Herbal Monograph

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A.N.P.A.
Australian Naturopathic Practitioners Association Inc.

Phone: 03 9811 9990 Toll Free: 1800 422 885
Fax: 03 9813 3581 Email: admin@anpa.asn.au
Suite 36/123 Camberwell Rd, East Hawthorn VIC 3123

Silybum marianum – ancient medicine for modern times

Maureen Boh
BA (Economics) UNSW, BCom (Accounting) UNSW
Student, Advanced Diploma of Naturopathy, Australasian College of Natural Therapies
mtnboh@gmail.com

Ian Breakspear
MHerbMed (USYD) ND DBM DRM CertPhyto FNHAA
Herbal & Naturopathic Clinician. Lecturer, Australasian College of Natural Therapies. Lecturer, Endeavour College of Natural Health
ianbreakspear@me.com

ABSTRACT

The use of *Silybum marianum* (Milk Thistle) in the treatment of the liver, spleen and gallbladder dates back some 2,000 years. The main active constituent of *Silybum marianum* considered important in modern times is silymarin, a flavonolignan complex, which is insoluble in water. Research has shown *Silybum marianum* to be antioxidant, anti-inflammatory, hepatoprotective, antifibrotic, and has the capability to chelate iron. Besides its well-known use as an antidote to *Amanita phalloides* poisoning in Europe, other global medicinal indications include toxic liver damage, chronic and alcoholic liver diseases, hypercholesterolemia, acute viral hepatitis, hepatitis C infection, and chemotherapy support. The absence of significant adverse events even at high doses of silibinin and its related compounds, and the ability to reduce the toxic side effects of chemotherapy make it a useful adjunct in a number of conditions. This monograph (an expansion of an assignment submitted by the principal author during 2013) will review *Silybum marianum's* primary medicinal properties and clinical usefulness in depth.

BOTANIC NAMES

Carduus marianus,[1,2]*Silybum marianum.*[1]

COMMON NAMES

St Mary's Thistle,[1,2] Fructus Silybi Mariae, Milk Thistle.[1]

BOTANICAL DESCRIPTION

Silybum marianum is indigenous to North Africa, South America, Australia, China and Central Europe. It is either an annual or biennial, growing up to 150 cm high. Other botanical features include:[1]

- Small (6-7 mm long) one-seeded fruit, 6-8 hard dry skins, white silky pappus (15-20 mm diameter) at the apex
- Green, spiny, 20-150 cm stem with a single large flower
- Leaves: alternate, cauline and basal, no petiole, large (25-50 cm long), broad (12-25 cm wide), glossy green, variegated with white veins, glabrous
- Vibrant red purple tubular hermaphrodite florets, large flower heads (2.5-4.0 cm diameter), thorny bracts

PARTS USED

In modern herbal medicine, the active ingredients of *Silybum marianum* are extracted from the fruit,[3] sometimes called seed[4] but is technically an achene[1].

Traditionally, the whole *Silybum marianum* plant was used as food - leaves; young shoots, flower heads and stem were baked or boiled. Powdered dried leaves were used as tea. It was used by herbalists dating back to Dioscorides who used a decoction of seeds for snake bites. Herbalist John Evelyn mentioned the seeds as a galactagogue; English herbalist John Gerard mentioned roots for treating melancholy; and Culpepper recommended infusing fresh roots and seeds for jaundice and oedema (dropsy), and boiling young plants as blood cleansers.[2,5]

RELEVANT CONSTITUENTS

The main constituents of *Silybum marianum* are:[1,3]

- Flavonolignans: 1.5-3% silymarin comprising mainly of:
    - 50% silybin or silibinin
    - Silychristin
    - Silydianin
    - 2, 3 –dehydrosilybin
    - 2, 3 –dehydrosilychristin
- Flavonoids:
    - 2, 3 –dihydroflavonol
    - Quercetin, taxifolin, dehydrokaempferol

- Lipids: 20% - 30%. Linoleic acid, oleic acid, palmitic acid
- Sterols: Cholesterol, campesterol, stigmasterol
- Other Constituents: Mucilages, sugars, amines, saponins

Figure 1 shows three structural components of silymarin.[6]

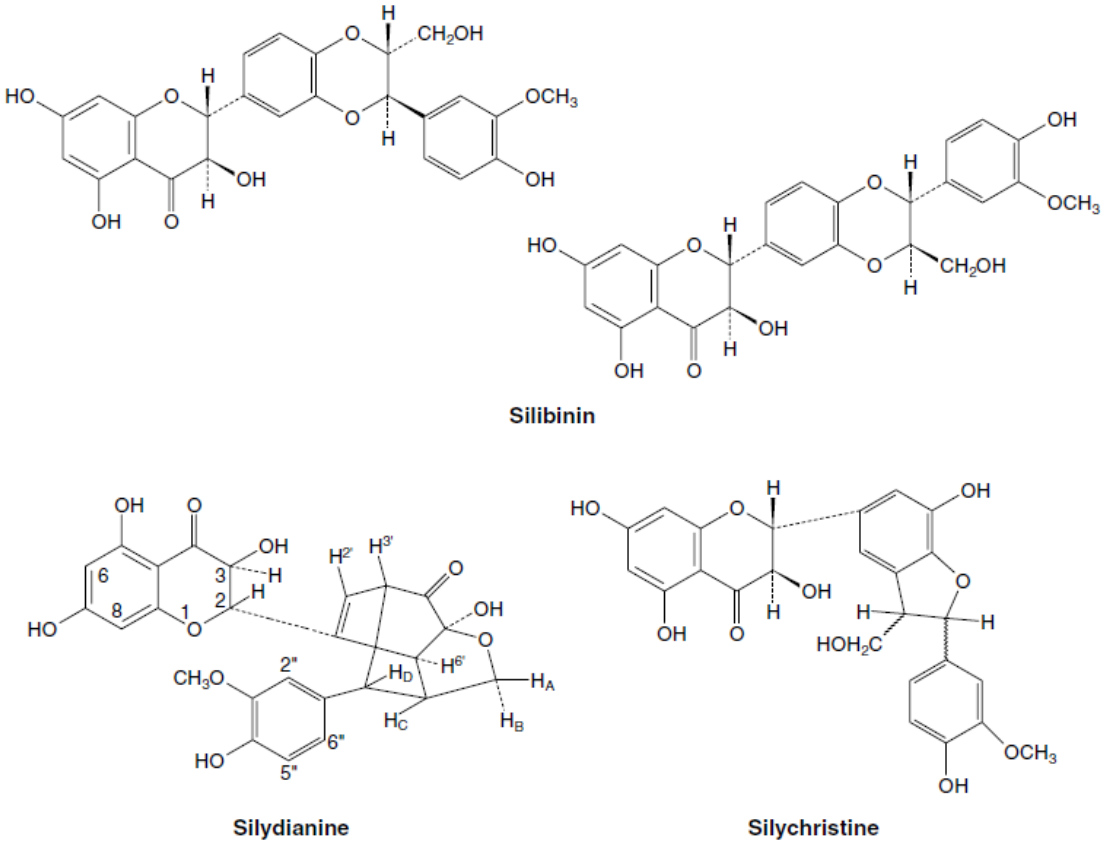

Fig. 1. The three structural components of silymarin: silibinin, silydianine, and silychristine.

PREPARATION FORMS

Traditional preparations included decoctions made by boiling seeds in water. Tinctures were prepared using equal parts of root and seeds with the hull still attached. Powdered dried leaves were made into infusion for headaches or inducing perspiration.[2]

According to Culpeper, infusions were made by pouring 1 pint of boiling water onto 1 oz of herb.[7]

Silybum marianum is available in Australia as seeds, capsules or tablets, liquid extracts, tinctures and silymarin complex. It is generally administered as capsules containing standardised extracts quantified to between 70%-80% silymarin.[8] The 'phytosome' preparation form is made by complexing silymarin components with phospholipids, mainly phosphatidylcholine, derived from soy, which is reputed to increase absorption.[9]

Infusions are made by steeping 150 mL boiling water containing 3.5 g crushed seeds for 10-15 minutes. Decoctions are made by gently simmering 3g seeds in 150 mL boiling water for 20-30 minutes before straining. A peppermint leaf can be used to add flavour.[10]

Legalon® (MZ 80) *Silybum marianum* capsules are made using a patented extraction technique specifically formulated to achieve high bioavailability. One capsule is equivalent to 7.2 g dry fruit stardardised to 140 mg silymarin.[11] Ulbricht and Basch revealed that Legalon® is prepared via extraction with ethyl acetate unlike other manufacturers who utilise ethyl alcohol extraction.[12]

Preparations that are available to Australian practitioners include:[13]

- 1:1 liquid extracts - 25.0 mg/mL silymarin (minimum)
- 1:1 glycetract - 10.0 mg/mL silymarin (minimum)
- Standardised preparations 7.2 g dry fruit equivalent to 140 mg, 70-80% silymarin

Products commonly available to Australian naturopaths and herbalists include:

- Flordis Legalon® (MZ 80) – standardised capsule
- Herbal Extract Company St Mary's Thistle hydroethanolic liquid extract (1:1)
- MediHerb St Mary's Thistle hydroethanolic liquid extract (1:1)
- MediHerb St Mary's Thistle glycetract liquid extract (1:1)
- MediHerb Silymarin – standardised tablet
- Metagenics Silymarin Intensive Care – standardised capsule
- Optimal Rx St Mary's Thistle hydroethanolic liquid extract (1:1)
- Thompson's Milk Thistle – standardised capsule

Many compound preparations of *Silybum marianum* are also available, combined with other herbs and sometimes nutrients.

HISTORICAL INFORMATION

The use of *Silybum marianum* for ailments relating to the liver, spleen and gall bladder dates back some 2,000 years to Pliny the Elder, and as far back as Dioscorides.[14]

Tales behind the white mottling appearance of the leaves of St Mary's thistle, Blessed thistle, and Holy thistle spoke of a drop of Virgin Mary's breast milk falling onto the leaves whilst feeding baby Jesus.[2] Culpeper thought such naming was the sacrilegious deed of 'some that had little holiness'.[15]

According to herbal astrology, *Silybum marianum* is associated with Mars. Its thorns act as barriers, signifying its protective ability. The thorny appearance depicts the combative spirit of Mars - removing body odours (as a deodorant or mouth wash) and the stench of urine (as a diuretic), and regrowing fallen hair (symbolic of a fighting spirit, rising up after having fallen). The fiery red flowers symbolise the power to cleanse blood. Mars, the medieval ruler of choler, who secretes phlegm in anger and

irritability, bestows upon *Silybum marianum* a remedial treatment for jaundice and other liver disorders.[16]

Silybum marianum has the energetics of a dry temperament, capable of removing obstructions through sweating and cleansing of the pores. It is a remedy for vertigo, deafness, stomach cramps, brain fog, intestinal worms and inflammation of the liver. Being a hot temperament herb, it is great for 'hot swellings' caused by ulcers, snake bites and being bitten by mad dogs.[15]

Holmes described *Silybum marianum* as pungent, bitter, warm, dry, stimulating, decongesting, astringent, restoring, dissolving, and softening. In contrast, the liver is associated with cold energetics and the tendency to cause stagnancy due to Yang deficiency, indigestion, nausea, headache, jaundice, constipation, and chilliness. Such ailments are remedied by the warm, stimulating energetics of *Silybum marianum* which restore the integrity of the liver by promoting bile flow, bowel movement, reducing liver congestion, and stopping free radical formation.[17]

MEDICINAL ACTIONS

The main contemporary medicinal actions of *Silybum marianum* include:[18]

- hepatoprotective
- hepatorestorative
- toxin blockade
- chelates iron
- antioxidant
- anti-inflammatory
- antifibrotic

MEDICINAL INDICATIONS

The main contemporary medicinal indications include:[18]

- Toxic liver damage
- Chronic liver diseases
- Alcoholic liver disease
- Acute viral hepatitis
- Hepatitis C infection
- Chemotherapy support
- Hypercholesterolemia

PHARMACOKINETICS

To overcome its insolubility in water, silymarin is often administered orally in encapsulated form of standardised extracts containing 70-80% silibin.[19] According to Fraschini, studies on rats indicated that silymarin is absorbed by the oral route with approximately 35% silymarin distributed in the alimentary tract.[20] Most studies cited maximum plasma concentration being achieved in 4-6 hours.[21] However, other studies have reported levels of 500 mg/L having been achieved in mice 90 minutes after oral administration of 200 mg/kg silymarin or purified *Silybum marianum* extract.[22]

According to Bulles, et al., silybin and other components undergo rapid conjugation in the liver with a negligible 2-5% excreted in urine as unmodified silibinin if administered orally or 8% if administered intravenously. Silibinin is excreted from the body mainly via the bile as metabolites regardless of the route of administration to higher degrees of 45% if administered orally and 80% if intravenously.[23] Studies seemed to indicate elimination half-life of between 6 and 8 hours.[22]

Studies on healthy volunteers[24] and hepatic cirrhosis patients[25] indicated that silybin-phosphatidylcholine complex has much higher bioavailability than silymarin.[3] More importantly, phosphatidylcholine enables silymarin to attach itself to cell membranes, thereby limiting the entry of toxins into the hepatocytes.[8]

Arcari et al. found that an inclusion complex of silibinin and beta-cyclodextrin showed 18 times greater bioavailability than silymarin.[26] Studies on nine healthy volunteers ingesting single oral doses of silymarin-phosphatidylcholine complex linked the increased bioavailability to the silibinin complex facilitating silymarin in crossing the gastrointestinal mucosa.[24]

PHARMACODYNAMICS

Comelli et al. discussed the possible synergistic action between silymarin and silibinin and the different conventional cytotoxic agents such as doxorubicin, cisplatin, and carboplatin. They suggested that the unifying mechanism lies in the early scavenging and antioxidant actions of silymarin and silibinin on Reactive Oxygen Species (ROS), thereby reducing cellular damage caused by various cytotoxics.[27]

Incorrect regulation of NF-kappa B has been linked to cancer, inflammatory and autoimmune diseases. Some authors postulated that the link between the anti-inflammatory and anticarcinogenic effects of silymarin, lies in its ability to inhibit activation of tumour necrosis transcription factor NF-kappa B by inhibiting phosphorylation and degradation of Iota kappa B alpha, hence preventing the translocation of NF-kappa B into the nucleus.[28]

Cancer patients undergoing ionizing radiation and chemotherapy frequently suffer from hepatotoxicity due to excessive ROS creating chronic oxidative stress and lipid peroxidation, and depletion of reduced glutathione (GSH) - hepatotoxic cellular events similar to those triggered by acetaminophen, antibiotics, antipsychotics, and anti-depressions.[29] Silymarin protects the liver against such hepatotoxicity by regulating membrane permeability, thereby blocking the release and reabsorption of free xenobiotice.[19]

Comelli et al. contended that knowing the time course of liver damage from chemotherapy, the full potential of *Silybum marianum* ought to be exploited by using silymarin as an adjunct treatment before and during administering the toxic agents.[30] The consequent reduction in side effects would enable full exploitation of chemotherapy regimes, otherwise hindered by dosage non-compliance and toxicity levels[27] as shown in the case of a 34-year old woman who was finally able to comply with treatment of promyelocytic leukemia after 4 months adjunct use of 800 mg silymarin.[31]

According to a study by Magliulo et al., silibinin significantly increases RNA, DNA and protein synthesis in experiments on hepatic injury in rats *in vivo* and *in vitro,* thus stimulating the regenerative ability of the liver.[32] However, protein synthesis, which is critical for structural integrity of damaged proteins and enzymes, was induced by silibinin only in injured livers: healthy livers were unaffected.[33] In a separate study, administration of silymarin was effective in shortening treatment times of acute viral hepatitis patients, showing improvement in serum levels of bilirubin, AST and ALT, the biomarkers of liver injury, while cases of chronic hepatitis experienced improved serum liver enzymes.[34] Dixit et al. shared the finding by Fehér et al.[35] that silymarin normalises serum liver enzyme and total bilirubin levels, thus improving liver tissue histology in patients with alcoholic liver disease. Of importance is the finding by Ferenci et al. that 420 mg per day, used long term, increased survival rates in liver cirrhosis patients.[36]

The three stages of *Amanita phalloides* (Death cap mushroom) poisoning occur over several days with no clinical symptoms in the first 6-12 hours, followed by painful abdominal cramping, vomiting, and possible profound dehydration from watery diarrhoea. The second stage, lasting over 2-3 days, is deceptive showing clinical improvement in spite of underlying hepatic and renal damage evidenced through laboratory tests. Left untreated, the condition could deteriorate in the final stage to fuminant hepatic failure and possibly death in 3-7 days.[37] Silymarin is used in North America and Europe mainly in animals as an antihepatotoxic herb against *Amanita phalloides* toxicity in preventing fatal haemorrhagic necrosis of the liver.[38] Furthermore, studies in mice have shown silymarin be 100% effective against amatoxin if administered within 10 minutes of ingestion and could, even if administered later but within 24 hours, prevent severe liver damage and possible death.[39]

Luper cited two cases of contemporary usage of silymarin in humans.[40] Firstly, 18 patients were treated with silymarin as late as 48 hours after ingesting an LD50 dose of *Amanita phalloides*, with the fatality of only one 'particularly high-dose suicide' patient.[41] Secondly, a 7-year old girl who went into a hepatic coma after extreme accidental poisoning survived as a result of high doses of G-penicillin and silymarin.[42]

Boigk asserted that silibinin is anti-fibrotic and inhibits the conversion of stellate hepatocytes into myofibroblasts. *In vivo* experiments in rats indicated that while 25 mg/kg/day silibinin proved ineffective, 50 mg/kg/day of silymarin for 6 weeks reduced hepatic fibrosis of biliary ducts that were completely occluded by 30% to 35%.[43] This demonstrates the importance of high dosages.

Favari et al. reviewed a study on rats with elevated levels of alkaline phosphatise and ALT induced by carbon tetrachloride. It is interesting to note that a 50 mg/kg combination of Colchicine and silymarin administered orally for 55 days fully prevented all alterations but alkaline phosphatise and

ALT remained unchanged and the glycogen content was not fully restored, and the collagen in the liver was reduced by only 55%. In the same experiment, the loss of glycogen was completely prevented in rats that were treated with silymarin alone.[44]

Franschini referred to the observations by Dehmlow et al. that *Silybum marianum's* anti-inflammatory activities include inhibiting neutrophil migration, inhibiting Kupffer cells, and significantly inhibiting leukotriene synthesis and formation of prostaglandins.[45]

Moreover, research by Katiyar et al. on nude mice subjected to UVB radiation showed the silymarin is anti-carcinogenic, reduces the incidence, multiplicity and volume of tumours, and protects against photocarcinogenesis.[46]

Of note was the finding by Krecman et al. that silymarin administered to rats with diet-induced hypercholesterolemia produced beneficial anticholesterolemic effects of increased LDL cholesterol clearance and raised HDL cholesterol levels.[47]

CAUTIONS

Silybum marianum is generally safe with only minor and infrequent side effects such as stomach upset or mild diarrhoea.[18]

Patients with type II diabetes and those on hypoglycaemic medications should exercise caution when using *Silybum marianum* and it should probably only be administered whilst under the care of a health professional. This is because *Silybum marianum* has the pharmacodynamic potential of reducing blood sugar levels.[48]

To avoid malabsorption of dietary iron, it is best to take *Silybum marianum* on an empty stomach with water rather than with a meal to prevent silybin from forming a complex with unchelated iron. This precautionary measure is to prevent a decrease in serum ferritin levels in the body.[49]

Ehrlich cautioned against concurrent use of medications metabolised by liver enzymes which *Silybum marianum* may also upregulate, such as:[8]

- Statins including lovastatin (Mevacor, Altocor)
- Alprazolam (Xanax), diazepam (Valium), and lorazepam (Ativan)
- Clopidogrel (Plavix) and warfarin (Coumadin)

However this should be balanced with the potential benefit on reducing hepatocellular adverse effects from some of these medications with concurrent use of *Silybum marianum*. Thus concurrent usage should only be recommended when the patient is under the care of a health professional.

Loguercio and Festi declared their one 'well-defined finding' to be the absence of significant adverse events even at high doses of silibinin and its compounds. Their univariate analysis found that even if no changes in liver tests or serum levels were observed, patients who consumed silybin experienced

lower incidence of symptoms and better quality of life compared to those who did not. Additionally, their multivariate analysis revealed positive outcomes in more than one aspect of quality of life.[50]

CONTRAINDICATIONS

Known allergy to plants from the Asteraceae species.[3]

DOSAGE

Typical adult dosages:

- Dry seeds – 12-15 g daily in divided doses[10]
- 1:1 Liquid extracts, 1:1 Glycetract - 30-60 mL per week[4]
- Flordis Legalon® *(MZ 80)* (*Silybum marianum* equivalent to 14.7 dry seed)[51]

  *(*Maintenance: 1 capsule 2 times a day)
- Tablets/capsules (equivalent to 14.7 g dry seed) - 1 tablet/capsule 2-3 times per day
  - MediHerb Silymarin[52]
  - Metagenics Silymarin Intensive Care[52]
  - Thompson's Milk Thistle (107 mg standardised extract, 84% flavonolignans 7,500 mg)[52]

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