Received: 30 March 2018 | Revised: 6 July 2018 | Accepted: 9 July 2018

DOI: 10.1002/ptr.6171

WILEY

REVIEW

Milk thistle (*Silybum marianum*): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases

Ludovico Abenavoli[1] | Angelo A. Izzo[2] | Natasa Milić[3] | Carla Cicala[2] | Antonello Santini[2] | Raffaele Capasso[4]

[1] Department of Health Sciences, University Magna Graecia, Catanzaro, Italy

[2] Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Naples, Italy

[3] Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[4] Department of Agricultural Sciences, University of Naples Federico II, Naples, Italy

Correspondence
Ludovico Abenavoli, Department of Health Sciences, University Magna Graecia, Viale Europa, 88100 Catanzaro, Italy.
Email: l.abenavoli@unicz.it

Milk thistle (MT; *Silybum marianum*), a member of the *Asteraceae* family, is a therapeutic herb with a 2,000-year history of use. MT fruits contain a mixture of flavonolignans collectively known as silymarin, being silybin (also named silibinin) the main component. This article reviews the chemistry of MT, the pharmacokinetics and bioavailability, the pharmacologically relevant actions for liver diseases (e.g., anti-inflammatory, immunomodulating, antifibrotic, antioxidant, and liver-regenerating properties) as well as the clinical potential in patients with alcoholic liver disease, non-alcoholic fatty liver disease, viral hepatitis, drug-induced liver injury, and mushroom poisoning. Overall, literature data suggest that, despite encouraging preclinical data, further well-designed randomized clinical trials are needed to fully substantiate the real value of MT preparations in liver diseases.

KEYWORDS

liver fibrosis, oxidative stress, silybin, silymarin

1 | INTRODUCTION

Silybum marianum (L.) Gaernt (Sm)., commonly known as milk thistle (MT), is an annual/biennial plant of the *Asteraceae* family, native of Mediterranean area and now growing and cultivated worldwide (Figure 1; Abenavoli, Capasso, Milic, & Capasso, 2010; Bijak, 2017).

MT has been used for centuries in medicine, mainly to treat kidney, spleen, liver, and gallbladder diseases (Flora, Hahn, Rosen, & Benner, 1998; Schadewaldt, 1969). The Roman naturalist and natural philosopher Pliny the Elder (23–79 AD) wrote that mixing the juice of this plant with honey was indicated to "carry off the bile." The Greek physician, pharmacologist, and botanist Dioscorides (i.e., the author of *De Materia Medica*) recommended it as tea against serpent bites. The medical use of MT was reported in the Middle Age in the Saxons records to ward off snakes and to treat the infectious disease contracted after being bitten by a rabid animal, nowadays known as hydrophobia. St. Hildegard vòon Bingen (1098–1179) recommended the herb root and leaves to treat swelling and erysipelas. Subsequently, in the 16th century, two famous English herbalists, that is, John Gerard and Nicholas Culpeper, recommended the use of MT against all melancholy diseases and to cure fever, respectively. MT was also popular in the German medical tradition and several scientists, including Johannes Gottfried Rademacher (1772–1850), recommended it to treat liver ailments.

In the USA, the popularity of MT derives from its use as a part of the naturopathic medical tradition of the Native Americans as well as of the Eclectic movement, a group of practitioners that recommended MT for varicose veins, menstrual problems, and congestion of the spleen, kidney, and liver in the first half of 19th century. Actually, MT is among the top-selling herbal dietary supplements in the USA with retail sales amounting to 2.6 million dollars in the mainstream multioutlet channel in 2015 (Andrew & Izzo, 2017).

The aim of this review is to provide an overview on the recent findings on the experimental and clinical pharmacology of MT related to liver diseases to update an earlier review published in this journal (Table 1) (Abenavoli et al., 2010). Articles on the potential therapeutic role of MT or of its active ingredients in other diseases such as cancer (Polachi et al., 2016; Zhu et al., 2016), diabetes (Stolf, Cardoso, & Acco, 2017), neurodegenerative disorders (Devi, Malar, Braidy,

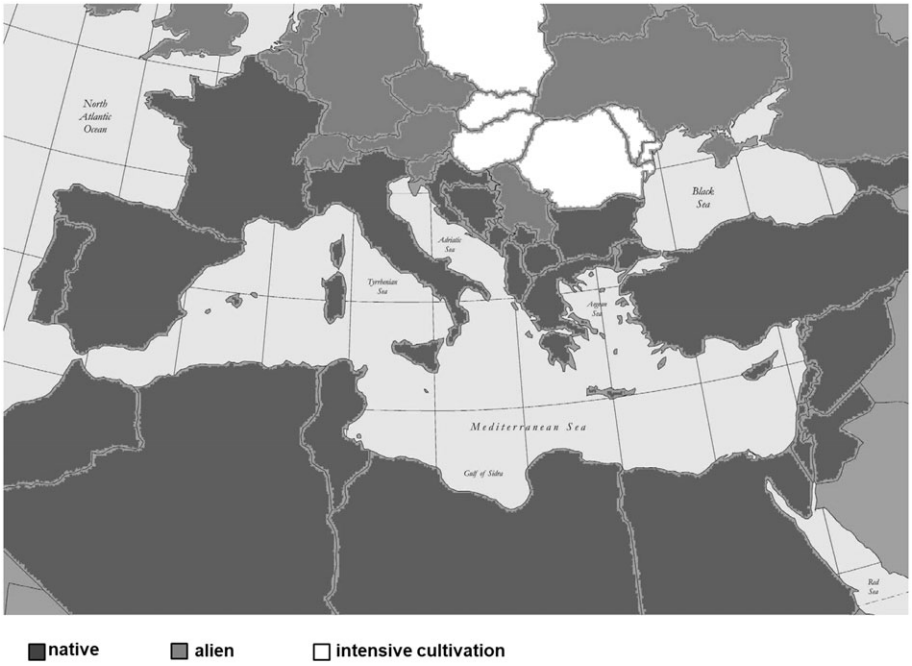

FIGURE 1 Milk thistle distribution in the Mediterranean area and Europe

Nabavi, & Nabavi, 2017), or β-thalassemia (Moayedi Esfahani, Reisi, & Mirmoghtadaei, 2015) can be found elsewhere.

2 | CHEMISTRY

Silymarin is a well-established MT seeds standardized dry extract containing mainly flavonolignans (about 70%–80% *w*/w) as well as polymeric and oxidized polyphenolic compounds consisting of a mixture of flavonoids. Flavonolignans, which have been first discovered in the seeds of *Silybum marianum*, are a relatively small subclass of compounds, where the flavonoid part of the molecule is fused with a lignan. The main silymarin flavonolignas are silybin, isosilybin (A and B), silydianin, and silychristin (Kvasnicka, Bíba, Sevcík, Voldrich, & Krátká, 2003; Figure 2). While many studies describe analytical separation and quantification of silymarin components in the extract in various plant parts, seasons, geographic locations, etc. (Poppe & Petersen, 2016), no comparison of detail flavonolignan profiles in various silymarin preparations is available to date (Chambers et al., 2017).

Silybin (silibinin)-(2R,3R)-3,5,7-trihydroxy- 2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydrobenzo [b] [1,4]dioxin-6-yl]chroman-4-one is, from a quantitative point of view, the main component of silymarin. It has a molecular formula of $C_{25}H_{22}O_{10}$ and a molecular weight of 482.441 (Bijak, 2017). In nature, silybin occurs in the form of two diastereoisomers, namely, silybin A [(2R,3R)-2-((2R,3R)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl)-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one] and silybin B [(2R,3R)-2-((2S,3S)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl)-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one], which are present in an approximately quasi-equimolar ratio. Silybin has a low solubility in water and in polar solvents, and it is insoluble in apolar solvents (Biedermann, Vavříková, Cvak, & Křen, 2014).

Silybin is a small, highly functionalized molecule with alternating carbocycles and heterocycles, and, due to its structure, it is quite resistant to reduction but oxidizes easily to 2,3-dehydrosilybin. It is stable under acidic conditions and becomes unstable in the presence of Lewis acids or in basic conditions since strong bases or heating can disrupt its structure. In neutral aqueous solutions, silybin behaves as a weak acid. The five hydroxyl groups can be derivatized and dived according to their nature in phenolic, secondary, and primary alcoholic group, assessing the reactivity of the molecule that can give esters, ethers, and a ketone (when the secondary alcoholic group is reacting), which mostly is present in its enol form. In year 2000,

TABLE 1 Literature evidence on the clinical application of milk thistle extracts in the treatment of different liver diseases

Etiology	Liver disease stage
Viral hepatitis	Acute, chronic, liver failure, and cirrhosis
Alcoholic liver disease	Acute, chronic, liver failure, and cirrhosis
Nonalcoholic liver disease	Acute, chronic, and cirrhosis
Cholestasis	Pregnancy and nonpregnancy related
Drug- and toxin-induced liver disease	Acute, chronic, liver failure, and cirrhosis
Primary liver malignancy	Hepatocellular carcinoma and cholangiocarcinoma

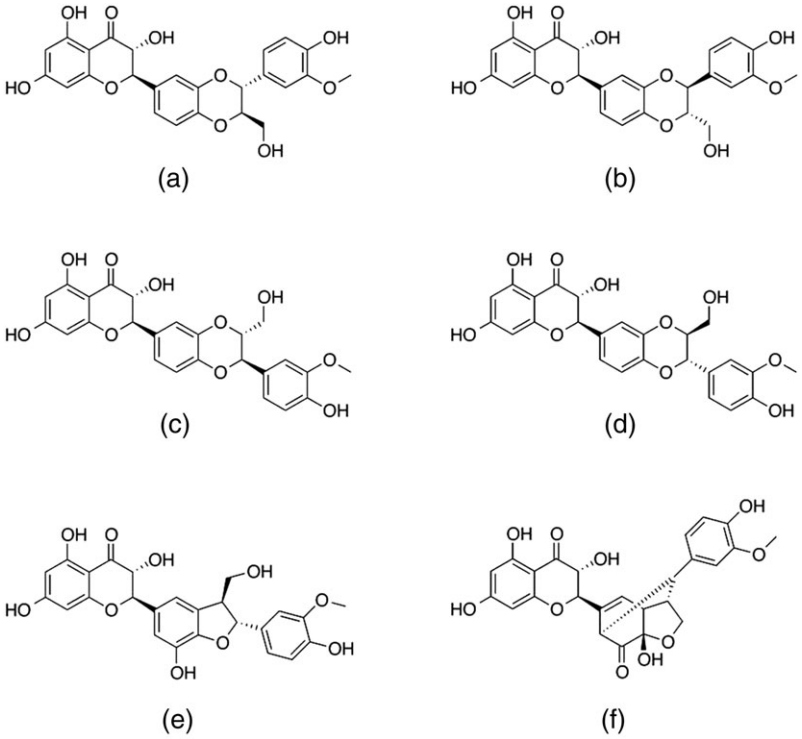

FIGURE 2 Chemical structures of main flavolignans contained in silymarin, namely, (a) silybin A, (b) silybin B, (c) isosilybin A, (d) isosilybin B, (e) silychristin, and (f) silydianin

silybin was enantioselective synthesized producing both silybin A and silybin B starting from ferulic acid adopting the sharpless oxidation reaction as the crucial step of the reaction (Gu, Chen, Pan, Chan, & Yang, 2000).

The biosynthesis pathway of silybin remains not fully understood. Biomimetic reactions indicated that silybin can be synthesized from coniferyl alcohol and taxifolin by the action of peroxidase. The concentration profiles of silybin and its precursors and RNA-seqencing analysis of gene expression revealed that the amount of taxifolin and the activity of peroxidase serve as the limiting factors in silybin biosynthesis. Five candidates for the peroxidase are involved in silybin production, among which Ascorbate Peroxidase 1 showed a good activity as well as the ability to synthesize silybin (Lv et al., 2017).

The main part of the literature available studies have been dedicated to flavonolignans giving less attention to minor components. This has led to problems in determining the exact composition of silymarin, which can vary depending on the processing, variety of the plant, soil composition, and climatic conditions during the plant growth. Silymarin contains also a mixture of undefined polyphenolic compounds, often referred to as "polymeric fraction" (Bijak, 2017). Nonetheless, the oil fraction, which contains linoleic, oleic, and palmitic acids, sterols, tocopherol (vitamin E), and phospholipids, has been not fully explored (Chambers et al., 2017).

3 | PHARMACOKINETICS

The pharmacokinetics of silymarin flavonolignans have been studied both in healthy volunteers and in liver disease patients.

In a dose-escalation study evaluating the pharmacokinetics of the six major flavonolignans in healthy volunteers after the oral administration of the standardized MT extract Legalon®, flavonolignans were rapidly absorbed and eliminated. The exposure of free (i.e., unconjugated) flavonolignans was greatest for silibinin A followed by silibinin B, isosilybin B, isosilybin A, silychristin, and silydianin (Zhu et al., 2013). Stereoselective metabolism was also observed, being the apparent clearance of silibinin B and isosilybin A greater than silibinin A and isosilybin B, respectively (Zhu et al., 2013). Other studies in healthy volunteers found that the bioavailability of silymarin flavonolignans was 0.45 ± 0.28% (Calani, Brighenti, Bruni, & Del Rio, 2012) and that they are quickly metabolized to their conjugates (Li et al. 2018) (mainly glucuronides), which are the primary components present in human plasma (Wen et al., 2008).

Studies have mainly been focused on silybin, the main active component of silymarin. In healthy volunteers, after administration of silymarin capsules (Legalon 140), it was found that silybin underwent extensive conversion to conjugated derivatives (only about 10% of total silibinin in plasma was found in the unconjugated form; Weyhenmeyer, Mascher, & Birkmayer, 1992). For unconjugated silibinin, the half-life was less than 1 hr. For total silybin, an elimination half-life of approximately 6 hr was estimated. About 5% of the dose was excreted into urine as total silibinin (Weyhenmeyer et al., 1992). A further study in healthy volunteers receiving single oral doses of a lipophilic silybin-phospatidylcholine complex (silipide, 80 mg expressed as silybin equivalents) found that free silybin levels peaked at 2.4 hr and declined with a half-life of about 2 hr, while conjugated peaked at a later time (about 3.8 hr; Gatti & Perucca, 1994). Finally, other studies found that a significant proportion of silybin is excreted in the bile (Barzaghi, Crema, Gatti, Pifferi, & Perucca, 1990; Javed, Kohli, & Ali, 2011; Lorenz, Lücker, Mennicke, & Wetzelsberger, 1984).

Silybin flavonolignans, including silybin, undergo extensive metabolism, mainly phase II metabolic processes (Wu, Lin, & Tsai, 2009). Although in vitro studies have reported that MT extracts and individual components may significantly inhibit specific cytochrome P450

enzymes (Albassam, Frye, & Markowitz, 2017; Sridar, Goosen, Kent, Williams, & Hollenberg, 2004; Venkataramanan et al., 2000), clinical trials have reliably shown that such inhibition does not occur in humans supplemented with orally administered MT extracts (Gurley et al., 2006; Izzo, 2012; Kawaguchi-Suzuki et al., 2014; Van Erp et al., 2005). During phase II, conjugation reactions result in the formation of silybin monoglucuronide, silybin diglucuronide, silybin monosulfate, and silybin diglucuronide sulfate (Javed et al., 2011). The silybin glucuronides formed in phase II can be transported by biliary flow to the intestine, where extensive enterohepatic circulation occurs (Hawke et al., 2010; Javed et al., 2011; Lorenz et al., 1984). Studies on human liver microsomes suggest that silybin glucuronidation can be apparently achieved by multiple Uridine 5'-diphospho (UDP) glucuronosyltransferases forms and there is stereoselective glucuronidation of silybin diastereomers by human UDP glucuronosyltransferases (Jancová et al., 2011). It should be also noted that the pharmacokinetic of silybin is influenced by ABCB1 C3435T polymorphism. Hence, the dosage adjustments may be needed for different genotype patients to guarantee comparative exposures.

The pharmacokinetics of silymarin flavonolignans have been also investigated in liver disease patients. Schrieber et al., 2008 showed that the pharmacokinetics of silymarin flavonolignans is altered in patients with hepatitis C virus (HCV) and nonalcoholic fatty liver disease (NAFLD), with the highest exposure of the major flavonolignans observed in cirrhotic patients having the highest plasma caspase-3/7. In noncirrhotic patients with chronic hepatitis C, oral doses of silymarin, ranging from 0.42–2.1 g/die for 7 days, were safe and well tolerated with silybin A and silybin B displaying nonlinear pharmacokinetics (Hawke et al., 2010). Finally, Schrieber et al., 2011 showed that disposition of silymarin and hence its efficacy changed on liver disease patients. Specifically, silymarin may have greater efficacy in patients with NAFLD compared with dose with HCV infection because of higher flavonolignan plasma concentrations and more extensive enterohepatic cycling.

Due to its highly hydrophobic and nonionizable chemical structure, silybin is poorly soluble in water resulting in a low bioavailability (Bijak, 2017). However, silybin bioavailability can be influenced by several factors including the content of the accompanying molecules such as flavonoids, phenol derivates, amino acids, and many other substances (Voinovich, Perissutti, Grassi, Passerini, & Bigotto, 2009). The systemic bioavailability of silybin can be improved in different ways, including the addition of solubilizing substances to MT extracts using phosphatidylcholine, combining it with vitamin E and phosphatidylcholine, forming micelles with bile salt and, notably, via the self-micro-emulsifying drug delivery system, a drug delivery system that uses a microemulsion for delivering hydrophobic drugs (Bijak, 2017; Yang et al., 2015). Very recently, highly bioavailable silybin nanoparticles (SB-NP) have been developed. Oral administration of SB-NP in rodents reveals higher serum levels and biodistribution in the liver compared with nonmodified silybin. In vitro, SB-NP reduced HCV infection of primary human hepatocytes, suggesting its potential as a cost-effective anti-HCV agent (Liu et al., 2017). Finally, it should be highlighted that the variation in the content, dissolution, and oral bioavailability of silybin among different commercially available silymarin products—despite the same declaration of the content—are significant (Kidd, 2009). Therefore, the comparisons of the studies should be carried out with caution, and the differences between the analytical methods used (thin-layer chromatography (TLC) vs. high-performance liquid chromatography (HPLC)) should be considered, and also whether free, conjugated, or total silybin has been measured.

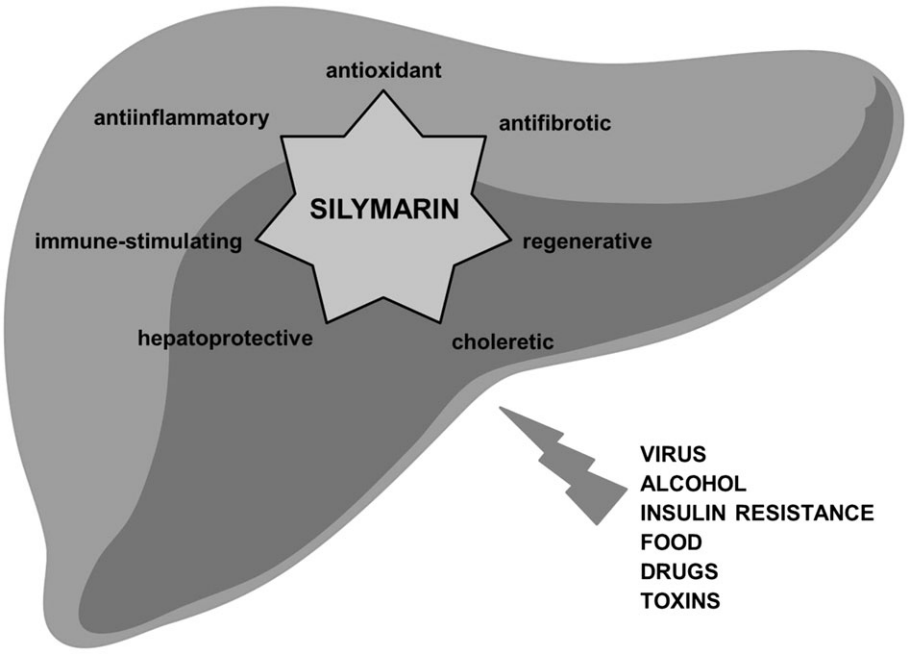

FIGURE 3 Different pharmacological functions of silymarin in liver diseases: antioxidant (direct free radical scavenger activity), antifibrotic (inhibits the conversion of stellate cells in myofibroblasts), regenerative (stimulate hepatic regeneration), choleretic (causes an upregulation of the bile salt export pump), hepatoprotective (suppress the release of cytokines), immunostimulating (prevents inflammasome activation), and anti-inflammatory (inhibition of NF-κB pathway)

In summary, silybin, the main flavonolignan of silymarin, is rapidly adsorbed from the gastrointestinal tract, where it undergoes to extensive enterohepatic circulation. Phase II metabolism mainly results in the formation of silybin glucuronides, with half lives of approximately 1–2 hr and 6 hr for free and conjugated forms, respectively. Biliary excretion is the major route for silybin elimination. The oral bioavailability of silybin is low, but it can be increased with new systems of drug delivery. Finally, the pharmacokinetics of silymarin flavonolignans, including silybin, may be altered in liver disease patients.

4 | EXPERIMENTAL PHARMACOLOGY

Experimental studies have revealed the multiple pharmacological properties of MT components potentially beneficial for liver diseases. The antioxidant, antifibrotic, regenerative, choleretic, hepatoprotective, immunostimulating, and anti-inflammatory actions (Figure 3) make MT as a potential candidate for liver disease.

4.1 | Anti-inflammatory and immuno-modulation activity

Silymarin exerts anti-inflammatory actions and attenuates autoimmune and immune-mediated liver diseases, possibly via suppression of oxidative and nitrosative immunotoxicity and T-lymphocyte function (Esmaeil, Anaraki, Gharagozloo, & Moayedi, 2017; Milić, Milosević, Suvajdzić, Zarkov, & Abenavoli, 2013). Anti-inflammatory activities of silymarin or MT extracts have been observed in a number of rat/mouse models of liver diseases, including cholestatic liver injury (Alaca et al., 2017), CCl4-induced hepatoxicity (Clichici et al., 2015), restraint stress-induced acute liver (Kim et al., 2016), the stelic animal model of steatohepatitis (Pais & D'Amato, 2014), zidovudine/isoniazid-induced liver toxicity (Raghu & Karthikeyan, 2016), and, finally, a model of steatohepatitis induced by a methionine and choline deficient diet (Aghazadeh, Amini, Yazdanparast, & Ghaffari, 2011).

A number of studies have shown that silymarin exerts anti-inflammatory action via suppression of the release of cytokines such as tumor necrosis factor-α (TNF-α), adhesion molecules, such as E-selectin, as well as via suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, nitric oxide and 5-lipoxygenase pathways (Altaei, 2012; Esmaeil et al., 2017; Kang, Park, Yang, & Kim, 2003). Specifically, silymarin inhibits/suppresses: (a) the TNF-α-induced activation of mitogen-activated protein kinase and c-Jun N-terminal kinase and as well as the TNF-α-induced cytotoxicity and caspase activation (Gharagozloo et al., 2013; Saller, Brignoli, Melzer, & Meier, 2008), (b) both the kappa B motif of NF-κB DNA binding activity and its dependent gene expression in hepatoma cells as well as the translocation of NF-κB p65 protein through phosphorylation to the nucleus without affecting its ability to bind the DNA, and (c) lipopolysaccharides (LPS)-induced production of NO in isolated mouse peritoneal macrophages (Kim, Lee, & Jeon, 2015). Finally, a recent relevant study has shown that the NAD+/SIRT2 pathway is an important mediator through which silybin prevents the NLRP3 inflammasome activation in mice with liver steatosis (Zhang et al., 2018).

In conclusion, silymarin has both anti-inflammatory and immunomodulatoy actions that can play a relevant role in its hepatoprotective effects. The potential mechanisms include inhibition of NF-κB pathway, suppression of TNFα, leukotrienes and nitric oxide biosynthesis, inhibition of adhesion molecules, and interference with the NAD+/SIRT2 pathway, as an immunomodulator agent silymarin attenuates the T-lymphocyte function.

4.2 | Enhanced protein synthesis

Regeneration of liver cells is necessary for the hepatic recovery from acute or chronic injury. In chronic disease, fibrosis occurs simultaneously with cellular regeneration. MT extracts, silymarin, and active components such as silybin have been shown to stimulate hepatic regeneration in partially hepatectomized rat livers (Sonnenbichler et al., 1986; Yormaz et al., 2012). The intraperitoneal administration of silybin has been shown to cause a marked increase in the synthesis of ribosomal RNA. Although the precise mode of action is still elusive, there is evidence that stimulation of polymerase I can play a role. In several preclinical studies, silybin stimulated ribonucleic acid (RNA) polymerase-I and ribosomal RNA, leading to a more rapid formation of ribosomes, which, in turn, accelerate protein synthesis (Bousserouel et al., 2012; Pradhan & Girish, 2006). The stimulating effect of silybin on ribosome formation can have therapeutic implications in the repair of damaged hepatocytes and the restoration of normal liver functions.

4.3 | Antifibrotic activity

Liver fibrosis is a result of hepatocyte injury leading to the activation of Kupffer cells and hepatic stellate cells. The conversion of hepatic stellate cells into myofibroblasts is considered a pivotal event in fibrogenesis. Liver fibrosis can result in remodeling liver architecture leading to hepatic insufficiency, portal hypertension, and hepatic encephalopathy (Seki & Schwabe, 2015). Animal studies have shown that in the early stages of the fibrotic process, silymarin is able to inhibit the fibrogenetic mechanisms and the progression of the initial liver fibrosis (Clichici et al., 2015; Clichici et al., 2016). In these studies, a reduction of collagen and pro-collagen III content after biliary obstruction in the rat by 30% with 50 mg/kg/day of silymarin have been observed (Clichici et al., 2015). Experiments aiming at investigating the mode of action have shown that silymarin (a) suppresses the expression of pro-fibrogenic pro-collagen-α1 and TIMP-1, most likely via down-regulation of TGF-β1 mRNA (Kim et al., 2012), inhibits NF-κB (Esmaeil et al., 2017); (b) retards the activation of HCS (Clichici et al., 2015); and (c) alters the expression of genes involved in cytoskeleton organization and mitochondrion electron-transfer chain (Li, Hsiang, Wu, & Ho, 2012).

Silymarin is also able to ameliorate liver fibrosis induced by carbon tetrachloride in rats in combination with sitagliptin, a dipeptidyl peptidase-4 inhibitor clinically used as an oral antidiabetic agent (Sokar, El-Sayad, Ghoneim, & Shebl, 2017). Interestingly, silymarin prevents liver fibrosis in a juvenile model of nonalcoholic steatohepatitis (Marin et al., 2017), which can have clinical relevance in the light of the increasing incidence of NAFLD in adolescents.

Finally, there is evidence that the antifibrotic action of silymarin could be improved with new formulations of silymarin as nanoparticles. Indeed, a special formulation silymarin-loaded Eudragit® RS100 nanoparticles has been shown to resolve cholestasis-induced liver

fibrosis by restoring hepatic regenerative capabilities (Younis, Shaheen, & Abdallah, 2016).

4.4 | Antioxidant effects

Natural antioxidants have been shown to have beneficial effects in the preclinical models of NAFLD as well as in the pilot clinical trials (Salomone, Godos, & Zelber-Sagi, 2016). Silymarin is a natural antioxidant and this action is believed to contribute to the hepatoprotective effects of MT preparations. The antioxidant actions of silymarin have recently been reviewed (Surai, 2015). The possible antioxidant mechanisms of silymarin include (a) prevention of free radical formation via inhibition of reactive oxygen species (ROS)-producing enzymes; (b) direct scavenging of free radicals actions; (c) ion chelation (Fe and Cu) in the intestine; (d) promotion of the synthesis of protective molecules (e.g., heat shock proteins, thioredoxin, and sirtuins) that provide protection against stressful stimuli (Surai, 2015); and (e) activation of antioxidant enzymes such as superoxide dismutase and nonenzymatic pathways, mainly via Nrf2 activation. For example, it has been reported that silymarin markedly increases the expression of superoxide dismutase in the patients with nonalcoholic steatohepatitis (Milosević, Milanović, Abenavoli, & Milić, 2014; Stiuso et al., 2014) and decreases the oxidative stress in the β-thalassemia patients (Darvishi-Khezri et al., 2018).

Silymarin has no direct effect on ethanol metabolism and has no role in reducing ethanol levels or on the rate at which ethanol is removed from the body. There is no evidence of an interaction of silymarin or silybin with cytochrome P450-2E1. Collectively, such results suggest that antitoxic effects of MT are likely due to its antioxidant and free radical scavenging properties (Abenavoli et al., 2010).

4.5 | Toxin blockade

Silymarin is a suitable candidate to treat drug-induced and toxic liver injury. It exerts a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against the xenobiotic injury (Serviddio et al., 2014). Also, silymarin can prevent the absorption of toxins into the hepatocytes by occupying the binding sites as well as by inhibiting many transport proteins at the cell membrane. The phalloidin-transporting system, (which is involved into the incorporation of phallotoxin into the hepatocytes) belonging to the hepatocyte-specific organic anion uptake transporters OATP2, is inhibited in a competitive way by silymarin with no influence on membrane fluidity (Trakulsrichai et al., 2017).

5 | MILK THISTLE AND LIVER DISEASES: CLINICAL EVIDENCE

5.1 | Alcoholic liver disease

Alcohol is responsible of almost 50% of all liver related cirrhosis, as well as 1% of globally causes of death (Masarone et al., 2016). Fatty liver is the first response to alcohol abuse, being it generally reversible by abstinence. The progression of alcoholic liver disease (ALD) is the consequence of a pathophysiology disequilibrium of hepatic lipid synthesis, lipid flux, and degradation with consequent cellular stress, inflammatory infiltration, damage, and fibrosis (Abenavoli et al., 2016).

The first clinical study related to MT products in patients with liver cirrhosis was carried out in Austria and included 170 patients, 92 of these with alcoholic liver cirrhosis (Ferenci et al., 1989). The patients of study group were treated orally with silymarin (140 mg, three times daily) and compared with the placebo (N = 83) followed for 2 years. The most important finding of this study was that in the alcoholic cirrhosis patients; the number of deaths in the placebo group was almost twice that in the silymarin group. In a randomized open-labelled study, the patients with alcoholic and viral chronic hepatitis were treated for 2 weeks with silybin at a dose of 160 mg/day (19 patients), 240 mg/day (17 patients), or 360 mg/day (18 patients). Statistically significant decrease in both alanine aminotransferase (ALT) and gamma-glutamyl transferase levels were observed in the groups treated with 240 or 360 mg silybin/day (Vailati et al., 1993). In a retrospective Indian study, the beneficial effects of Liverubin™/day (a patented, water-soluble liver formulation, with 140 mg of silymarin per tablet), with the improvement of hepatic biochemical profile, was detected in the ALD patients after 11 months of treatment (Nanda et al., 2014). In a double blind randomized placebo-controlled study, 106 patients with acute or subacute ALD were divided into a treatment group that receive Legalon®420 mg/day and a control group receiving a placebo. After 4 weeks of treatment, the authors found statistically significant reduction in hepatic blood profile associated with the improvement of histology and liver functionality in the Legalon®group, compared with the placebo group (Salmi & Sarna, 1982). The biochemical profile and the antioxidative effect of silymarin during 6 months of the treatment were investigated in patients with alcoholic liver cirrhosis. Seventy patients were randomized into two groups receiving 150 mg silymarin/day or placebo. This study confirmed the antioxidant action of silymarin with an increased glutathione level and antifibrotic effects in the *verum* group (Lucena et al., 2002). On the other hand, a previous randomized double-blind trial (N = 116 patients, including 58 with liver cirrhosis) showed no statistically significant changes in the histological score and in the transaminase levels after three-months of the treatment with silymarin (420 mg/day; Trinchet et al., 1989). A more detailed randomized, double-blind multicenter study was carried out in Spain with the patients with the alcoholic liver cirrhosis diagnosis (Parés et al., 1998). Two hundred patients were randomly assigned to receive either 450 mg of oral silymarin (150 mg, three times/day) or a placebo. After a 2-year follow-up, there was no significant difference in the survival between the two groups.

In conclusion, the clinical data on ALD and silymarin seem to be contradictory with a lack of high-quality evidence. A number of trials are obsolete having a poor study design, lack of control group, high attrition rate, absence or underestimation of clinical endpoints as primary criteria and frequently insufficient histological data. Considering the new noninvasive tools to study liver disease development and progression, qualitatively well-performed randomized clinical trials are needed to recommend silymarin in the ALD. Accordingly, a recent systematic review on the use of nutraceuticals in the ALD patients have concluded that further high-quality clinical trials are needed to

validate the beneficial role of silymarin (Ghorbani, Hajizadeh, & Hekmatdoost, 2016).

6 | NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is the most common chronic liver disease worldwide (Araújo, Rosso, Bedogni, Tiribelli, & Bellentani, 2018). The real global incidence of NAFLD is not known. Nevertheless, its prevalence in general population is estimated to be 20%–30% in Western countries and 5%–18% in Asia, and it is increasing over time. NAFLD is characterized by the presence of a significant fat accumulation in the liver (>5% of hepatocytes) in the absence of alcohol abuse or any other causes of liver disease. The term NAFLD includes different clinical entities, ranging from a fat accumulation into the hepatocytes, also known as steatosis, to nonalcoholic steato-hepatitis (NASH,i.e., steatosis associated to necro-inflammation), fibrosis and, finally, cirrhosis with its complications. NAFLD affects around 25%–30% of the general population, with difference related to gender, age, ethnicity, and metabolic features (Abenavoli et al., 2016; Masarone, Federico, Abenavoli, Loguercio, & Persico, 2014).

Silymarin represents one of the best examples how a herbal preparation can be developed from the traditional herbal medicine (Abenavoli & Bellentani, 2013). The clinical use of silymarin in the treatment of NAFLD is experimentally supported by its anti-inflammatory, antioxidant, antifibrotic, and proregenerative effects, as well as by its metabolic actions on insulin resistance and hyperlipidaemia (Abenavoli, Aviello, Capasso, Milic, & Capasso, 2011; Cacciapuoti, Scognamiglio, Palumbo, Forte, & Cacciapuoti, 2013; Milosević et al., 2014).

In two Iranian randomized controlled trials, 140 mg per day of orally administered silymarin for two or 6 months significantly reduced transaminase levels compared with placebo (Hajaghamohammadi, Ziaee, & Raflei, 2008; Hashemi, Hajiani, & Sardabi, 2009). These data were confirmed by a further randomized study, reporting the efficacy of silymarin (210 mg/daily for 2 months; Solhi, Ghahremani, Kazemifar, & Hoseini Yazdi, 2014). More recently, a double-blind randomized controlled trial (RCT) trial that assessed the effect of silymarin (700 mg, 3 times/day for a year) in adult patients with biopsy-proven NASH demonstrated that silymarin did not reduce NAFLD score by 30% or more (i.e., the primary efficacy outcome) compared with the placebo, although it reduced liver fibrosis and stiffness (Wah Kheong, Nik Mustapha, & Mahadeva, 2017).

There is evidence that the combination of silybin with vitamin E can be effective in the treatment of NAFLD. In this context, two Italian randomized studies showed the ability of Realsil®, a patented formulation containing silybin-phospatidylcholine complex plus vitamin E, to improve hepatic biochemical profile, anthropometric parameters, lipid and glycemic metabolisms, and ultrasonographic score of liver steatosis (Abenavoli et al., 2015; Loguercio et al., 2007). These data were supported by a multicenter randomized controlled clinical trial (Loguercio et al., 2012). Recently, the efficacy of an antioxidant complex containing silymarin in association with a personalized hypocaloric Mediterranean diet, on hepatic fat accumulation, metabolism, and on anthropometric parameters in NAFLD overweight patients was evaluated (Abenavoli et al., 2017). The patients were randomized into three groups (Groups A–C). A personalized low-calorie Mediterranean diet was prescribed to Group A and B patients for 6 months. In association with a diet, the patients of Group B took two pills of Bilirel® complex (composition of one pill was silymarin 120 mg, chlorogenic acid 7.5 mg, protopine 0.04 mg, l-methionine 150 mg, and l-glutathione 10 mg) for 6 months. The patients of Group C did not receive any treatments. The study showed that diet alone or in association with the antioxidant complex improved anthropometric parameters and reduced hepatic fat accumulation and liver stiffness. Moreover, in the patients treated with diet and Bilirel®, a significant improvement in insulin sensitivity was also observed (Abenavoli et al., 2017).

Finally, a very recent meta-analysis that included eight RCTs involving 587 patients concluded that silymarin represented a promising treatment to improve liver function in the NAFLD patients, with a global positive efficacy in reducing transaminase levels (Zhong et al., 2017). Importantly, compared with the previous analyses, all the included trials were of high quality, thus reaching the Level 1 of evidence. Overall, the clinical data on the use of silymarin in NAFLD are promising, but they need to be confirmed in further prospective, standardized, multicenter, and larger sample sized RCTs.

7 | VIRAL HEPATITIS

Viral hepatitis is a global and often underestimated health problem, mainly in the developing countries. Chronic infection with the hepatitis B and/or C virus and/or human immunodeficiency virus (HIV) causes significant morbidity and mortality. In the last years, new treatments that have attenuated viral replication or induced immunity against the infection have been launched in the clinical practice (Stanaway et al., 2016). However, the cost of these treatments is often expensive and the cure is not accessible to everyone. In such a context, a herbal medicine might constitute an attractive alternative to these novel treatments.

Experimentally, silybin has been shown to inhibit the HCV infection in human hepatocytes (Blaising et al., 2013) and silymarin to attenuate cellular functions involved in T-cell activation, proliferation, and HIV-1 infection (McClure, Margineantu, Sweet, & Polyak, 2014). Furthermore, some traditional Chinese preparations containing silymarin have been approved in China for the treatment of hepatic diseases such as HBV chronic infection (Qi et al., 2013). However, despite this encouraging background, the analysis of the literature reveals the paucity and poor quality of the trials investigating the efficacy of silymarin or silybin in viral hepatitis. A relevant multicenter double-blind placebo-controlled trial, published in JAMA, evaluated the effects of silymarin on liver disease activity in patients with HCV infection, unsuccessfully treated with interferon-based therapy (Fried et al., 2012). Participants were randomly assigned to receive 420-mg silymarin, 700-mg silymarin, or matching placebo administered 3 times per day for 24 weeks. The authors found that silymarin did not significantly reduce serum ALT levels more than placebo in HCV patients unsuccessfully treated with interferon-based therapy.

Two systematic reviews/meta-analyses have recently been published. The first, including 12 randomized clinical trials for a total of 1,096 patients, showed that silymarin was equivalent to antiviral agents with respect to the reduction of transaminase levels and viral load. Also, silymarin, associated with the use of antivirals, was able to promote a greater effect on serum reduction of transaminase levels when compared with the antiviral drug treatments alone. However, it was concluded that a firm conclusion on the use of silymarin in the HBV infection cannot be drawn giving the general poor quality of the analysed studies (Wei et al., 2013). A further meta-analysis summarized five placebo-controlled randomized clinical trials (N = 389 HCV patients) related to the efficacy of MT extracts (Yang, Zhuang, Lu, Xu, & Chen, 2014). Serum HCV-RNA relatively decreased in patients treated with silymarin compared with the placebo, but the effect was not statistically significant. Furthermore, no statistical differences were found on transaminase levels between the silymarin patients and the placebo. The authors concluded that there was no evidence supporting the use of silymarin in the HCV patients, although the use of intravenous silybin requires further investigation (Yang et al., 2014). To this point it is worth noting that a pilot study highlighted the efficacy of a lead-in with intravenous silybin administration (20 mg/kg/day for 2 weeks) before triple therapy, to increase the probability of the HCV treatment success in difficult-to-treat the HIV/HCV-coinfected patients with advanced liver fibrosis and a previous failure of peginterferon-ribavirin (Braun et al., 2014). Finally, an Egyptian randomized study on 62 chronic HCV-decompensated cirrhotic patients, not included in the above-reported meta-analyses, reported that a high dose of silymarin (1.050 mg/day for 12 weeks) was more efficacious than a silymarin standard dose (420 mg/day for 12 weeks) to improve hepatic blood profile, albumin level, and consequently the child score in these patients (Fathalah, Abdel Aziz, Abou, Soud, & El Raziky, 2017).

In conclusion, despite some positive results, the available evidence does not support the use of silymarin/silybin in the HCV patients.

7.1 | Iatrogenic liver diseases

In spite of a large number of the preclinical studies, clinical trials on the effects of MT extracts in iatrogenic liver diseases are limited and the results are contradictory. An early study showed that silymarin might attenuate gastrointestinal side effects due to the administration of tacrine, an anticholinesterase drug used in the treatment of Alzheimer's disease (Allain et al., 1999). More recently, the studies related to the effect of silymarin on the hepatotoxicity due to antitubercular drugs have reported mixed results. Specifically, a double-blinded RCT found that patients treated with silymarin (140 mg three times daily, along with antituberculosis drugs) had a statistically significant improvement of the ALT levels compared with the placebo (Luangchosiri et al., 2015). By contrast, an RCT evaluating the hepatic effects of silymarin-containing capsules (200 mg twice/daily) in patients treated with isoniazid, rifampicin, pyrazinamide, and ethambutol for the period of 6–8 months found no significant preventive effect of silymarin in lowering the risk of liver injury (Zhang et al., 2016).

8 | MUSHROOM POISONING

The *Amanita phalloides* (the so-called death cap) mushroom poisoning is associated with a severe morbidity and a high mortality rate due to progressive fulminant hepatic failure. The main toxic agents of *Amanita phalloides* are amatoxins, that is, DNA-dependent RNA polymerases II inhibitors that dysregulate protein synthesis causing liver necrosis (Santi et al., 2012). The human lethal dose is approximately 0.1 mg/kg body weight. There are no worldwide accepted guidelines on the treatment of amatoxins-induced liver failure. Clearly, due to the ethical reasons, there are no controlled clinical studies available. However, uncontrolled trials and several case reports describe successful treatment with an intravenous silybin administration, even in the severely poisoned patients (Mengs, Pohl, & Mitchell, 2012). Empiric experience suggests the administration of 5 mg/kg silybin every 4 hr for 3–4 days after mushroom ingestion in association with N-acetylcysteine and multiple-dose activated charcoal (Karvellas et al., 2016; Trakulsrichai et al., 2017).

9 | HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) represents a leading cause of cancer-related death worldwide (Dimitroulis et al., 2017). It occurs in the setting of chronic liver inflammation, and it is most closely linked to chronic viral hepatitis infection, exposure to toxins such as alcohol, and metabolic liver disease, including NASH (Ghouri, Mian, & Rowe, & J.H., 2017). The current treatments of this condition are inadequate, thus herbal medicinal products have emerged as a therapeutic possibility to be chased (Bae et al., 2017; Chen, Qiu, Hu, Wang, & Wang, 2016; Safe & Kasiappan, 2016; Tariq et al., 2017).

The effect and the mode of action of silymarin and of its main ingredient silybin in the antiliver-cancer mechanisms have been extensively evaluated in several in vitro and in vivo assays (Mastron, Siveen, Sethi, & Bishayee, 2015). A number of studies have shown that silymarin and silybin suppressed the growth of cancer liver cells. Interestingly, a combined treatment with silybin and either sorafenib or gefitinib enhances their growth-inhibiting effects in HCC cells (Gu et al., 2015). More in depth investigations have revealed that silymarin could act additively or synergistically with doxorubicin in inhibiting telomerase activity in hepatic carcinoma cells (Yurtcu, Darcansoy Iseri, & Iffet Sahin, 2015). This study is relevant in the light of the observation that HCC is resistant to the conventional antitumoral drugs such as doxorubicin.

The antitumoural actions of silymarin/silybin have been confirmed in animal models of HCC. By using carcinogenic models of hepatic cancer for chemoprevention, transgenic animal models, or xenograft injection of HCC cells in immunodeficient mice, a number of studies have shown that silymarin or silybin could inhibit different stages of hepatocarcinogenesis, that is, initiation, promotion, and progression. The key mechanisms underlying the inhibition of experimental hepatocellular carcinogenesis include the inhibition of oxidative stress, proapoptotic actions, induction of cell cycle arrest, and interference with extrinsic and intrinsic mitochondrial pathways (Mastron et al., 2015). There is also experimental evidence that the

antitumoral effect of orally administered silybin could improve if silybin is administered as nanoparticles (Zhang, Wang, & Liu, 2016). Finally, it is noteworthy that silybin has been shown to attenuate antitumoral drugs toxicity via the inhibition of signal transducer and activator of transcription 3 that exert a pivotal role in mediating resistance to the antitumoral drugs (Bosch-Barrera, Queralt, & Menendez, 2017).

Despite such encouraging preclinical studies, the anti-HCC activity of silymarin or silybin has not yet been clearly demonstrated in the clinical trials (Siegel & Stebbing, 2013). A phase I dose-finding study of silybin phosphatidylcholine in the advanced HCC patients failed to determine the maximum tolerated dose since the patients died soon after the enrollment (Mastron et al., 2015; Siegel et al., 2014).

10 | CONCLUSION

Despite its anti-inflammatory, antioxidant, and antifibrotic properties observed in experimental studies, the current efficacy of MT preparations in patients with liver diseases is not fully compelling. By way of example, a very recent systematic review with meta-analysis of randomized and controlled clinical trials showed that silymarin minimally reduced, but without clinical relevance, the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (de Avelar, Pereira, de Farias Costa, de Jesus, & de Oliveira, 2017). Some evidence of efficacy has been reported in patients with ALD and NAFLD. It is incumbent to carry out high-quality trials with a special care to the standardization of the doses and the treatment timing, the impact of gender, ethnicity and age, and the use of well-identified validated outcomes. Finally, silymarin and the MT preparations have been shown to be well tolerated in the patients, and the potential of drug interaction is low.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ORCID

Ludovico Abenavoli http://orcid.org/0000-0002-5922-1524

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How to cite this article: Abenavoli L, Izzo AA, 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. *Phytotherapy Research*. 2018;1–12. https://doi.org/10.1002/ptr.6171