished caspase 3 and Bax proteins, dropping apoptosis and hindering illness evolution in refined rat cortex neurons, and amplified norepinephrine, serotonin, and dopamine concentrations in some areas of the rat's brain. When poisons were given to silymarin-treated rats, the amount of glutathione in their liver cells augmented, oxidative stress reduced, and liver enzymatic activity reduced **[38, 39]**.

1.9. Formulation Strategies Designed to Improve the Bioavailability of Silymarin

Various approaches especially developed for silymarin supply will be intentional and logically secret in the subsequent subsets, along with the proper cross references stated in the text **(Figure 2)**. represents the several designs that have been created to advance silymarin solubility and bioavailability, the popular of which are envisioned for said use. To recognise the silymarin powdered mine and its major purified active ingredient silybin or silibinin **[40]**.

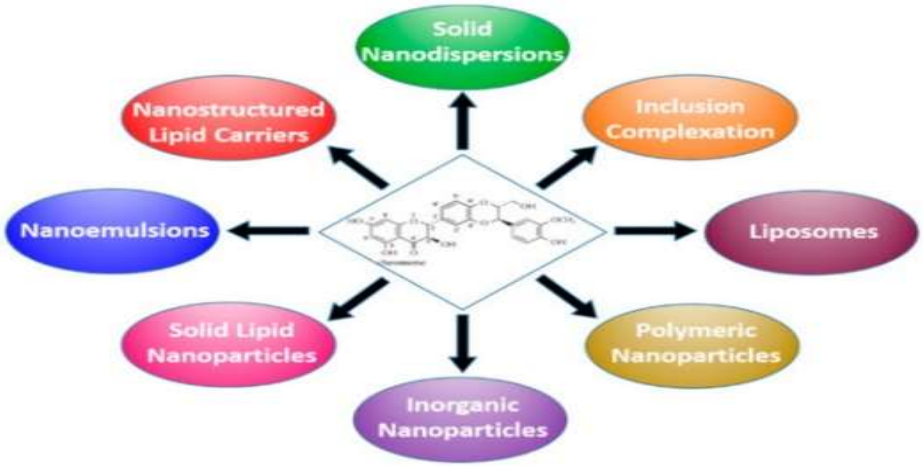

Figure 2: Applicable design strategies currently accessible to improve the bioavailability of silymarin

1. **Nanocrystals, Nanosuspensions and Solid Dispersions**

Surfactants or polymeric steric stabilisers calm sub-micron colloidal scatterings of pure drug elements in drug nanosuspensions. Nanonization skills surge the oral bioavailability and softening rates of carefully soluble remedies while also spreading their half-life. Another study used the nanoemulsification procedure with

PVP as a transporter to generate highly reachable SIL NPs with a mean size of 200 nm and an EE of 97%to assess antiviral efficacy in vitro **[41]**.

2. **Complexes with Cyclodextrins and Phospholipids**

delivery systems, pharmaceuticals, food technology, cosmetics, and the biochemical businesses all use normal cyclodextrins (CDs). They are contemporary in over-the-counter behaviours such as eye drops, pills and ointments.Ghosh *et al*. described designs based on SLM presence complexes with -CD. Kneading, Physical mixing, co-precipitation, and solvent evaporation were among the actions used to make them. The inclusion complex shaped using the co-precipitation slant fashioned the highest fallouts in terms of long-term drug issue **[42-44]**.

3. **Formulations of Lipid-based**

A prevalent preparation system uses lipid-based colloidal vehicles as a efficacious choice for transporting SIL with low water solubility. Self-emulsifying formulations, Nano-emulsions, oils, proliposomes, surfactant dispersions and liposomes, solid lipid nanoparticles and lipid nanocarriers, are used to surge the oral bioavailability of faintly water-soluble medicinal particles. (O/W) emulsions (LEs) and solid lipid nanoparticles are the two types of lipid formulations that can be found (SLNs) **[45, 46]**.

4. **Polymer-based Nanocarriers**

Investigators have advanced a variety of habits to professionally summarize SIL in biocompatible and decomposable polymeric nanosystems such as composites, polymeric micelles, nano-dispersions, which have been available in the literature. They offer a highly effectual method for scattering a unwell water-soluble medication into an sluggish hydrophilic polymer matrix. The burdened drug is released in the procedure of very minor atoms as the polymeric corrosion continues, consenting for fast melting **[47, 48]**.

3.4.1. Polymeric Matrices Inclusion

According to WHO compared spray drying, kneading and co-precipitation courses in the formation of SLM-loaded solid dispersions exploiting HPMC as a hydrophilic polymeric carrier, the devising technique is dangerous for enhancing the performance of the final product. In vitro tests showed that co-precipitation (2.5 fold) > spray drying (1.9 fold) > kneading

improved SLM dissolving compared to pure drug (1.5 fold) **[49]**.

3.4.2. Polymeric Nanoparticles and Dendrimers

dendritic macromolecules are hyperbranched biocompatible polymers that are regularly used as nanocarriers for the encapsulation and supply of medicines by supramolecular complexation or covalent attachment. Each novel dendrimer group outlines the molecular size, weight, and number of primary amine sites for each repeated branching **[50]**.

5. **Inorganic Compounds and Nanostructured Materials**

   Since of their varied nanostructure, functional characteristics, and skilful drug release behaviours, inert nanomaterials are currently stared strong and very well-organized drug carriers. Still, they have extraordinary biodegradability, biocompatibility, in vivo stability, little cytotoxicity, and nonimmunogenic features, making them suitable candidates for oral and parenteral medication delivery **[51]**.

1.10 Conclusions and Outlook

Pre-eminent digestion, scarce gastric interest, squat water solubility, and speedy elimination in urine and bile are the main sources of poor silymarin bioavailability. Because of these variables, silymarin must be put into a form that will surge its bioavailability. As a result, silymarin solubilization is grave for realizing ideal and effective bioavailability, and formulation practises expected at snowballing its solubility are life-threatening. The revised exploration show that the development of nanotechnologies and nanosystems planned to advance the management of poorly water-insoluble drugs and vigorous principle elements has sensibly trailed the fruition of silymarin-based preparations.

The status and success of shapeless solid dispersions and lipid-based drug delivery systems and the exploitation of supersaturated solutions, are painted by current solubilization methodologies. However, the majority of devising preparations include flaws such as complex methods and lack of reproducibility, which make them difficult to adapt to industrial production. may be successful in increasing silymarin bioavailability and targeting it to hepatocytes.

REFERENCES

[1] A. Valenzuela, A.Garrido, Biochemical bases of the pharmacological action of the flavonoid silymarin and of its structural isomer silibinin. Biol. Res. 1994;27:105-112.

[2] P. Morazzoni, E. Bombardelli, *Silybum marianum (Carduus*

marianus). Fitoterapia. LXVI: 1995; 3-42.

[3] J. Lecomte, Les propriétés pharmacologiques de la silybine et de la silymarine. Rev. Med. Liege. XXX: 1975;110-114.

[4] H.Wagner, P. Diesel, M. Seitz, Zur chemie und analytik von silymarin aus *Silybum marianum* gaertn. Arzneimittelforschung. 1974;24: 466-71,

[5] G.Vogel, W. Trost, R. Braatz, Untersuchungen zu pharmakodynamik, angriffspunkt und wirkungsmechanismsus von silymarin, dem antihepatotoxischen prinzip aus Silybum mar. (L.) gaertn. Arzneimittel forschung. 1975;25: 82-9,

[6] A. Desplaces, J. Choppin, G. Vogel, The effects of silymarin on experimental phalloidine poisoning. Arzneimittelforschung. 1975;25: 89-96

[7] J. Choppin, A. Desplaces, The effects of silybin on experimental phalloidine poisoning. Arzneimittelforschung. 1978;28: 636-641.

[8] G. Vogel, W. Trost, Zur anti-phalloidinaktivität der silymarine silybin und disilybin. Arzneimittelforschung. 1975;25: 392-393.

[9] F. Barbarino, E. Neumann, J. Deaciuc, Effect of silymarin on experimental liver lesions. Rev. Roum. Med. Intern . 1981;19: 347-357.

[10] H .Schriewer, R. Badde, G. Roth, Die antihepatotoxische wirkung des silymarins bei der leberschädigung durch thioacetamid. Arzneimittelforschung. 1973;23: 160-161.

[11] C.P. Siegers, A. Frühling, M. Younes, Influence of dithiocarb, (+) catechin and silybine on halothane hepatotoxicity in the hypoxic rat model. Acta. Pharmacol. Toxicol (Copenh). 1983;53:125-129.

[12] M. Mourelle, P. Muriel, L. Favari, Prevention of CCl4-induced liver cirrhosis by silymarin. Fundam. Clin. Pharmacol. 1989;3: 183-891.

[13] S. Luper, A review of plants used in the treatment of liver disease: part I. Altern. Med. Rev1998; 3: 410-421.

[14] N. Skottova, V. Kreeman, Silymarin as a potential hypocholesterolaemic drug. Physiol. Res.1998; 47: 1-7.

[15] P. Ferenci, B. Dragosics, H. Dittrich, Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J. Hepatol. 1989;9: 105-113.

[16] S. Luper, A review of plants used in the treatment of liver diseases: Part 1. Altern. Med. Rev. 1998;3: 410-421.

[17] H. Wagner, P.Diesel, M. Seitz, The chemistry and analysis of silymarin from Silybum marianum Gaertn. Arzneimittelforschung. 1974;24: 466-471.

[18] R. Saller, R. Meier, R. Brignoli, The use of silymarin in the treatment of

liver diseases. Indian Drugs. 2001;61 : 2035-2063.

[19] A. Vailati, L. Aristia, E. Sozze, F. Milani, V. Inglese, P. Galenda, Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia. 1993;64 : 219-231.

[20] P. Kosina, V. Kren, R. Gebhardt, F. Grambal, J. Ulrichova, D. Walterova, Antioxidant properties of silybin glycosides. Phytother. Res. 2002;16: 533-539.

[21] M. P. Miguez, I. Anundi, L. A. Sainz-Pardo, K. O. Lindros, Hepatoprotective mechanism of silymarin: no evidence for involvement of cytochrome P4502E1. Chem. Biol. Interact.1994; 91: 51- 63.

[22] A.L.Miller, Antioxidant flavonoids: Structure, function and clinical usage. Altern. Med. Rev. 1996;1: 103-11.

[23] H.Wiseman, Dietary influences on membrane function: Importance in protection against oxidative damage and disease. J. Nutr. Biochem. 1996;7: 2-5.

[24] P. Muriel, M. Mourelle, Prevention by silymarin of membrane alterations in acute CCl4 liver damage. J. Appl. Toxicol. 1990;10: 275-279.

[25] J. Sonnenbichler, I. Zetl, Biochemical effects of the flavonolignan silibinin on RNA, protein, and DNA synthesis in rat liver. Progr. Clin. Biol. Res. 1986;213: 319-331.

[26] R. Saller, R. Meier, R.Brignoli, The use of silymarin in the treatment of liver diseases. Indian Drugs. 2001; 61: 2035-2063.

[27] C. Dehmlow, J.Eahard, H.D.Goot, Inhibition of Kupffer cells as an explanation for the hepatoprotective properties of silibinin. Hepatol. 1996;23: 749-754.

[28] C. Saliou, B. Rihn, J.Cillard, T.Okamoto, L.Packer, Selective inhibition of NF-κB activation by the flavonoid hepatoprotector silymarin in HepG2. FEBS Lett. 1998;440: 8-12.

[29] V.J. Johnson, M.F. Osuchowski, Q.He, R.P.Sharma. Physiological responses to a natural antioxidant flavonoids mixture, silymarin, in BALB/c mice: II. Alterations on thymic differentiation correlate with changes in c- myc gene expression. Planta. Med. 2002;68: 961-965.

[30] R.Gebhardt, Oxidative stress, plant-derived antioxidants and liver fibrosis. Planta. Med. 2002;68:289-296.

[31] P.Morazzoni, A. Montalbetti, S. Malandrino, Comparative pharmacokinetics of silipide and silymarin in rats. Eur. J. Drug. Metab. Pharmacokinet. 1993;18: 289-297.

[32] R. Schandalik, G. Gatti, E. Perucca, Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung.1992;42: 964-968.

[33] J.Pepping, Milk thistle: Silybum marianum. Am. J. Health. Syst. Pharm. 1999;56: 1195-1197.

[34] B. Janiak B., Kessler, W. Kunz, Die wirkung von silymarin auf gehalt und function einiger durch einwirkung von tetrachlorkohlenstoff bzw. Halothan beeinflussten mikrosomalen Leberenzyme. Arzneimittelforschung. 1973;23: 1322-1326.

[35] W. Mennicke. What is known about the metabolism and pharmacokinetics of silymarin. In: Braatz R, Schneider CC, editors. Symposium on the pharmacodynamic of silymarin. Munich, Berlin, Vienna: Urban & Schwarzenberg; 1976;98-102.

[36] P. Ferenci, B. Dragosics, H. Dittrich, Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J. Hepatol . 1989;9: 105-113.

[37] A. Valenzuela, R. Guerra. Differential effect of silybin on the Fe2+ -ADP and t-butyl hydroperoxide-induced microsomal lipid peroxidation. Experientia. 1986;42: 139-141.

[38] L. Mira, M. Silva, C.F. Manso, Scavenging of reactive oxygen species by silibinin dihemisuccinate. Biochem. Pharmacol. 1914;48: 753-759.

[39] E. Bosisio, C. Benelli, O. Pirola, Effect of the flavanolignans of Silybum marianum L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. Pharmacol. Res. 1992;25: 147-154.

[40] L. Cavallini, A. Bindoli, N. Siliprandi, Comparative evaluation of antiperoxidative action of silymarin and other flavonoids. Pharmacol. Res. Commun. 1978;10: 133-136.

[41] H. Farghali, L. Kamenikova, S. Hynie, Silymarin effects of intracellular calcium and cytotoxicity: a study in perfused rat hepatocytes after oxidative stress injury. Pharmacol Res. 2000;41: 231-237.

[42] J.C. Davila, A. Lenherr, D. Acosta, Protective effect of flavonoids on drug-induced hepatotoxicity in vitro. Toxicology. 1989;57: 267-286.

[43] Abenavoli L., Izzo A.A., Milić N., Cicala C., Santini A., Capasso R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother. Res.2018;32:2202–2213.

[44] Bijak M. Silybin, a major bioactive component of milk thistle (Silybum

marianum L. Gaernt.)—Chemistry, Bioavailability, and Metabolism. Molecules.2017;22:1942.

[45] Dressman J.B., Vertzoni M., Goumas K., Reppas C. Estimating drug solubility in the gastrointestinal tract. Adv. Drug. Deliv. Rev.2007;59:591–602.

[46] Patra J.K., Das G., Fraceto L.F., Campos E.V.R., del Pilar Rodriguez-Torres M., Acosta-Torres L.S., Diaz-Torres L.A., Grillo R., Swamy M.K., Sharma S., *et al*. Nano based drug delivery systems: Recent developments and future prospects. J. Nanobiotechnol.2018;16:71–103.

[47] Obeid M.A., Al Qaraghuli M.M., Alsaadi M., Alzahrani A.R., Niwasabutra K., Ferro V.A. Delivering natural products and biotherapeutics to improve drug efficacy. Ther. Deliv2017.;8:947–956.

[48] K. Flora, M. Hahn, H. Rosen, K. Benner, and K. Benner, "Milk thistle (Silybum marianum) for the therapy of liver disease," The American Journal of Gastroenterology, vol. 1998;93:139–143.

[49] N.-C. Kim, T. N. Graf, C. M. Sparacino, M. C. Wani, and M. E. Wall, "Complete isolation and characterization of silybins and isosilybins from milk thistle (Silybum marianum)," Organic and Biomolecular Chemistry, 2003;.1(10): 1684–1689.

[50] K. Wellington and B. J. Adis, "Silymarin: a review of its clinical properties in the management of hepatic disorders," BioDrugs, 2001;15 (7): 465–489.

[51] E. Bosisio, C. Benelli, and O. Pirola, "Effect of the flavanolignans of *Silybum marianum* L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes," Pharmacological Research, 1992;25(2): 147–165.