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Milk thistle (Silybum marianum)

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Milk thistle (*Silybum marianum*)

Abstract and key points

Milk thistle herbal products are made from seeds of *Silybum marianum*. Milk thistle has a long history of medicinal use. It is widely used to treat digestive and liver disorders. Claims in relation to cancer are that milk thistle prevents cancer initiation, reduces cancer development, reduces adverse effects of chemotherapy and radiotherapy, and supports the action of some anticancer drugs.

- Milk thistle herbal preparations are produced from the seeds of *Silybum marianum* (L.) Gaertn.
- Several potential uses of milk thistle in cancer are supported only by pre-clinical evidence
- Milk thistle is generally considered safe

While numerous animal and in vitro models support these claims, they are not supported by data from clinical studies. Only one randomised pilot study is available which is merely showing a trend towards a reduction of hepatic toxicity.

Milk thistle is generally well tolerated and appears safe.

In summary, currently there is insufficient clinical evidence to support or refute the claims for milk thistle in relation to cancer management.

What is it?

Description

Milk thistle (*Silybum marianum* (L.) Gaertn.) synonym *Carduus Marianus* L. is a herbaceous plant belonging to the carduae tribe of the Asteraceae (daisy) family. The seeds are the part used [1](#).

Names

Milk thistle has many common names including lady's thistle, St Mary's thistle, holy thistle, and variegated artichoke [1,2](#). Examples of available products containing silymarin include Legalon SIL® and Thisilyn™:

dried seed extracts standardized to 80% silymarin content. Siliphos™ and Silipide™ are silymarin extracts complexed with lipids. Leviaderm™ is a cream, containing silymarin amongst other herbal ingredients [2](#).

Ingredients / Components

The main effects of milk thistle are thought to stem from the flavonolignans combined with other ingredients [2,3](#). A crude extract of dried seeds of milk thistle contains 65 – 80% of a flavonolignan complex termed silymarin [4](#). Silymarin itself is a complex of at least seven flavonolignans (silybin A and B, isosilybin A and B, silychristin, isosilychristin and silydianin) and the flavonoid taxifolin. Silybin A and B, isosilybin A and B are isomers. Silybin, synonymous with silibin and silybinin, is the processed form of silymarin and contains the isomers silybin A and B in equal amounts. Silybin is considered the main active ingredient of the milk thistle [4,5,6](#). The seeds also contain fatty acids such as linoleic acid.

Application and dosage

Milk thistle is taken orally as tablets, tea or tincture [2,7](#). It may also be applied topically as cream. Injectable preparations have been used in research studies and are available in German speaking countries (Legalon SIL®). Various oral dosages have been used, generally relating to use for hepatoprotection, in the range 12-15g milk thistle [2,8](#) containing 200 - 600 mg silymarin/ day in divided doses. Silymarin is only poorly water-soluble: bio-availability has been increased by lipid formulation of silybinin in oral form such as silybinin phosphatidylcholine (Siliphos™ and Silipide™). In a phase II study the daily dosage of Siliphos™ was 13g silybinin divided up into 3 doses. These high dosages are used for achieving high plasma levels [3,9](#). Silybinin and silymarin have a short half-life (1.8 – 5 hours) after ingestion. The major part of orally taken silybinin is found as glucuronosised and sulfatated metabolites in blood following hepatic metabolism [10](#). It is not clear whether these metabolites also have anti-carcinogenic properties [3](#).

History and providers

Milk thistle originates from North Africa, Asia Minor and southern Europe. It is now widely naturalized across Europe, Africa, the Americas and Australasia, as a weed and cultivated plant [1](#). Milk thistle is so called because of the white markings (variegation) on the leaves, which have been consumed as a vegetable. Roasted seeds have been used as a coffee substitute [2](#). The mature untreated seeds of milk thistle have been used for 2000 years in traditional medicine to treat melancholy, headache, digestive and liver complaints, detoxification and promote lactation [2,7,8,11](#). In the 1960s the ingredients of milk thistle were investigated. The mixture found was named silymarin [4,12](#). Research concentrated primarily on the use of milk thistle in the treatment of liver disorders and protection from liver injury [2,5](#). In the 1990s reports based on pre-clinical models suggested preventative, and therapeutic, potential in cancer warranted further research [4,13-15](#).

Claims of efficacy/ alleged indications

The main claim made for milk thistle is that it protects the liver [2,8](#). Milk thistle fruits have a positive

European Scientific Cooperative on Phytotherapy (ESCOP) monograph for the following therapeutic indications: toxic liver damage; supportive treatment in patients with chronic inflammatory liver conditions and hepatic cirrhosis [9](#). Orally, milk thistle is used for liver disorders including toxic liver damage caused by chemicals, *Amanita phalloides* mushroom poisoning, jaundice, chronic inflammatory liver disease, hepatic cirrhosis, chronic hepatitis, gallbladder complaints, hangover and indigestion [2,8,12](#). It has also been used in prostate cancer, pleurisy, malaria, depression, uterine complaints, allergic rhinitis, stimulating breast milk and menstrual flow [2,8,17](#). Intravenously, milk thistle is used as a supportive treatment for *Amanita phalloides* (death cap) mushroom poisoning [2,8](#). In cancer the claims are that milk thistle can be protective by inhibiting tumour development, and supportive in ameliorating adverse treatment effects as well as enhancing chemotherapeutic effect [14,15](#). These claims rest on presumed and acknowledged effects of milk thistle extracts in pre-clinical trials and case reports [16,18-20](#).

Mechanism(s) of action

The precise mechanism of action is unclear with silymarin considered a multi-functional, multi-target drug [17](#). Several mechanisms are thought to contribute to therapeutic effect in liver disease [2](#). Silymarin reduces hepatocyte membrane permeability to toxins [2,8](#). Antifibrotic action has been demonstrated by silybin in an in vitro model of human hepatic fibrogenesis [5](#). Silymarin demonstrates antioxidant and anti-inflammatory effects in several animal cell models [2,5](#). Silybinin is thought to have anti-cancer properties in different tumour types via e.g. apoptotic, tumour growth modulating, anti-carcinogenic, anti-inflammatory, anti-metastatic and anti-angiogenic mechanisms [3,5](#). The presumed modes of action are varied and include enhancement of pro-apoptotic molecules (e.g. caspases), enhancement of growth inhibitory proteins, presumed interaction with tumour necrosis factor (TNF), and inhibition of cell proliferation via a number of pathways including inhibition of various protein kinases (e.g. mitogen activated protein kinase MAPK), and inhibition of anti-apoptotic signalling [3,5,20](#).

In animal experiments and in vitro studies, anti-carcinogenic effects were seen for skin cancer, breast cancer, lung cancer, colon cancer, urinary bladder cancer, prostate cancer, ovarian cancer, leukaemia and cervical cancer [3,16,20](#). In in-vitro studies a synergistic action with different chemotherapeutic agents has been seen [3,21,22](#).

Prevalence of use

Milk thistle use has been reported in between 2% [23](#) and 7% [24,25](#) of cancer sufferers.

Legal issues

Milk thistle products are widely available in pharmacies, health food and grocery stores and on the Internet. In the US, milk thistle is included in the United States Pharmacopoeia-National Formulary. It is available as a “dietary supplement” under the Dietary Supplement Health and Education act 1994 [2,8,12](#). In the UK it is available as a registered traditional medicine under the Traditional Herbal Medicines Directive [26](#). Silymarin extracts have drug status in several countries. Milk thistle is covered by a Commission E

monograph [27](#), an ESCOP monograph [9](#) and the European Medicines Agency has a community monograph in preparation [28](#).

Cost(s) and expenditures

On the Internet prices for milk thistle tablets can vary from £8-40 for 90 capsules. A month's dose of 7-12 g milk thistle seed containing 400-600 mg silymarin a day could cost £28 in the UK or 32 Euros: in mainland Europe silymarin extracts are more expensive.

Does it work?

Systematic reviews, meta-analyses

Systematic reviews of the effectiveness of milk thistle have been published but are limited to its use in the treatment of liver disorders, and on pharmacokinetics [17,29](#).

Narrative reviews

A narrative review of milk thistle published in 2007 summarises clinical trials on pharmacokinetics, liver diseases and cancer: the studies are included below under either clinical trials or safety if they were investigating pharmacokinetics [30](#).

Clinical trials

In a randomised double blind placebo controlled trial of fifty children with acute lymphoblastic leukaemia (ALL) with hepatic toxicity, receiving chemotherapy, oral milk thistle administration, at 5.1mg/kg/day for 28 days was reported to result in a trend towards a reduction of hepatic toxicity at 56 days: (liver enzymes aspartate transaminase (AST) were significantly reduced, with alanine transaminase (ALT) showing a trend towards reduction) [31](#). In this multi-centred pilot trial, groups were well matched and all participants accounted for. The placebo was indistinguishable from milk thistle in appearance and odour.

Small trials using combination products including milk thistle have produced contradictory results on PSA levels in prostate cancer patients [32,33](#). One study investigated a combination cream including milk thistle as an adjunct to radiotherapy [34](#). Because these trials were of combination products, it is not possible to evaluate milk thistle's individual action in these trials.

No studies were found investigating the effect of the chemo-preventive properties of milk thistle extract on humans.

Despite great scientific interest in the chemo-preventive and therapeutic actions of milk thistle extract in oncology, the number of clinical trials is very small. Currently the clinical evidence supporting milk thistle's use in cancer is scant.

Pre-clinical studies

In animal experiments and in vitro studies an anti-carcinogenic effect was seen for skin cancer, breast cancer, lung cancer, colon cancer, urinary bladder cancer, prostate cancer, ovarian cancer, leukaemia and cervical cancer [3,20](#). In in-vitro studies a synergistic action with different chemotherapeutic agents has been seen [3,21,22](#). Tests of in vitro effects of silibin on the chemotherapeutic agents vincristine and L-asparaginase on an experimental acute lymphoblastic leukaemia cell line showed no inhibition of their chemotherapeutic effects at low concentrations and a synergistic effect at higher concentrations with vincristine but not L-asparaginase [31](#). In an animal experiment with nude mice exposed to UV-B rays topical cutaneous application of silymarin was investigated in skin carcinogenesis. A reduction in skin cancer incidence was seen [20](#).

Is it safe?

Adverse events

Orally milk thistle is usually well-tolerated [2,3,30](#). The rate of adverse events of milk thistle was low in clinical trials and in one randomized controlled trial equal to the placebo group [9-11,31-36](#). Described adverse effects were difficult to distinguish from symptoms of the underlying condition. In rare cases there were complaints of intestinal symptoms, headache and dizziness [2,10,31,33](#). In a phase I trial in which high doses of silybin phytosome (up to 20g) were given mild transient elevation of bilirubin, and the liver enzymes aspartate transaminase and alanine transaminase (AST and ALT) were reported [37](#). One participant receiving high dose silybin phytosome who subsequently had surgery developed a thrombo-embolism: this could have been due to the surgery [10](#).

Contraindications

Milk thistle has been assessed as likely safe when used orally and appropriately [2](#). There is insufficient information to assess safety in pregnancy and lactation [2](#).

Interactions

Milk thistle extract might work as an inhibitor of CYP2C9 [2,6,36](#). There is contradictory evidence about the effect of milk thistle on CYP3A4 [2,29,35](#). A phase II clinical trial of 600mg silymarin in cancer patients found no in vivo effect on irinotecan, CYP3A4 or UGT1A1 pharmacokinetics [35](#).

Warnings

In an animal experiment and in an experiment with an oestrogen responsive breast cancer cell line (MCF-7) a tumour growth was seen when adding silymarin [3](#). This raises the theoretical risk silymarin could have an oestrogen-like action in women with oestrogen-responsive breast cancer. However the more commonly used

milk thistle seed extracts are not known to have oestrogenic effects in vivo [2.8](#). Cautions have been recommended in patients with a known hypersensitivity to plants in the Asteraceae family [2.8,12](#).

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