

ST MARY'S THISTLE

Silybum marianum (L) Gaertn.

Family

Asteraceae or Compositae (the daisy or sunflower family). Synonyms include *Carduus marianus* L.¹

Parts Used

Seed.

Description

St Mary's thistle is a hardy and often invasive plant indigenous to the Mediterranean, North Africa and the Middle East whose achenes, often referred to as seeds or fruit, have been valued for their medicinal qualities. It is an annual or biennial plant which grows wild but can also be cultivated. The wild-growing species appear as biannual grassy plants with solitary composite flower heads, about

five centimetres in diameter, consisting of purple-red disc florets, whereas cultivated species behave as annuals and reach up to 1.5m in height. The flower heads of St Mary's thistle differ from other thistles by the presence of leathery bracts that are also tipped with stiff spines. The variegated green leaves, with deep lobed, spiny margins, are large and have white spots around the veins.

When broken the leaves and stems exude a milky sap. The black, shiny seeds are crowned with a white, silky pappus (an appendage) of fine bristles with feathery tufts, like those of dandelion seeds, but these are not used in the extract preparation.^{2,3}

Traditional Use

St Mary's thistle is a medicinal plant whose therapeutic history dates back 2000 years. Traditionally St Mary's thistle has been used to treat



a range of liver and gallbladder disorders including hepatitis, cirrhosis and jaundice, and to protect the liver against poisoning from chemical and environmental toxins, including snakebites, insect stings, mushroom poisoning and alcohol.⁴

Nearly every part of the plant, from root to hull, has been used in some way. Traditionally the seeds were made as an infusion or decoction. They have been roasted for use as a coffee substitute and also used as animal feed in pig, cattle and horses. In her famous book, *A Modern Herbal*, Maud Grieve explained several ways St Mary's thistle can be eaten including the heads like an artichoke, raw stalks (which are considered palatable and nutritious) and the leaves as a salad. It has various other common names such as milk thistle, blessed milk thistle, variegated thistle, sow thistle and Scotch thistle.⁵

The genus name, *Silybum*, derived from a Greek word *silybon* or *silybos* which means tassel or tuft, is attributed to Dioscorides, the first-century Greek physician who gave the name to a number of edible thistles. His use is one of the oldest known references of the medicinal use of this plant. He suggested preparing it in a tea 'for those that be bitten of serpents'. The specific species name *marianum* preserves the legend that the white mottling surrounding the venation of the leaves was a result of a single drop of the Virgin Mary's milk as it gently fell onto the leaf surface. This medicinal plant is traditionally used as a galactagogue (stimulating milk production), perhaps contributing to the word origins of the common name milk thistle along with the milky sap it exudes. In Traditional Chinese Medicine the seeds are known as Shui Fei Ji and they are considered bitter, warm and dry. They are used specifically to protect the liver, increase bile production and to protect against oxidative exposure, including oxidative exposure from radiation treatments. It is also commonly used in China to treat cirrhosis, gallbladder ailments and as an antioxidant and antiviral. In Ayurvedic medicine St Mary's thistle is used to enhance immunity, treat psoriasis and as a liver tonic.^{6,7}

First-century Roman writer, Pliny the Elder recommended a formulation of St Mary's thistle which involved the juice extract and honey for improving digestion by stimulating the flow of bile. The British herbalist Gerard referred to it as 'the best remedy that grows against all

melancholy diseases.' Melancholy, a term that is often equated with depression, derives its name from the Greek words 'black bile' and was treated historically with liver herbs, in addition to mood-enhancing plants. Culpepper, the famous British herbalist, recommended its use in the treatment of disorders affecting the liver and spleen, the kidneys in provoking the flow of urine, to break and expel stones and also to treat dropsy (oedema). In the United States St. Mary's thistle enjoyed popularity in the 19th century with the Eclectics movement, an officially recognised branch of North American medicine that predominantly used Native American herbs. The Eclectics used St Mary's thistle for varicose veins, menstrual difficulty and congestion of the liver, spleen and kidneys. A German physician from the 19th century, Johannes Gottfried Rademacher, developed a tincture made from St Mary's thistle seeds for his liver patients. Rademacher's Tincture is an ethanol extract from the seeds used for liver and spleen disorders.^{8,9}

A series of investigations into St Mary's thistle performed by German researchers in the 1960s led to flavonolignans (also flavanolignans or flavolignans) being isolated from the seeds. The term *silymarin*, a clever condensation of the plant's Latin binomial, was introduced originally in 1968 by the revered German phytochemist, Professor Hildebert Wagner, and his colleagues to describe the mixture of flavonolignans that had been characterised at the time (*silybin*, *isosilybin*, *silydianin* and *silychristin*). This discovery gave a strong impetus for research in many countries aimed at creating hepatoprotector preparations based on these extracts. This effort resulted in the appearance of drugs such as *legalon*, *carsil* and *silybor* which produced a unique hepatoprotector action.¹⁰

In the early 1990s several reports began to appear suggestive of St Mary's thistle as a potential cancer chemopreventive agent. A 1994 report demonstrating *silymarin*'s inhibition of tumour promotion *in vivo* is viewed widely as the catalyst for studying St Mary's thistle as a cancer preventative and potential treatment. Today St Mary's thistle extracts are now under intense study in the experimental therapeutics of cancer for chemoprevention, treatment and amelioration of chemotherapy side effects.^{11,12}

It is a popular treatment in Germany for numerous liver conditions including hepatitis and cirrhosis. Intravenous silybin has recently been studied for use as a supportive treatment of liver damage from *Amanita phalloides* (death cap) mushroom poisoning. For ethical and practical reasons there are no controlled clinical studies available for any amatoxin treatments but observational studies and case reports describe successful treatment with intravenous silybin. European healthcare practitioners prescribe St Mary's thistle for conditions that may not be as clearly related to liver health such as female hormonal problems, poor digestion, constipation and skin conditions such as acne and psoriasis. For many Europeans St Mary's thistle extract is viewed as a daily health insurance against environmental pollutants, over-the-counter drugs such as paracetamol and overindulgence in alcohol and rich foods.^{13,14}

Constituents

Often silymarin is referred to as the active constituent but in fact it is a complex of flavanolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin A, silychristin B and silydianin), a flavonoid taxifolin and a bioflavonoid quercetin. The principal component of silymarin is silybin (commonly referred to as silibinin) and is identified as a major biologically active component. The oil fraction contains linoleic, oleic and palmitic acids, sterols, tocopherol (vitamin E) and phospholipids. The oil from St Mary's thistle has been suggested as a novel raw material to produce biodiesel. Due to the poor water solubility of silymarin only a small fraction (<10%) of silymarin is released into an aqueous infusion. Solubility of silymarin in ethanol has been measured in one experiment as 350.1 mg/mL.

Despite the lower absorption and bioavailability of silymarin the author could not find any data to indicate whether maximum efficacy could be achieved with whole St Mary's thistle seeds which is comprised of other phytochemical groups that make up its complex natural environment. Studies on other plants have demonstrated that isolation of the 'most-active fraction' or single constituents from whole extracts may compromise the therapeutic efficacy.^{15,16,17,18,19,20,21,22}

As silybin is the main component of silymarin the literature mainly focuses on this compound ignoring all other components however the other flavanolignans in silymarin could contribute to, or even be responsible for, distinct beneficial effects of silymarin. For example only silybin B and taxifolin were found to stimulate an oestrogen responsive reporter plasmid construct in breast cancer cells *in vitro*. Silybin is a semipurified fraction once thought to be a single compound but now recognized as a 1:1 mixture of two diastereoisomers, silybin A and silybin B. Standardised or quantified extracts of St Mary's thistle often express the level of flavanolignans as 'calculated as silybin'. This leads to problems in reproducibility of scientific results as the exact composition of silymarin is often unknown and can vary to a certain degree depending on the processing, chemo-variety of the plant used and climatic conditions during the plant growth. There are studies dealing with the analytical separation and quantification of silymarin components as well as studies focused on silymarin content in clinically used drugs, in various plant parts, seasons, geographic locations etc. However, no comparison of detailed flavanolignan profiles in various silymarin preparations was available in 2017. Also, as a result of the focus on the flavanolignans, the oil fraction has been neglected. This means that precision in nomenclature is extremely important for interpretation of scientific studies with the use of precisely defined chemical mixtures being recommended in studies. The distinction between silymarin and silybin is not only important to understanding the historical literature but is essential to thorough characterisation and use of chemically defined mixtures in preclinical and clinical studies.^{23,24}

Having said this the terms St Mary's thistle, silymarin and silybin appear to be used interchangeably in the literature however they are not synonymous and each of these compounds has specific characteristics and actions with an intrinsic beneficial or toxic effects. In the last 10 years about 12000 papers have been published on these substances which are used as hepatoprotectants, antioxidants, chemopreventives and anticancer agents. Scientific interest in these molecules, or classes of molecules, is high worldwide. The cost of the use of silymarin reaches \$180 million in Germany

alone. Despite the wealth of literature no firm clinical evidence exists. This discrepancy is attributed to various factors such as quality of clinical trials, heterogeneity of diagnoses, lack of standardised preparations and frequently inconsistent dosing and outcome parameters. Part of this uncertainty is due to the lack of data on their pharmacokinetics and optimal dosing regimens. Because of the complexity of the absorption, metabolism and disposition nature of various flavonoids it is still unclear which form (i.e. the parent flavonoid or its metabolite(s)) contributes to the overall effects in the body. Although flavonoids are rapidly absorbed after oral ingestion their plasma concentrations are very low, whereas the phase II metabolites such as glucuronides, sulfates and methylated conjugates seem to be predominant in blood circulation. Extensive first-pass metabolism in the intestine and the liver are responsible for low oral bioavailabilities of flavonoids.^{25,26}

The common procedures used for silymarin extraction are based mainly on slow, high-temperature solvent-extraction methods (e.g. hexane, petroleum ether, methanol or acetone at 125°C). The drawbacks associated with these techniques have led to the search for new alternative extraction processes that additionally could improve silymarin extract quality. This is particularly important because the silymarin extracts could contain toxic organic residues that need to be removed to meet consumer acceptability. In the attempt to improve the process of silymarin extraction and make it more effective and environmentally friendly microwave-assisted solvent extraction, ultrasound-assisted solvent extraction, pressurized liquid extraction, enzyme-assisted extraction, supercritical fluid extraction and especially subcritical water extraction also known as pressurized hot water extraction methods have recently been developed and applied.^{27,28,29}

Actions

Hepatoprotective, hepatorestorative, choleric (stimulates bile flow from the liver), cholagogue (stimulates gallbladder contractions), chelates iron, antioxidant, anti-inflammatory, antifibrotic (inhibits or reduces the formation of excess fibrous connective tissue), hypoglycaemic, galactagogue

(appears to stimulate prolactin; possibly oestrogenic³⁰)

Pharmacological Activity

Whole plant St Mary's thistle studies are scarce so a selection of recent studies with emphasis on ethanolic extracts, and isolated constituents, will be reviewed here. As stated above the vast majority of clinical studies on St Mary's thistle have employed the concentrated, standardised extract. Because certain standardised extracts, such as St Mary's thistle extract with 80% silymarin, have been proven through funded research to be effective against liver poisons and toxins, this does not mean that the whole non-standardised herb may not have equally beneficial properties. In fact there are traditional uses for St Mary's thistle seeds, such as for enlarged spleen, menstrual irregularities and varicose veins, for which the standardised extract is not as suitable.³¹

Therefore, for the purposes of this monograph, extrapolating silymarin data to the use of the galenical liquid extract based on dosage considerations is reasonable provided that the raw material meets British Pharmacopoeia specifications that it contains at least 25mg of flavanolignans as silymarin per mg.³²

Hepatoprotective, Antioxidant and Anti-inflammatory Activity

The term hepatoprotective agent is based on data in experimental animals showing that pretreatment with silybin prevents or mitigates hepatic injury by toxins (i.e., ethanol, galactosamine, phalloidin and CCl₄) or progression of fibrosis. Translation of these observations to human disease is difficult; except for a few case reports, there is no evidence that silybin can prevent liver disease induced by drugs or chemicals. Possibly the largest experience is the prevention of death cup (*Amanita phalloides*) intoxication by intravenous silybin. Silybin is a specific antidote of amanitin.

The effect in mushroom poisoning is, in part, explained by the stimulation of nucleolar polymerase A, which increases ribosomal protein synthesis and inhibits lipid peroxidation. Again, no controlled data is available. In conclusion, silybin is a pharmacological active compound with many properties that have

the potential to improve liver diseases of various causes. Unfortunately, well controlled prospective studies are missing to document its clinical efficacy. Furthermore, the limited bioavailability of oral silymarin limits its use in medicine.³³

Silybin increases antioxidant concentrations and improves outcomes in hepatic diseases resulting from oxidant injury. Silybin treatment has been associated with protection against hepatic toxins and also has resulted in decreased hepatic inflammation and fibrosis.³⁴

A randomised, double-blind, placebo-controlled trial, in three teaching hospitals in New South Wales, Australia, of 118 chronic hepatitis C participants showed that treatment with silymarin (720mg silybin per day) and 12 vitamin and phytochemical based antioxidants achieved a higher rate of alanine aminotransferase (ALT, a liver enzyme) normalisation compared to placebo or silymarin at week 24 of 12 months (six months of active treatment or placebo with six months follow up).

There was also a significant improvement in overall mental wellbeing in the active treatment group. Oxidative stress is one of the key mechanisms by which liver injury occurs in hepatitis C. The Hep573 study hypothesised that the use of antioxidant compounds would reduce the oxidative stress, hepatic necroinflammation (loss of blood supply plus inflammation) and fibrosis resulting from chronic hepatitis C infection.³⁵

A phase III, double-blind clinical trial assessing the effects of silybin, plus phosphatidylcholine, on patients with nonalcoholic fatty liver disease showed positive outcomes over the 12 month treatment program. Patients were given a product comprised of 94mg silymarin, 194mg phosphatidylcholine and 89.28mg vitamin E acetate 50%. Treatment with the silybin product for 12 months was associated with improvement in liver enzymes, insulin resistance and liver histology, without increases in body weight. It was suspected that the herb's antioxidant activity is chiefly responsible for the beneficial effects observed.³⁶

A recent review assessing the beneficial and harmful effects of St Mary's thistle, or its constituents, versus placebo or no intervention, in patients with alcoholic liver disease and/or hepatitis B and/or C liver diseases found that liver-related mortality was

significantly reduced by St Mary's thistle in all trials but not in high-quality trials.³⁷

Silybin may be a potential agent in the treatment of osteoarthritis. A 2017 study aimed to assess the effects of silybin on osteoarthritis both *in vitro* and *in vivo*. The results showed that silybin significantly inhibited the interleukin-1 β -induced inflammatory response. It has been known that excess production of the inflammatory cytokines play vital roles in the development of osteoarthritis. Among these cytokines, interleukin-1 β has been shown to play a pivotal role in osteoarthritis as it contributes to cartilage matrix degradation which results in decreased synthesis of collagen and proteoglycan during the pathogenesis of the disease.³⁸

A recent study demonstrated that an ethanol extract of St Mary's thistle has potent hepatoprotective and *in vivo* and *in vitro* antioxidant effects. The hepatoprotective effect of the seeds may be due to the decreased liver enzyme levels with significant improvement to the histological picture of liver.

The activity of antioxidant enzymes are significantly increased *in vivo*. Inhibition of reaction reactive rate by St Mary's thistle extract *in vitro* confirms that it is a potent free radical scavenger.³⁹

The flavanolignans of St Mary's thistle have demonstrated antioxidant activity and protection against drug-induced liver damage in clinical studies. The antioxidant activity was shown for example, in patients with cirrhosis or alcoholic liver damage by the increase in superoxide dismutase activity of lymphocytes and erythrocytes, and the increase in patient serum levels of glutathione and glutathione peroxidase. Silymarin (280 or 420mg/day) was prescribed. Antioxidant activity was also demonstrated in granulocytes taken from healthy volunteers who had taken 240mg of silybin. Silymarin (240mg/day) also improved liver function in patients with liver disease caused by exposure to toxic levels of toluene or xylene.⁴⁰

The efficacy of silymarin in preventing drug-induced liver damage in patients taking psychotropic drugs long-term has been investigated and silymarin was found to reduce damage to the liver caused by lipid peroxidation in patients taking butyrophenones or phenothiazines. In a double-blind, placebo-controlled study 60 patients were treated for 90 days with silymarin (800mg/d) or placebo.⁴¹

A study in 2010 found that eight major compounds that comprise St Mary's thistle, including seven flavonolignans silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin and one flavonoid, taxifolin, are inhibitors of HCV RNA-dependent RNA polymerase, suggesting potential in treating liver damage related to Hepatitis C.⁴²

St Mary's thistle can slow down aging of the skin because of its radical-inhibiting activity. A 2012 *in vivo* study was designed to formulate and evaluate the antiaging effects of a topical cream (water in oil emulsion) containing St Mary's thistle.⁴³

Research with an animal model of asthma showed that pretreatment with silybin prevented the development of airway hyperresponsiveness, significantly inhibited airway inflammatory cell recruitment and peribronchiolar inflammation and reduced the production of various cytokines in bronchoalveolar fluid.⁴⁴

Chelating Activity

St Mary's thistle interacts with iron in a number of ways. Excess iron increases oxidative stress and St Mary's thistle exerts antioxidant activity thereby decreasing the pathological consequences of excessive oxidative stress.⁴⁵

Oral administration of silybin (100mg/kg/day, administered as silybin- β -cyclodextrin complex) protected against iron-induced hepatic toxicity in rats. Simultaneous treatment with silybin reduced oxidative damage and lipid peroxidation. It also reduced the hepatic function impairment. In addition to the prominent antioxidant activity of silybin this protective effect may be due to its strong ability to chelate iron.⁴⁶

Scientists found that silybin strongly binds ferric ion (Fe(III)) even at acidic pH. The complex of this molecule with iron demonstrated remarkable stability. The results showed the possible role of silybin in relation to the chelation therapy of chronic iron overload.⁴⁷

In lead and cadmium poisoning the structural and histochemical hepatic changes were significantly prevented by silymarin.⁴⁸

Silybin acts indirectly to reduce iron-induced damage by protecting mechanisms, such as the expression of hepcidin, that regulates iron uptake

and by potentially directly chelating iron to reduce its absorption, making it a useful adjunct in the treatment of haemochromatosis.^{49,50}

Protection of liver cells by silymarin, and its components, has been demonstrated against a number of substances *in vitro* or *in vivo* including carbon tetrachloride-induced liver cirrhosis, ethanol, paracetamol-induced liver peroxidation, cyclosporine, phenothiazine, butyrophenone, erythromycin, emitriptyline and nortriptyline, oestradiol, *Amanita phalloides*, tacrine, iron overload and induced lung cancer.⁵¹

Antifibrotic Activity

Oral silymarin reduced steatohepatitis (a type of fatty liver disease characterised by inflammation of the liver with concurrent fat accumulation in liver), raised nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), and reduced tumour necrosis factor (TNF)- α mRNA expression in the liver in insulin-resistant rats, suggesting its antifibrotic effect is achieved through anti-inflammatory, antioxidant and hepatoprotective effects.⁵²

Cancer Prevention and Treatment Activity

Based on the results of preclinical studies St Mary's thistle, or silymarin, could be beneficial in oncology patients especially for the treatment of the side effects of anticancer chemotherapeutics. Evidence from clinical studies shows that it has mainly beneficial effects in hepatotoxicity and radiotherapy-induced skin and mucosa damage at dosages of 160 to 600mg daily. The aim of a 2017 review was to provide comprehensive information on the potential therapeutic effects of St Mary's thistle in oncology patients and potential indications for its use as a supportive therapy either as an anticarcinogenic agent or as an agent that attenuates the side effects of oncological treatments. The findings were supported mainly by *in vitro* studies and the results of animal research, but the number of clinical trials in oncology patients is increasing.⁵³

In the past two decades silybin has demonstrated remarkable anticancer as well as cancer chemopreventive efficacy in preclinical cell culture and animal models of several cancer models

including skin, breast, lung, bladder, colon, prostate, lung and kidney carcinomas.⁵⁴

A randomised, double-blind, placebo-controlled study of 37 men, two to three months after radical prostatectomy were randomised to receive 570mg of silymarin and 240mcg selenium or placebo daily for six months. The combination of silymarin and selenium significantly reduced two markers of lipid metabolism associated with prostate cancer progression, LDL and total cholesterol which suggests that silymarin and selenium may be effective in reducing prostate cancer progression.⁵⁵

A 2010 randomised double-blind placebo controlled study of 50 children found that silybin was associated with a trend towards reduced liver damage in children receiving chemotherapy. Each capsule contained 240mg of St Mary's thistle, standardized to 80mg of silybin (silybin A and B). The target dose of silybin was 5.1mg/kg/day. Given the capsule sizes and wide range in body weight of study participants, the following dose ranges were prescribed: 15 to 20kg = 80mg/day; 21 to 40kg = 160mg/day; 41 to 60kg = 40mg/day; 61 to 70kg = 320mg/day.⁵⁶

Silymarin's potential as a unique hepatoprotective agent was demonstrated in a case of hepatotoxicity in a patient undergoing reinduction therapy for acute myelogenous leukemia. The patient had transaminitis (too many enzymes in the liver) presumed secondary to chemotherapy which did not resolve with supportive care but was shown to respond to silymarin at 280mg twice daily. The patient had an immediate decrease in liver function tests and showed decreased elevation in levels upon treatment with subsequent chemotherapy regimens.⁵⁷

Cholesterol Reducing Activity

A seven month open clinical trial involving 14 subjects with type 2 hyperlipidaemia found that treatment with silymarin (420mg/day) slightly reduced total cholesterol and HDL cholesterol levels.⁵⁸

Cholesterol reduction has been demonstrated for silymarin in studies of rats fed a high cholesterol diet.⁵⁹

Nephroprotective and Antidiabetic Activity

St Mary's thistle is regarded as a potent agent against insulin resistance and diabetes-induced hyperglycaemia.⁶⁰

A randomised, controlled study consisted of a sample of 60 patients with type 2 diabetes. The patients were on maximum doses of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least six months. A dose of 140mg of silymarin three times a day led to a 50% reduction in urinary albumin excretion, urinary TNF α levels, and urinary and serum MDA levels in almost half of the patients in the treatment group.⁶¹

In a sample of 25 patients, treated for four months with 200mg silymarin three times a day before meals, there was a significant reduction in blood glucose levels, compared to an increase in the placebo-treated group. This confirms previous hypotheses from *in vivo* studies that silymarin reduces blood glucose levels via mechanisms that are independent of insulin production. Also, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, AST, and ALT levels were significantly reduced.⁶²

Hydroethanolic extracts of St Mary's thistle seed and leaves, and silymarin, reduce induced nephrotoxicity *in vivo* via their antioxidant and anti-inflammatory actions.⁶³

Antiepileptic Activity

A 2016 *in vivo* experiment concluded that the antiepileptic activity of St Mary's thistle seeds was due to its antioxidant property. The study evaluated the antiepileptic potential of an ethanolic extract of St Mary's thistle (100, 200 and 300mg/kg). St Mary's thistle (300mg/kg) provided significant protection against induced convulsions (seizure intensity, latency and lethality) comparable with the reference drug (valproic acid). The 300mg/kg/day dose was also effective in preventing oxidative stress causing a significant decrease in the lipid peroxidation and increased superoxide dismutase and catalase activity of mice brains when compared to the induced untreated group.⁶⁴

Antifungal Activity

St Mary's thistle possesses notable antifungal effects *in vitro* particularly with regard to preventing the growth of dermatophyte fungi (three types of fungus that commonly causes skin disease in animals and humans. These anamorphic (asexual or imperfect fungi) genera are: Microsporum, Epidermophyton and Trichophyton).⁶⁵

Brain and Neuroprotective Activity

Some preliminary research has suggested that St Mary's thistle may be as effective as the common medication fluoxetine in the treatment of obsessive-compulsive disorder. In this pilot double-blind and randomised trial 35 patients were randomly assigned to receive either a capsule of the St Mary's extract extract (600mg/day) or fluoxetine (30mg/day) for eight weeks.⁶⁶

According to an *in vitro* study silybin may have potential as both a preventive and an active treatment for Alzheimer's disease as it reduced the formation of amyloid plaque and also protected cells from amyloid plaque-induced oxidative stress in a dose-dependent manner.⁶⁷

Indications

- Liver disease including toxic liver damage, chronic liver diseases, alcoholic liver disease, acute viral hepatitis, hepatitis C infection
- Preventing gallstones, gallbladder support
- Hypercholesterolemia (high cholesterol)
- Chemotherapy support, exposure to conventional drugs and chemical pollutants
- Digestive disorders, dyspepsia, hangover
- Skin conditions involving liver dysfunction
- To support breast milk production during breast feeding

Energetics

Bitter, warm and dry.

Use in Pregnancy

No known restrictions.

Contraindications

Contraindicated in individuals with an allergy to the Asteraceae or Compositae (daisy) family.

Drug Interactions

Caution with risperidone (antipsychotic agent), sirolimus (selective immune-suppressing drug) and tamoxifen (hormonal therapy used to treat breast cancer). Monitor with metronidazole (antibiotic). The combination may be beneficial with doxorubicin and cisplatin (chemotherapy medications) and hepatotoxic substances.

Administration and Dosage

Liquid Extract: 1:1

Alcohol: 45%

Weekly Dosage: 20 to 80mL

High doses are required for serious liver disease. For chronic conditions St Mary's thistle must be taken over an extended period for efficacy. An oral form standardised to contain 70 to 80 percent silymarin appears to be safe for up to 41 months of use. Most clinical trials have used daily dosages of 420 to 480mg silymarin, divided into two or three doses daily. All clinical trials conducted in the past have demonstrated safety and efficacy of silymarin at doses of 1,200 to 1,500mg/day. The typical oral adult dose of silymarin is 240 to 800mg/day in two or three divided doses. To obtain a midpoint of 500mg of silymarin from a 1:1 herbal extract, assuming 1mL of herbal extract contains 25mg of silymarin, then 20mL/day of the St Mary's thistle extract is required.^{69,70,71}

References

1. The Plant List. [Internet]. Kew and Missouri: Royal Botanic Gardens, Kew and Missouri Botanical Gardens; c2013 Version 1.1 [cited 2018 January 3] Available from <http://www.theplantlist.org/tpl1.1/record/gcc-114114>
2. Bijak M. Silybin, a Major Bioactive Component of Milk Thistle (*Silybum marianum* L. Gaertn.)-Chemistry, Bioavailability, and Metabolism. *Molecules*. 2017 Nov 10;22(11). pii: E1942. doi: 10.3390/molecules22111942.
3. Ramadan SI, Shalaby MA, Afifi N, El Banna H. Hepatoprotective and Antioxidant Effects of *Silybum marianum* Plant in Rats. *IJAVMS*. 2011;5: 541- 547. 10.5455/ijavms.12230.
4. Alemardan A, Karkanis A, Saheli R. Breeding Objectives and Selection Criteria for Milk Thistle [*Silybum marianum* (L.) Gaertn.] Improvement. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, [S.I.]. 2013;41(2):340-347, dec. 2013. ISSN 1842-4309. Available at: <<http://www.notulaebotanicae.ro/index.php/nbha/article/view/9298>>. Date accessed: 12 jan. 2018. doi:<http://dx.doi.org/10.15835/nbha4129298>.
5. Ramadan SI, Shalaby MA, Afifi N, El Banna H. Hepatoprotective and Antioxidant Effects of *Silybum marianum* Plant in Rats. *IJAVMS*. 2011;5: 541- 547. 10.5455/ijavms.12230.
6. Milk Thistle.[Internet] White Rabbit Institute of Healing. c2018 [Accessed Jan 18 2018] Available from <https://www.whiterabbitinstituteofhealing.com/herbs/milk-thistle/>
7. Mulrow, C. Milk Thistle: Effects on Liver Disease and Cirrhosis and Clinical Adverse Effects. *AHRQ Publication* 2000 Oct;No. 01-E025.
8. Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res*. 2010 Oct;24(10):1423-32. doi: 10.1002/ptr.3207.
9. Ross SM. Milk thistle (*Silybum marianum*): an ancient botanical medicine for modern times. *Holist Nurs Pract*. 2008 Sep-Oct;22(5):299-300. doi: 10.1097/01.HNP.0000334924.77174.6d.
10. Kurkin, V.A. Saint-Mary thistle: A source of medicinals. *Pharm. Chem. J*. 2003, 37, 189-202.
11. Agarwal R, Katiyar SK, Lundgren DW, Mukhtar H. Inhibitory effect of silymarin, an anti-hepatotoxic flavonoid, on 12-O-tetradecanoylphorbol-13-acetate-induced epidermal ornithine decarboxylase activity and mRNA in SENCAR mice. *Carcinogenesis*. 1994 Jun;15(6):1099-103.
12. Lahiri-Chatterjee M, Katiyar SK, Mohan RR, Agarwal R. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. *Cancer Res*. 1999 Feb 1;59(3):622-32.
13. Ross SM. Milk thistle (*Silybum marianum*): an ancient botanical medicine for modern times. *Holist Nurs Pract*. 2008 Sep-Oct;22(5):299-300. doi: 10.1097/01.HNP.0000334924.77174.6d.
14. Mengs U, Pohl RT, Mitchell T. Legalon® SIL: the antidote of choice in patients with acute hepatotoxicity from amatoxin poisoning. *Curr Pharm Biotechnol*. 2012 Aug;13(10):1964-70.
15. Yang C, Gundala SR, Mukkavilli R, Vangala S, Reid MD, Aneja R. Synergistic interactions among flavonoids and acetogenins in *Graviola* (*Annona muricata*) leaves confer protection against prostate cancer. *Carcinogenesis*. 2015 Jun;36(6):656-65. doi: 10.1093/carcin/bgv046. Epub 2015 Apr 11.
16. Karna P, Chagani S, Gundala SR, Rida PC, Asif G, Sharma V, et al. Benefits of whole ginger extract in prostate cancer. *Br J Nutr*. 2012 Feb;107(4):473-84. doi: 10.1017/S0007114511003308. Epub 2011 Aug 18.
17. Braun L, Cohen M. *Essential Herbs and Natural Supplements*. Chatswood:Elsevier. 2017. p. 860
18. Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease: A meta-analysis (PRISMA) of randomized control trials. *Medicine* (Baltimore). 2017 Dec;96(49):e9061. doi: 10.1097/MD.00000000000009061.
19. Milk Thistle: Clinical Overview. The ABC Clinical Guide to Herbs.2003. Available from cms.herbalgram.org/ABCGuide/GuidePDFs/Milk_Thistle.pdf
20. Woo JS, Kim TS, Park JH, Chi SC. Formulation and biopharmaceutical evaluation of silymarin using SMEDDS. *Arch Pharm Res*. 2007 Jan;30(1):82-9.
21. Javed S, Kohli K, Ali M. Reassessing bioavailability of silymarin. *Altern Med Rev*. 2011 Sep;16(3):239-49.
22. Fadhil AB, Ahmed KM, Dheyab MM. *Silybum marianum* L. seed oil: A novel feedstock for biodiesel production. *Arabian Journal of Chemistry*. 2017;10:S683-S690
23. Chambers CS, Holečková V, Petrásková L, Biedermann D, Valentová K, Buchta M, et al. The silymarin composition... and why does it matter??? *Food Res Int*. 2017 Oct;100(Pt 3):339-353. doi: 10.1016/j.foodres.2017.07.017. Epub 2017 Jul 12.
24. Kroll DJ, Shaw HS, Oberlies NH. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies. *Integr Cancer Ther*. 2007 Jun;6(2):110-9.
25. Ferenci, P. Silymarin in the treatment of liver diseases: What is the clinical evidence?. *Clinical Liver Disease*.2016;7: 8-10. 10.1002/cld.522.
26. Loguercio C, Festi D. Silybin and the liver: From basic research to clinical practice. *World Journal of Gastroenterology : WJG*. 2011;17(18):2288-2301. doi:10.3748/wjg.v17.i18.2288.
27. Wianowska D, Gil M. Silymarin Extraction From *Silybum marianum* L. Gaertner. *Water Extraction of Bioactive Compounds*.2017;385-397. 10.1016/B978-0-12-809380-1.00015-2.
28. Wianowska D, Wiśniewski M. Simplified procedure of silymarin extraction from *Silybum marianum* L. Gaertner. *J Chromatogr Sci*. 2015 Feb;53(2):366-72. doi: 10.1093/chromsci/bmu049. Epub 2014 Jun 3.
29. Jadwiga A, Martinelli T, Sadowska, K. *Silybum marianum*: Non-medical exploitation of the species. *Annals of Applied Biology*. 2015;167. . 10.1111/aab.12232.
30. Foong SC, Tan ML, Marasco LA, Ho JJ, Foong WC. Oral galactagogues for increasing breast-milk production in mothers of non-hospitalised term infants (Protocol). *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD011505. DOI: 10.1002/14651858.CD011505.
31. Tierra M. Standardized herbal extracts: An herbalist's perspective.
32. Bone K. *A Clinical Guide to Blending Liquid Herbs*. Missouri:Elsevier. 2003 p.327
33. Ferenci, P. Silymarin in the treatment of liver diseases: What is the clinical evidence?. *Clinical Liver Disease*.2016;7: 8-10. 10.1002/cld.522.
34. Hackett ES, Twedt DC, Gustafson DL. Milk thistle and its derivative compounds: a review of opportunities for treatment of liver disease. *J Vet Intern Med*. 2013 Jan-Feb;27(1):10-6. doi: 10.1111/jvim.12002. Epub 2012 Nov 9.
35. Salmond SJ, George J, Strasser S, Byth K, Batey R. Hep573 study—a randomised double-blind placebo-controlled trial of silymarin alone or combined with antioxidants in chronic hepatitis C. *Proceedings of Digestive Diseases Week, AASLD*. 2010 Gastroenterology New Orleans, LA
36. Loguercio C, Andreone P, Brisc C, Brisc MC, Bugianesi E, Chiamonte M, et al. Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *Free Radic Biol Med*. 2012 May 1;52(9):1658-65. doi: 10.1016/j.freeradbiomed.2012.02.008. Epub 2012 Feb 15.
37. Rambaldi A, Jacobs BP, Iaquinto G, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases--a systematic cochrane hepato-biliary group review with meta-analyses of randomized clinical trials. *Am J Gastroenterol*. 2005 Nov;100(11):2583-91.

38. Zheng W, Feng Z, Lou Y, Chen C, Zhang C, Tao Z. Silibinin protects against osteoarthritis through inhibiting the inflammatory response and cartilage matrix degradation *in vitro* and *in vivo*. *Oncotarget*. 2017 Aug 24;8(59):99649-99665. doi: 10.18632/oncotarget.20587. eCollection 2017 Nov 21.
39. Ramadan SI, Shalaby MA, Afifi N, El Banna H. Hepatoprotective and Antioxidant Effects of *Silybum marianum* Plant in Rats. *IJAVMS*. 2011;5: 541- 547. 10.5455/ijavms.12230.
40. Wellington K, Jarvis B. Silymarin: a review of its clinical properties in the management of hepatic disorders. *BioDrugs*. 2001;15(7):465-89.
41. Palasciano G, Portincasa P, Palmieri V, Ciani D, Vendemiale G, Altomare E. The effect of silymarin on plasma levels of malon-dialdehyde in patients receiving long-term treatment with psychotropic drugs. *Current Therapeutic Research*. 1994;55(5):537-545, ISSN 0011-393X, [https://doi.org/10.1016/S0011-393X\(05\)80184-5](https://doi.org/10.1016/S0011-393X(05)80184-5). <http://www.sciencedirect.com/science/article/pii/S0011393X05801845>
42. Polyak SJ, Morishima C, Lohmann V, Pal S, Lee DY, Liu Y, et al. Identification of hepatoprotective flavonolignans from silymarin. *Proc Natl Acad Sci U S A*. 2010 Mar 30;107(13):5995-9. doi: 10.1073/pnas.0914009107. Epub 2010 Mar 15.
43. Rasul A, Akhtar N. Anti-aging potential of a cream containing milk thistle extract: Formulation and *in vivo* evaluation. *African Journal of Biotechnology*. 2012 11:1509-1515
44. Choi YH, Jin GY, Guo HS, Piao HM, Li LC, Li GZ, et al. Silibinin attenuates allergic airway inflammation in mice. *Biochem Biophys Res Commun*. 2012 Oct 26;427(3):450-5. doi: 10.1016/j.bbrc.2012.07.112. Epub 2012 Jul 27.
45. Braun L, Cohen M. *Essential Herbs and Natural Supplements*. Chatswood:Elsevier. 2017. p. 861
46. Pietrangelo A, Borella F, Casalgrandi G, Montosi G, Ceccarelli D, Gallesi D, et al. Antioxidant activity of silybin *in vivo* during long-term iron overload in rats. *Gastroenterology*. 1995 Dec;109(6):1941-9.
47. Borsari M, Gabbi C, Ghelfi F, Grandi R, Saladini M, Severi S, et al. Silybin, a new iron-chelating agent. *J Inorg Biochem*. 2001 Jun;85(2-3):123-9.
48. Barbarino F, Neumann E, Deaciuc I, Ghelberg NW, Suciu A, Cotuțiu C, et al. Effect of silymarin on experimental liver lesions. *Med Interne*. 1981 Oct-Dec;19(4):347-57.
49. Hutchinson C, Bomford A, Geissler CA. The iron-chelating potential of silybin in patients with hereditary haemochromatosis. *Eur J Clin Nutr*. 2010 Oct;64(10):1239-41. doi: 10.1038/ejcn.2010.136. Epub 2010 Jul 14.
50. Choi J. Oxidative stress, endogenous antioxidants, alcohol, and hepatitis C: pathogenic interactions and therapeutic considerations. *Free Radic Biol Med*. 2012 Apr 1;52(7):1135-50. doi: 10.1016/j.freeradbiomed.2012.01.008. Epub 2012 Jan 25.
51. Braun L, Cohen M. *Essential Herbs and Natural Supplements*. Chatswood:Elsevier. 2017. p. 861
52. Kim M, Yang SG, Kim JM, Lee JW, Kim YS, Lee JI. Silymarin suppresses hepatic stellate cell activation in a dietary rat model of non-alcoholic steatohepatitis: analysis of isolated hepatic stellate cells. *Int J Mol Med*. 2012 Sep;30(3):473-9. doi: 10.3892/ijmm.2012.1029. Epub 2012 Jun 14.
53. Frassová Z, Rudá-Kučerová J. [Milk Thistle (*Silybum marianum*) as a Supportive Phytotherapeutic Agent in Oncology]. [Article in Czech] *Klin Onkol*. 2017 Winter;30(6):426-432. doi: 10.14735/amko2017426.
54. Braun L, Cohen M. *Essential Herbs and Natural Supplements*. Chatswood:Elsevier. 2017. p. 871
55. Vidlar A, Vostalova J, Ulrichova J, Student V, Krajicek M, Vrbkova J, et al. The safety and efficacy of a silymarin and selenium combination in men after radical prostatectomy - a six month placebo-controlled double-blind clinical trial. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010 Sep;154(3):239-44.
56. Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, et al. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). *Cancer*. 2010 Jan 15;116(2):506-13. doi: 10.1002/cncr.24723.
57. McBride A, Augustin KM, Nobbe J, Westervelt P. *Silybum marianum* (milk thistle) in the management and prevention of hepatotoxicity in a patient undergoing reinduction therapy for acute myelogenous leukemia. 2012 Sep;18(3):360-5. doi: 10.1177/1078155212438252. Epub 2012 Feb 29.
58. Somogyi A, Ecsedi GG, Blázovics A, Miskolczi K, Gergely P, Fehér J. Short term treatment of type II hyperlipoproteinaemia with silymarin. *Acta Med Hung*. 1989;46(4):289-95.
59. Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and *Silybum marianum* extracts prevent liver damage. *Food Chem Toxicol*. 2010 Mar;48(3):803-6. doi: 10.1016/j.fct.2009.12.011. Epub 2009 Dec 23.
60. Kazazis CE, Evangelopoulos AA, Kollas A, Vallianou NG. The therapeutic potential of milk thistle in diabetes. *Rev Diabet Stud*. 2014 Summer;11(2):167-74. doi: 10.1900/RDS.2014.11.167. Epub 2014 Aug 10.
61. Fallahzadeh MK, Dormanesh B, Sagheb MM, Roozbeh J, Vessal G, Pakfetrat M, et al. Effect of addition of silymarin to renin-angiotensin system inhibitors on proteinuria in type 2 diabetic patients with overt nephropathy: a randomized, double-blind, placebo-controlled trial. *Am J Kidney Dis*. 2012 Dec;60(6):896-903. doi: 10.1053/j.ajkd.2012.06.005. Epub 2012 Jul 7.
62. Huseini HF, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, Toliati T, et al. The efficacy of *Silybum marianum* (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res*. 2006 Dec;20(12):1036-9.
63. Ahmed OM, Mahmoud AM, Abou Zid SF, Saber NY. Silymarin and Hydroethanolic Extracts of *Silybum marianum* Leaves and Fruits Attenuate Diethylnitrosamine/Phenobarbital-Induced Nephrotoxicity via Their Antioxidant and Anti-Inflammatory Actions. *American Journal of Biochemistry*. 2016;6(2):21-29. doi: 10.5923/j.ajb.20160602.01.
64. Waqar H, Khan HM, Anjum AA. Antiepileptic potential of *Silybum marianum* seeds in pentylenetetrazol-induced kindled mice. *Bangladesh Journal of Pharmacology*. 2016;11(3).
65. Salehi M, Hasanloo T, Mehrabian S, Farahmand S. Effects of *Silybum marianum* (L.) Gaertn seeds extract on dermatophytes and saprophytes fungi *in vitro* compare to clotrimazol. *Pharmaceutical Sciences*. 2011;16:203-210.
66. Sayyah M, Boostani H, Pakseresh S, Malayeri A. Comparison of *Silybum marianum* (L.) Gaertn. with fluoxetine in the treatment of Obsessive-Compulsive Disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010 Mar 17;34(2):362-5. doi: 10.1016/j.pnpbp.2009.12.016. Epub 2009 Dec 24.
67. Yin F, Liu J, Ji X, Wang Y, Zidichouski J, Zhang J. Neurochem Silibinin: a novel inhibitor of Aβ aggregation. *Int J*. 2011 Feb;58(3):399-403. doi: 10.1016/j.neuint.2010.12.017. Epub 2010 Dec 24.
68. Gurley BJ, Fifer EK, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. *Planta Med*. 2012 Sep;78(13):1490-514. doi: 10.1055/s-0031-1298331. Epub 2012 May 7.
69. Javed S, Kohli K, Ali M. Reassessing bioavailability of silymarin. *Altern Med Rev*. 2011 Sep;16(3):239-49.
70. Braun L, Cohen M. *Essential Herbs and Natural Supplements*. Chatswood:Elsevier. 2017. p. 873
71. Rainone F. Milk thistle. *Am Fam Physician*. 2005 Oct 1;72(7):1285-8.