Milk Thistle

Species (Family)

Silybum marianum (L.) Gaertn. (Asteraceae/Compositae)

Synonym(s)

Carduus marianus L., Lady's Thistle, Marian Thistle, Mediterranean Milk Thistle, St. Mary's Thistle.

Part(s) Used

Fruits (often referred to as 'seeds'), herb

Pharmacopoeial and Other Monographs

BHP 1996[G9]
Complete German Commission E[G3]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

Milk thistle is not included in the GSL.[G37]

Constituents[G2,G43]

Fruit

Flavolignans 1.5–3% silymarin, a mixture containing approximately 50% silibinin (= silybin, silybinin), silichristin and silidianin, as well as silimonin, isosilichristin, isosilibinin, silandrin, silhermin, neosilihermins A and B, 2,3-dehydrosilibinin and tri- to pentamers of silibinin (silybinomers).[1]

Flavonoids Quercetin, taxifolin and dehydrokaempferol.[1]

Lipids 20–30%. Linoleic acid, oleic acid and palmitic acid.

Sterols Cholesterol, campesterol and stigmasterol.

Other constituents Mucilages, sugars (arabinose, rhamnose, xylose, glucose), amines and saponins.[1]

Leaves

Flavonoids Apigenin, luteolin and kaempferol and their glycosides.[1]

Other constituents β-Sitosterol and its glucoside, and a triterpene acetate.[1]
 Silymarin is not found in the leaves.

Food Use

Milk thistle is not used in foods.

Herbal Use[G2,G32,G34,G35,G50,G64]

Traditionally, milk thistle fruits have been used for disorders of the liver, spleen and gall bladder such as jaundice and gall bladder colic. Milk thistle has also been used for nursing mothers for stimulating milk production, as a bitter tonic, for haemorrhoids, for dyspeptic complaints and as a demulcent in catarrah and pleurisy. It is stated to possess hepatoprotective, antioxidant and choleretic properties.[1,2]
 Current interest is focused on the hepatoprotective activity of milk thistle and its use in the prophylaxis and treatment of liver damage and disease.
 The leaves have also been used for the treatment of liver, spleen and gall bladder disorders and as an antimalarial, emmenagogue and for uterine complaints. Milk thistle leaf preparations are available today, although most research has been conducted with preparations of the fruit since the leaf does not contain the pharmacologically active component silymarin.

Dosage

Fruit Crude drug 12–15 g daily in divided doses (equivalent to silymarin 200–400 mg daily).[G3]

Herb Approximately 1.5 g of finely chopped material as a tea, two or three cups daily.

The doses of silymarin used in clinical trials have ranged from 280 to 800 mg/day (equivalent to milk thistle extract 400–1140 mg/day standardised to contain 70% silibinin).[3] For hepatic disorders, doses of up to 140 mg (equivalent to 60 mg silibinin) two or three times daily have been suggested.[G43]

In Germany, the recommended regimen for treatment of *Amanita phalloides* poisoning with a standardised silymarin preparation (Legalon) is a total dose of silibinin (as the disodium dihemisuccinate) (20 mg/kg body weight) over 24 hours, divided into four intravenous infusions each given over a 2-hour period.[G43,G55]

Pharmacological Actions

Several pharmacological activities have been documented for milk thistle fruit, including hepatoprotective, antioxidant, anti-inflammatory, antifibrotic and antitumour properties, as well as inhibition of lipid peroxidation, stimulation of protein biosynthesis and acceleration of liver regeneration. Silymarin (an isomer mixture comprising mainly silibinin, silichristin and silidianin) is the pharmacologically active component of milk thistle fruit; silibinin is the main component of silymarin. There is an extensive literature on the pharmacological effects of silymarin and silibinin, particularly with regard to their hepatoprotective activity which provides supporting evidence for the clinical uses. The pharmacology and clinical efficacy of milk thistle have been reviewed.[1–3,G50,G55] The following represents a summary of selected publications on this subject.

There is a lack of research investigating the pharmacological effects of preparations of milk thistle leaf.[G2,G32,G35]

In vitro and animal studies

Antioxidant activity Silymarin and silibinin (silybin) are antioxidants that react with free radicals (e.g. reactive oxygen species) transforming them into more stable and less reactive compounds.[1,4–6] Silymarin and silybin have been reported to inihibit lipid peroxidation induced by iron-linked systems in rat liver microsomes[7,8] and protect against phenylhydrazine-induced lipid peroxidation in rat erythrocytes.[1] Furthermore, in rats, intraperitoneal silymarin has been shown to increase total glutathione in the liver, intestine and stomach and to improve the reduced glutathione to oxidised glutathione ratio.[9] Silymarin has been shown to inhibit

copper-induced oxidation of human low-density lipoprotein (LDL) *in vitro* in a concentration-dependent manner.[10] Silybin appears to be the constituent of silymarin responsible for the LDL antioxidant effect. In contrast, silichristin and silydianin appeared to act as pro-oxidants, but without significantly reducing the total LDL antioxidant capacity of silymarin.

Free radicals are recognised as having an important role in several pathological processes, including inflammation, necrosis, fibrosis, atherosclerosis, carcinogenesis and ageing and in the hepatotoxic mechanisms of various substances. The antioxidant activity of silymarin is thought to contibute to its hepatoprotective properties.[11,G55]

Hepatoprotective properties In *vitro* studies using isolated hepatocytes have documented the protective activity of silymarin and several of its components against cell damage induced by various cytotoxic substances.[1]

In *vivo* studies in rats and mice have demonstrated the hepatoprotective activity of silymarin and silybin in acute liver toxicity induced by various toxic agents with different mechanisms of action, including carbon tetrachloride, galactosamine, thioacetamide, ethanol, paracetamol (acetaminophen), thallium, phalloidin and α-amanitin (the main toxic constituents of the mushroom A. *phalloides*).[1] Experimental studies in chronic liver toxicity induced by repeated administration of carbon tetrachloride, heavy metals, thioacetamide and several drugs, including azathioprine and indomethacin, have also demonstrated that administration of silymarin and silybin protects against damage.[1] Other studies have reported protective effects of silymarin against liver injury induced by ischaemia[12] and gamma irradiation.[13]

Studies in rabbits fed a high-fat diet for 12 weeks have shown that histopathological alterations were least advanced in animals which also received a silymarin–phospholipid complex.[14] In rats, silymarin inhibited the development of diet-induced hypercholesterolaemia.[15] The hypocholesterolaemic effects of silymarin may be due to the effects of silymarin on lipoprotein metabolism.[16]

The effects of silymarin on biliary bile salt secretion have been seen in studies in rats.[17] Intraperitoneal silymarin (25, 50, 100 and 150 mg/kg/day) for five days induced a dose-dependent increase in bile flow and bile salt secretion. Stimulation of bile salt secretion was mainly accounted for by an increase in the biliary secretion of the hepatoprotective bile salts β-muricholate and ursodeoxycholate.

Nephroprotective properties Silibinin injected into rats prior to administration of cisplatin afforded protection of glomerular and proximal tubular function.[18,19] Silibinin does not affect the cytotoxic activity of cisplatin.[19] Intraperitoneal silibinin (5 mg/kg) administered to rats 30 minutes before cyclosporin decreased cyclosporin-induced lipid peroxidation but produced no protective effect on the glomerular filtration rate.[20]

Anticancer activity Silybin at concentrations of 0.1–20 μmol/L inhibited the growth of drug-resistant ovarian cancer cells and doxorubicin-resistant breast cancer cells *in vitro*.[21] Furthermore, silybin in the range of 0.1–1.0 μmol/L potentiated the effect of cisplatin and doxorubicin in experimental tumour cell lines. When applied to the skin of SENCAR mice, silymarin gave protection against the effects of the tumour promoters 12-O-tetradecanoylphorbol (TPA) and okaidic acid (OA).[22] Topical application of silymarin prior to that of TPA and OA completely inhibited induction of tumour necrosis factor α (TNFα) mRNA expression in the epidermis. Substantial protection from photocarcinogenesis in mice treated with phorbol ester or 7,12-dimethylbenz(*a*)anthracene has been demonstrated.[23] The antitumour effect is primarily at stage 1 tumour promotion and silymarin acts by inhibiting cyclooxygenase 2 (COX-2) and interleukin 1α (IL-1α).[24] Such effects may involve inhibition of promoter-induced oedema, hyperplasia, the proliferation index and oxidant state.[25]

Treatment of serum-starved human prostate carcinoma DU145 cells with silymarin resulted in significant inhibition of transforming growth factor α (TGFα)-mediated activation of the epidermal growth factor receptor erbB1.[26] There was also a decrease in tyrosine phosphorylation of an immediate downstream target, the adaptor protein SHC, together with a decrease in binding to erbB1. In the silymarin-treated cell lines there was a significant induction of the cyclin-dependent kinase inhibitors (CDKIs) Cip1/p21 and Kip/p27 concomitant with a significant decrease in CDK4 expression, but no changes in the levels of CDK2 and CDK6 and their associated cyclins E and D1, respectively. Additional experiments showed that there was a significant inhibition of constitutive tyrosine phosphorylation of both erbB1 and SHC, but no changes in their protein levels. The results indicated that silymarin may exert a strong anticarcinogenic effect against prostate cancer and that this effect is likely to involve impairment of the erbB1–SHC-mediated signalling pathway, induction of CDKIs and resultant G_1 arrest.[26]

There was a significant inhibition of mitogen-activated protein kinase (MAPK) ERK activity at lower doses in epidermal A431 cells treated with silymarin, whereas higher doses activated MAPK/JNK1.[27] Silymarin exerted a strong anticarcinogenic effect against human breast carcinoma cells MDA-MB468 with G_1 arrest in cell cycle progression and also induction in protein expression of the CDKI Cip/p21.[28]

The cancer chemoprevention and anticarcinogenic effects of silymarin have been shown to be due to its major constituent silibinin.[29] Silibinin decreases prostate-specific antigen (PSA) in hormone-refractory human prostate carcinoma LNCaP cells and inhibits cell growth via G_1 arrest.[30]

Silibinin was fed orally to SENCAR mice and its tissue distribution investigated.[31] Free silibinin mainly accumulated in the liver, although it was also distributed in other organs. Increases in glutathione-*S*-transferase and quinone reductase activities in the liver, lung, stomach, skin and small bowel were observed. The results demonstrated the bioavailability of and phase II enzyme induction of silibinin in different tissues where silymarin has been shown to be a strong cancer chemopreventive agent.

Anti-inflammatory activity Silymarin administered orally reduced foot-pad abscesses in a dose-dependent manner in the carrageenan rat paw oedema test ($ED_{50} = 62.4$ mg/kg).[32] In the xylene-induced inflammation test, topically applied silymarin was comparable with indomethacin.[32] Silymarin given intraperitoneally to mice resulted in inhibition of leukocyte accumulation in inflammatory exudates and reduced the neutrophil count.[32] Activation of NF-κB induced by TNF, phorbol ester, okaidic acid and ceramide was blocked by silymarin in a dose-dependent manner.[33] Silymarin also inhibited TNF-induced activation of mitogen-activated protein kinase and *c*-Jun N-terminal kinase.[33] The inhibition of activation of NF-κB and the kinases may provide part of the molecular basis for the anti-inflammatory and anticarcinogenic effects of silymarin.[33] Silymarin potently suppressed both NF-κB–DNA binding activity and its dependent gene expression induced by okaidic acid in the hepatoma cell line Hep G2. [34] In addition, silymarin inhibits COX-2 and IL-1α.[24]

Gastric ulcer protective effects Oral administration of silymarin to rats prevented gastric ulceration induced by cold-restraint stress.[35] Gastric secretion volume and acidity were not affected, but histamine concentration was significantly decreased. It was

suggested that the anti-ulcerogenic effect of silymarin may be related to inhibition of enzymic peroxidation by the lipoxygenase pathway.[35] The protective effect of silymarin on gastric injury induced in rats by ischaemia–reperfusion and its effects on mucosal myeloperoxidase has been compared with that of allopurinol.[36] The mean ulcer indexes (4.75, 4.50 and 3.63 ui, respectively) of rats treated with 25, 50 and 100 mg/kg silymarin were significantly lower than in control rats, although allopurinol was considerably more potent (2.3 ui; 100 mg/kg).[36]

Other effects   Silymarin has been shown to prevent alloxan-induced diabetes mellitus in rats, possibly due to its antioxidant activity and increases in plasma and pancreatic glutathione concentrations.[37]

It has been reported that *Silybum marianum* and silymarin beneficially affect skin elasticity. A phospholipid–silymarin complex (Silymarin–Phytosome) evaluated for its topical effects against croton oil dermatitis in mice and UV-induced erythema in humans showed reduction of oedema and inhibition of myeloperoxidase activity.[38] A standardised extract of *S. marianum* significantly inhibited porcine elastase *in vitro*.[39] An 80% ethanol extract of *S. marianum* aerial parts showed activity against *Bacillus subtilis, Staphylococcus aureus, Streptococcus haemolyticus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* and *Salmonella typhi*.[40]

Clinical studies

Clinical trials with milk thistle preparations have focused on their use in alcoholic liver disease, cirrhosis and acute viral and chronic hepatitis. However, several trials have included patients with liver disease of different aetiology, e.g. alcoholic and non-alcoholic cirrhosis. There is also interest in the use of silymarin in toxin- and drug-induced hepatitis, for example following ingestion of the death cap mushroom *A. phalloides*.

A randomised, double-blind, placebo-controlled, multicentre trial involving 200 alcoholic patients with histologically or laparoscopically proven liver cirrhosis investigated the effects of administration of silymarin (150 mg) three times daily.[41] The results indicated that silymarin had no effect on survival and the clinical course in these patients: 125 patients (silymarin $n = 57$ and placebo $n = 68$) completed the two-year study period, during which 29 died ($n = 15$ and 14 for silymarin and placebo, respectively; no statistically significant difference).

In a randomised, double-blind, placebo-controlled trial, patients with alcoholic ($n = 91$) or non-alcoholic ($n = 79$) cirrhosis received silymarin (140 mg) three times daily or placebo for two years.[42] The four-year survival rate was significantly higher in silymarin-treated patients than in placebo recipients (58 versus 39%, respectively, $p = 0.036$). Subgroup analysis indicated that the effect of silymarin on mortality was more pronounced in those patients with alcoholic cirrhosis.

Another randomised, double-blind, placebo-controlled trial carried out over four years reported a significantly higher survival rate in patients with alcoholic cirrhosis treated with silymarin (420 mg) daily compared with placebo recipients, although the effect in patients with non-alcoholic cirrhosis was less marked.[43]

Other controlled trials have investigated the effects of silymarin in patients with alcohol-related liver damage. Several of these,[44,45] but not all,[46] reported statistically significant benefits with silymarin, e.g. on serum transaminases, compared with placebo.[1]

In a randomised controlled trial, 60 patients with diabetes caused by alcoholic liver cirrhosis received silymarin (600 mg/day) or no silymarin treatment for six months.[47] At the end of the study period, the mean values for fasting blood glucose, daily blood glucose, daily glycosuria, glycosylated haemoglobin, daily insulin requirement, malondialdehyde and glucagon-stimulated C peptide were significantly lower in silymarin-treated patients than in those who did not receive silymarin treatment.

A pilot study involving 20 patients with chronic active hepatitis randomised to receive a silybin–phosphatidylcholine complex preparation (IdB1016; Silipide) (240 mg) twice daily or placebo for seven days reported significant reductions in the mean serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (GGT) and total bilirubin in silybin complex-treated patients compared with values in placebo recipients.[48] The same preparation has been reported to reduce serum concentrations of liver enzymes (AST and ALT) in 65 patients with chronic persistent hepatitis in a randomised placebo-controlled trial.[49]

The hepatoprotective effects of silymarin in 222 *de novo* tacrine-treated patients with mild to moderate dementia of the Alzheimer type were investigated in a randomised, double-blind (for silymarin), placebo-controlled, multicentre, 12-week trial.[50] Patients received tacrine plus silymarin (420 mg/day) ($n = 110$) or tacrine plus placebo ($n = 112$); silymarin (and placebo) were initiated one week before tacrine (40 mg/day for six weeks then 80 mg/day for six weeks). An intention-to-treat analysis indicated that there was no difference in

serum ALT concentrations between the two groups, but that silymarin-treated patients experienced significantly fewer gastrointestinal and cholinergic side-effects without any impact on cognitive status than did placebo recipients.[50]

The effects of silymarin in preventing psychotropic drug-induced hepatic damage have been investigated in a randomised, double-blind, placebo-controlled trial.[51] Sixty women aged 40–60 years who had been taking phenothiazines or butyrophenones for at least five years and who had AST and ALT activity twice normal values were randomised to continued treatment with psychotropic agents or suspension of treatment and to silymarin (800 mg/day) or placebo for 90 days. The findings indicated that treatment with silymarin reduced the lipoperoxidative hepatic damage associated with prolonged administration of butyrophenones and phenothiazines and that the protective effect was greater when treatment with these psychotropic agents was suspended for three months.[51]

There have been numerous case reports, many of which report favourable outcomes, on the therapeutic use of silymarin and silibinin, usually given in combination with standard treatment, in poisoning caused by ingestion of the death cap mushroom *A. phalloides*, although there are no controlled trials in this indication.[1,51–54,G55] Silibinin is usually given intravenously and case reports have indicated that early administration appears to be important.[55,56]

Pharmacokinetics Studies of the pharmacokinetics of silymarin and its components and of a silibinin–phosphatidylcholine complex preparation (IdB 1016; Silipide) in both healthy volunteers and patients with cirrhosis and those who have undergone cholecystectomy have been reviewed.[1,G50,G55] Approximately 20–50% of silymarin is absorbed following oral administration and approximately 80% of the dose, whether administered orally or intravenously, is excreted in the bile.[57] Studies in healthy volunteers have reported an elimination half-life of approximately 6 hours following administration of single doses of silymarin corresponding to approximately 240 mg silibinin.[58,59] Other studies have compared the pharmacokinetics of different silymarin preparations and shown statistically significant differences in bioavailability.[60,61]

The bioavailability of a silybin–phosphatidylcholine complex preparation (IdB 1016) has been shown to be several times greater than that of silymarin in single-dose studies involving healthy volunteers[62] and patients with hepatic cirrhosis.[63]

Side-effects, Toxicity

No adverse events were noted in a pharmacokinetic study involving healthy male volunteers following single oral doses of silymarin corresponding to up to 254 mg silibinin.[59]

Clinical trials involving patients with liver disorders of various origin and who received oral silymarin at doses of up to 600–800 mg/day for up to six months have reported that no adverse effects were observed.[42,47,51]

Data from drug monitoring studies involving more than 3500 patients, including one study involving 2637 patients with various types of chronic liver disease treated with silymarin (Legalon) (560 mg/day) for eight weeks, have indicated that the frequency of adverse effects with silymarin is approximately 1%. Adverse effects are mainly transient, non-serious, gastrointestinal complaints.[4,64,G55] It is stated that silymarin may occasionally produce a mild laxative effect.[G3]

A case report from Australia described a reaction associated with a preparation of milk thistle. The symptoms included episodes of severe sweating, abdominal cramping, nausea, vomiting, diarrhoea and weakness and these were verified by rechallenge.[65] Another report described a case of anaphylactic shock in a 54-year-old man with immediate-type allergy to kiwi fruit.[66] He experienced facial oedema, swelling of the oral mucosa, bronchospasm, respiratory distress and decreased blood pressure after taking a preparation of milk thistle; a skin-prick test of an extract of milk thistle fruit elicited an immediate-type reaction.

The acute toxicity of oral and intravenous silymarin and silibinin has been investigated in various animal species (mice, rats, rabbits and dogs).[1] Oral silymarin administered to mice and dogs at doses of 20 and 1 g/kg, respectively, did not cause adverse effects or mortality. Long-term oral administration of silymarin (100 mg/kg/day) to rats for 16 or 22 weeks did not reveal any adverse effects.

Contra-indications, Warnings

None documented. In view of the lack of long-term safety data, excessive use of milk thistle should be avoided (except where its use may help to prevent toxicity caused by other substances).

Milk thistle is contra-indicated for individuals with hypersensitivity to species of Asteraceae.

Pregnancy and lactation In view of the lack of toxicity data, use of milk thistle preparations during pregnancy and lactation should be avoided unless the

expected benefit is thought to outweigh any unknown risks to the fetus.

Pharmaceutical Comment

The chemistry of milk thistle is well-documented and there is good evidence that silymarin and its components, particularly silibinin, are responsible for the pharmacological effects.

Documented scientific evidence from *in vitro* and animal studies provides supportive evidence for some of the uses of milk thistle, particularly those relating to hepatoprotective properties.

There have been several controlled clinical trials investigating the effects of milk thistle in a range of liver disorders, including acute viral hepatitis, chronic hepatitis, alcoholic liver disease, cirrhosis and toxic liver damage. The results of these studies are not entirely consistent or conclusive. In addition, some trials have methodological shortcomings, for example the inclusion of patients with different liver disorders, small numbers of patients and failure to control or monitor alcohol intake.[67] Further, well-designed, clinical trials in clearly defined patient groups are required in order to establish the efficacy of milk thistle and its components in different liver disorders. In Germany, milk thistle is approved for the treatment of toxic liver disorders and as a supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis.[G3]

Teas prepared from milk thistle fruits or herb are not commonly used as only a small proportion of silymarin gets into the aqueous extract such that pharmacologically active doses are not attained.[68] For this reason, in Germany teas are recommended only as supportive treatment in functional gall bladder disorders and not for antihepatotoxic effects.[G2] In Germany, milk thistle fruit (3–5 g) as an infusion three or four times daily is also indicated for mild digestive disorders.[G2]

There are some toxicity and safety data for milk thistle which, together with data on the adverse effects reported in clinical trials, provide good evidence for the safety of milk thistle when used at recommended doses in the short term. However, further data on the long-term safety of milk thistle use are required.

Patients wishing to use milk thistle should be advised to consult a pharmacist, doctor or other suitably trained healthcare professional for advice.

References

See General References G2, G3, G9, G34, G36, G43, G50 and G64.

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