St Mary's Thistle:

Research & Clinical Indications Beyond Liver Support

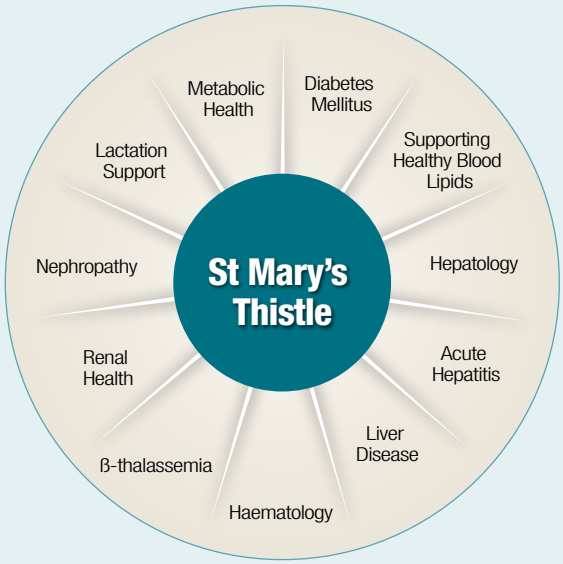
Silybum marianum, or St Mary's Thistle has a long history of traditional use and is still one of the most widely prescribed herbs for conditions associated with the liver, gallbladder and digestive system.[1] The primary active constituents in St Mary's Thistle are the flavanolignans, collectively known as silymarin.[2] These include silybin, (isosilybin A and B), silychristin (silychristin A and B), and silydianin. Silybin, or silibinin is thought to be the most biologically active flavinolignan, and accounts for approximately 50-70% of total silymarin.[2]

Pharmacological studies on the active constituents silymarin and silybin have demonstrated hepato-protective, antioxidant, anti-inflammatory, hepatorestorative and antifibrotic actions.[3] These constituents are also thought to be responsible for St Mary's Thistle's galactogoue actions.[3] Figure 1 outlines the therapeutic roles and functions of St Mary's Thistle as well as the proposed mechanism of action.

Figure 1: The vast roles and functions of silymarin

Function	Proposed Mechanism of Action
Supports cell regeneration[1,4]	Silymarin has been shown to stimulate nuclear polymerase A. This results in increased ribosomal protein synthesis and subsequently formation of hepatocytes and other cells.[1,4]
Assists detoxification processes[5,6]	St Mary's Thistle is thought to enhance phase II glucuronidation and regulate intracellular glutathione production in the liver.[5,6] Its ability to inhibit betaglucuronidase prevents hydrolysis of glucuronides into toxic metabolites in the liver and intestines.[7]
Maintains normal healthy gallbladder function and supports healthy digestion[2,1]	St Mary's Thistle's choleretic action supports liver, gallbladder and digestive function. St Mary's Thistle is thought to increase the solubility of bile.[2,1]
Reduces inflammation[2]	Silymarin inhibits the production and release of inflammatory mediators, tumour necrosis factor (TNF) and TNF-α, nitrous oxide, interleukin-1 and interleukin-6, lipooxygenase, cyclooxygenase and prostaglandin synthesis.[2]
Provides protection for hepatocytes[7]	St Mary's Thistle has been shown to influence hepatocyte cell membranes, acting as a stabiliser and permeability regulator to prevent hepatotoxic agents from entering cells.[7]
Reduces oxidative damage[7]	Silymarin scavengers free radicals and inhibits tumour necrosis factor and lipid peroxidation.[7] It is thought to increase the redox state and total glutathione levels of the liver and intestines.[2]

Figure 2: The broad clinical scope of St Mary's Thistle



For supporting research in relation to the indications above see Figure 4.

Figure 3: Key considerations when selecting a high quality St Mary's Thistle extract[8,9]

- **SUSTAINABILITY:** Ensure the extract has been produced from a St Mary's Thistle grown sustainably in optimal geographic regions
- **HARVESTING:** Choose an extract produced from St Mary's Thistle dried soon after harvest which protects vital active constituents from changing or degrading
- **INDEPENDENTLY TESTED:** Select an extract that has very low levels of heavy metals, aflatoxins and pesticide residue, and one that has been independently tested and authenticated in an Australian TGA approved laboratory
- **REFERENCE STANDARD:** Ensure that the extract references stringent and highly regarded pharmacopoeias
- **STANDARDISATION:** Select a standardised extract containing a consistent level of silymarin or silybin, which ensures consistent therapeutic activity from batch to batch, and also ensures that dose aligns with the current available research and clinically trialled dosages

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*** Silybin or silibinin is the primary and most biologically active silymarin constituent.[2]**
Levels of silybin can vary significantly, making up between 50-70% of total silymarin.[2,7] This variation can be dependent on geographical source, as well as harvesting and processing methods.[7] Selecting standardised extracts of St Mary's Thistle ensures a consistent level of active constituent from batch to batch.[10]

Current research on St Mary's Thistle demonstrates positive and promising results. However as with many medicinal herbs, whilst empirical use is strong, large scale, high-quality human clinical trials are currently limited. This is due to a variety of challenges and study limitations, such as; sample size, lack of herbal standardisation, uniformity of population treated, inconsistent outcome measures, variability in dosages used and ethical issues. The studies included in this literature review highlight some of St Mary's Thistle therapeutic benefits when used alone or in conjunction with pharmaceutical medications; in conditions ranging from hepatology, metabolic health and haematology, through to renal health and lactation.

Figure 4: Research based insights into the clinical use of St Mary's Thistle

CONDITION	DOSE AND DURATION	RESULTS	STUDY DESIGN
HEPATOLOGY			
The antioxidant and anti-inflammatory actions of silymarin, along with its ability to act as a cell membrane stabiliser, are the likely mechanisms behind its therapeutic benefit in liver disease.[11] *In vitro* studies of silybin show a dose dependent inhibitory effect on HMG-CoA reductase activity, which may explain its therapeutic role in supporting healthy blood lipid levels.[2,12] The following studies demonstrate the ability of silymarin to significantly reduce signs and symptoms common in acute hepatitis, reduce serum alanine aminotransferase (ALT) and aspartate transaminase (AST) levels in patients suffering alcohol induced acute and subacute liver disease, and reduce biliary cholesterol concentration and saturation index in patients with gallbladder disease.[11-13]			
Acute Hepatitis[11] • **Hepatitis A** • **Hepatitis B** • **Hepatitis C** • **Hepatitis E** • **Epstein-Barr Virus** • **Cytomegalovirus**	• Arm 1 – 38 subjects, 140mg silymarin three times daily • Arm 2 – 36 subjects, placebo multivitamin and mineral compound (combined with an inactive dilutant, so that three capsules contained no more than RDA) • Duration – eight weeks	Over an eight week period, treatment with silymarin showed a significantly faster resolution in signs and symptoms of acute hepatitis. Arm 1 showed a significantly faster resolution of impaired biliary excretion compared to arm 2. This was measured through markers including dark urine, jaundice, and scleral icterus. There was also a significant reduction in indirect/unconjugated bilirubin in arm 1. Furthermore, arm 1 had a significantly faster resolution of symptoms such as fatigue, malaise, and anorexia compared with arm 2.	Double-blind, randomised, placebo-controlled trial
Patients with Alcohol Induced Mild Acute and Subacute Liver Disease[13]	• Arm 1 – 47 subjects, 420mg silymarin per day • Arm 2 – 50 subjects, placebo daily • Duration – 4 weeks • Sample – diagnosed on the basis of increased transaminase levels	Following four weeks of treatment, arm 1 had a significantly greater mean percentage decrease in ALT, and AST when compared to arm 2. There was also a greater tendency towards normalisation in bromsulphalein retention, following the bromsulphalein test, an obsolete test for liver function, when compared to arm 2. No side effects were recorded in any of the subjects in arm 1.	Randomised, double-blind clinical trial
Biliary Cholesterol Saturation in Patients with Radiolucent Gallstones or Post Cholecystectomy[12]	• Arm 1 – 4 subjects with gallstones, 420mg silymarin daily • Arm 2 – 6 subjects with cholecystectomies, 420mg silymarin daily • Arm 3 – 9 subjects with cholecystectomies, placebo daily • Duration – 30 days	Following 30 days of treatment arm 1 and 2 showed a significant decrease in biliary cholesterol concentration which resulted in a decrease in biliary saturation index, when compared to baseline measurements. Changes in biliary cholesterol concentration and biliary saturation index were not statistically significant in arm 3.	Placebo-controlled clinical trial

SGOT: Serum glutamic oxaloacetic transaminase (SGOT), is now referred to as aspartate aminotransferase (AST).[14] It is defined as an enzyme involved in the transamination of amino acids.[14] Measuring AST is often used to assist in the diagnosis of acute myocardial infarction and acute liver conditions.[14]

SGPT: Serum glutamic pyruvic transaminase (SGPT) is now referred to as alanine aminotransferase (ALT).[14] It is also defined as an enzyme involved in the transamination of amino acids.[14] Measuring ALT is often used to assist in the study and diagnosis of acute liver disease.[14]

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CONDITION	DOSE AND DURATION	RESULTS	STUDY DESIGN
METABOLIC HEALTH			
Reactive oxygen species and oxidative stress are a major cause and contributor of insulin resistance.[15] Although the mechanisms underlying St Mary's Thistle's effect on glucose homeostasis are unclear, it is thought that the powerful antioxidant properties of silymarin may reduce oxidative stress and therefore have a positive effect on metabolic abnormalities.[15] *In vitro* studies with St Mary's Thistle have demonstrated reduced glycolysis through inhibitory actions on pyruvate kinase activity and oxidative phosphorylation, as well as reduced metabolic flow-driven reactive oxygen species.[4,15] The following studies demonstrate the many benefits of silymarin for metabolic health, and as an adjuvant in the treatment of type II diabetes to reduce biomarkers of glucose control, blood lipid markers, serum glutamic oxaloacetic (SGOT), serum glutamic pyruvic transaminase (SGPT), oxidative stress markers, and body mass index (BMI).[15-18]			
Type II Diabetes[15]	• Arm 1 – 25 subjects, 200mg silymarin three times daily before meals • Arm 2 – 26 subjects, placebo three times daily before meals • All subjects in both arms took conventional hypoglycaemic medication (Metformin or Glibenclamide) • Duration – 4 months • Sample – aged 40-65 years, diagnosed over 2 years prior	Silymarin therapy in combination with oral hypoglycaemics significantly improved glycaemic and lipid profiles in patients with type II diabetes. After four months of treatment, arm 1 showed a significant reduction in average fasting blood glucose, glycosylated haemoglobin (HbA1c), total cholesterol, low density lipoproteins (LDLs), triglycerides, SGOT, and SGPT when compared to baseline and arm 2. A slight, however non-significant reduction in weight and systolic and diastolic blood pressure was also observed in arm 1.	Randomised, double-blind placebo-controlled clinical trial
Type II Diabetes[16]	• Arm 1 – 18 subjects, 200mg daily silymarin • Arm 2 – 20 subjects, placebo • Arm 3 – 21 subjects, control • All subjects in all arms took 10mg/day Glibenclamide • Duration – 120 days • Sample – aged 35-58 years, diagnosed at least 5 years prior	Silymarin in combination with Glibenclamide therapy significantly improved glycaemic control in patients with type II diabetes. Following 120 days of treatment, arm 1 demonstrated a significant reduction in fasting and postprandial plasma glucose, HbA1c, and BMI when compared with baseline levels and in comparison to arm 2 and 3.	Multi-centre, randomised, double-blind, placebo controlled study
Cirrhotic Patients with Secondary Diabetes[17]	• Arm 1 – 30 subjects, 200mg silymarin in granular preparation dissolved in water three times daily • Arm 2 – 30 subjects, no treatment • Arm 3 – 30 healthy control subjects, no treatment • Both arm 1 and 2 receiving insulin only, for 5 years prior at a stable dose for 2 years prior • Duration – 6 months • Sample – aged 45-70 years	Following six months of treatment, silymarin demonstrated significant improvements in glucose homoeostasis and markers of lipid peroxidation. Arm 1 showed a significant decrease in mean fasting blood glucose, mean daily blood glucose, mean daily glucosuria, HbA1c, mean daily insulin requirements, fasting insulineamia, blood malondialdehyde and basal and glucogon – stimulated C-peptide when compared with baseline measurements and arm 2. Improved glycaemic control was not associated with an increase in hypoglycaemic episodes.	Randomised, controlled clinical trial
Insulin Treated Type II Diabetic Patients with Alcoholic Liver Cirrhosis[18]	• Arm 1 – 30 subjects, 600mg silymarin daily • Arm 2 – 30 subjects, no treatment • Duration – 12 months • Sample – aged 45-70 years	Silymarin was shown to significantly improve glucose homeostasis and markers of oxidative damage. Subjects in arm 1 showed a progressive and statistically significant reduction in fasting blood glucose levels, and mean daily blood glucose values compared to baseline measurements and arm 2. These results were noted after just six months and continued to improve throughout the duration of the study. A significant reduction was also seen in total daily glucosuria, fasting insulin values, C-peptide, malondialdehyde levels, SGOT and SGPT values in arm 1 compared to baseline measurements and arm 2. HbA1c also showed a significant improvement at all six evaluation time points compared to baseline and arm 2.	Randomised, open, controlled, long-term study

CONDITION	DOSE AND DURATION	RESULTS	STUDY DESIGN
HAEMATOLOGY			
Silybin has iron chelating properties and has been proven efficient at reducing the iron burden associated with ß-thalassemia.[19,20] Silymarin protects against free radical damage, stimulates intracellular glutathione production and promotes the synthesis of ribosomal RNA, leading to hepatocellular regeneration.[1,4] These are thought to be the mechanisms by which St Mary's Thistle protects the liver from oxidative damage associated with iron overload in ß-thalassemia.[20] Silymarin in combination with Desferrioxamine, a common chelating medication has been shown to be more effective than Desferrioxamine alone.[19,20] It is thought that the small hydrophobic, low molecular weight of the flavonolignans which comprise silymarin may increase the iron chelating effect of Desferrioxamine through an iron mobilising shuttle effect.[19] The following studies demonstrate silymarin's therapeutic potential as an adjuvant in the treatment of haematological disorders such as ß-thalassemia.[19,20]			
ß-Thalassemia Major[19]	• Arm 1 – 48 subjects, 140mg silymarin three times daily in addition to Desferrioxamine therapy • Arm 2 – 49 subjects, placebo daily in addition to Desferrioxamine therapy • Duration – 9 months • Sample – no significant differences in clinical parameters except for ferritin which was significantly higher in arm 1	Following a nine month period, silymarin in combination with Desferrioxamine improved iron homeostasis in comparison with Desferrioxamine treatment alone. Results reveal that serum ferritin levels decreased significantly from baseline in arm 1. The fall in serum ferritin in arm 1 was seen in 65%, 77% and 75% of subjects, after 3, 6 and 9 months of treatment respectively. There were also significant falls in serum iron and total iron-binding capacity (TIBC) levels in arm 1. At completion of the trial, arm 1 showed a statistically significant decrease in serum hepsidin and soluble transferrin receptor (sTfR) compared to baseline values. Arm 1 also showed a significant decrease in serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine transaminase (ALT) in comparison to arm 2.	Randomised, double-blind, placebo-controlled clinical trial
Homozygous ß-Thalassemia Major[20]	• Arm 1 – 29 subjects, 140mg silymarin three times daily • Arm 2 – 30 subjects, placebo daily • Both arms taking Desferrioxamine at a mean dose of 40-50mg/kg per infusion over 8-12 hours, 5-6 days per week • Duration – 3 months	Combined Desferrioxamine and silymarin therapy was demonstrated more effective at reducing serum ferritin than Desferrioxamine therapy alone. Following nine months of treatment, arm 1 showed a significant decrease in serum ferritin compared to baseline measurements. Significant improvements in alkaline phosphatase (ALP) and red blood cell glutathione levels were also demonstrated in arm 1 in comparison to baseline values and arm 2.	Randomised, double-blind placebo-controlled trial
RENAL HEALTH			
Oxidative stress and inflammation are major factors contributing to nephropathy.[21] Silymarin is thought to be protective of renal cells by reducing oxidative stress and inflammation, as well as increasing renal cell proliferation.[21] The following studies demonstrate the benefits of silymarin in supporting patients with nephropathy.[21,22]			
Overt Nephropathy and Macroalbuminuria in Type II Diabetes[22]	• Arm 1 – 28 subjects, 140mg silymarin three times daily • Arm 2 – 28 subjects, placebo three times daily • All subjects in both arms were also receiving the maximum dosage of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), treatment with oral hyperglycaemic agents or insulin, and hypercholesterolaemia medications at a stable dose for a minimum of six months • All subjects diagnosed with diabetic retinopathy • Duration – 3 months • Sample – aged 30-70 years	Silymarin administration resulted in a significant reduction in markers of proteinuria and inflammation in type II diabetics with proteinuria. Following three months of treatment, mean urinary albumin-creatine ratio (UACR) levels, serum and urinary tumor necrosis factor alpha (TNF-α) and urinary transforming growth factor beta (TGFß) levels decreased in both arms. However decrement of both mean UACR and urinary TNF-α was significantly greater in arm 1. The mean urinary malondialdehyde (MDA) also showed a significant reduction in arm 1 in comparison to arm 2 which showed an increase. Mean serum TGFß in arm 1 showed a decrease in comparison to an increase in arm 2.	Randomised, double-blind, placebo-controlled, two-arm parallel-group, phase II clinical trial

CONDITION	DOSE AND DURATION	RESULTS	STUDY DESIGN
RENAL HEALTH			
Haemodialysis Patients with Type II Diabetes[21]	• Arm 1 – 20 subjects, 140mg silymarin three times daily • Arm 2 – 20 subjects, 400IU vitamin E daily • Arm 3 – 20 subjects, 140mg silymarin three times daily and 400IU vitamin E daily • Arm 4 – 20 subjects, control group, receiving no treatment • Duration – three weeks	Silymarin in combination with vitamin E demonstrated a significant improvement in markers of lipid peroxidation and endogenous antioxidants in haemodialysis patients. Mean values of red blood cell glutathione peroxidase were significantly higher in arm 1, 2 and 3 after three weeks in comparison to arm 4. The effect was most significant in arm 3. A significant reduction in malondialdehyde (MDA), a marker of lipid peroxidation was noted after three weeks in arm 3 when compared with arm 4. Although not significant, arm 1 and 2 also demonstrated a reduction in MDA after 3 weeks. Haemoglobin was significantly increased in arms 1, 2 and 3 after three weeks.	Randomised-controlled clinical trial
LACTATION			
St Mary's Thistle has been traditionally used as a galactogogue.[2] Although very few studies have explored this therapeutic action, the following randomised placebo controlled clinical trial demonstrates the benefit of silymarin in increasing daily breast milk production in lactating mothers with border line normal daily milk production.[23]			
Healthy Lactating Mothers[23]	• Arm 1 – 25 subjects, 420mg silymarin daily • Arm 2 – 25 subjects, placebo daily • Duration – 63 days • Sample – mothers with borderline normal milk production, 9 month old babies	Following 63 days of treatment arm 1 showed an 85.94% increase in daily breast milk production in comparison to arm 2 which had a 32.09% increase. Analysis of biochemical parameters of the breast milk such as water, fats, carbohydrates and proteins did not change from baseline measurements in both arm 1 and 2. No drop outs or adverse reactions were reported in either arm.	Randomised, placebo-controlled clinical trial
St Mary's Thistle has been used traditionally as a galactogogue and according to many herbal texts is considered safe and compatible with breastfeeding with no adverse effects expected.[2,24,25] The galactogogue effects of St Mary's Thistle are thought to be secondary to an increase in prolactin levels, which has been demonstrated in animal studies.[23] Although limited, the current available research has indicated that silymarin components are not excreted into the breast milk in measurable quantities.[26] As St Mary's Thistle is generally thought to be poorly absorbed, it is unlikely to adversely affect breastfed infants.[26]			

St Mary's Thistle drug interactions and considerations:

It is often advised to prescribe certain supplements at least two hours away from pharmaceutical medicines, in order to avoid any potential interactions. Herb-drug interactions are a common consideration for practitioners, especially when combining herbs with drugs that have a narrow therapeutic window.[24] The current level of evidence on herb-drug safety and interactions with *Silybum marianum* appears to be somewhat limited and inconclusive. *In vitro* studies have shown that *Silybum marianum* has the potential to inhibit cytochrome P450 enzymes, decrease glucuronidation enzymes, in particular uridine diphosphoglucuronyl transferase (UGT) 1A isozymes, and may also affect p-glycoproteins; however many *in vivo* human clinical studies have failed to demonstrate these potential interactions.[27] Consideration and care must be taken when prescribing St Mary's Thistle alongside any pharmaceutical medication, as co-administration may lead to reduced clearance, increased efficacy, reduced exposure, or increased adverse reactions.[27] Interestingly, research has discovered the benefit of St Mary's Thistle in combination with some medications, notably tacrine and deferoxamine.[27] Figure 5 outlines the currently known or suspected herb-drug interactions.

Figure 5: St Mary's Thistle drug interactions – potential benefits and cautions[27]

DRUG CLASS	DRUG	INTERACTION	CLINICAL IMPLICATION/ PRESCRIBING RECOMMENDATION
POTENTIALLY BENEFICIAL			
Cholinesterase inhibitors	Tacrine (eg. Cognex)	Co-administration of tacrine and St Mary's Thistle at 420mg/day, has been demonstrated as potentially beneficial in a single, large multi-centre study in patients with Alzheimer's.[28] The results of this study indicate a potential benefit in reducing the rate of gastrointestinal and cholinergic side effects without any impact on cognitive status.[28]	An interaction between St Mary's Thistle and tacrine is unlikely, and based on the current evidence concomitant use is likely to be beneficial.[27]
Detoxifying agent/antidotes	Deferoxamine (eg. Desferrioxamine, Desferal)	*In vitro* studies have shown that the active components of St Mary's Thistle may be effective iron chelators.[27] A double-blind, randomised controlled trial in patients with beta-thalassaemia major, studied the effects of Silymarin 140mg three times daily in combination with conventional iron chelation therapy (Desferrioxamine) on serum ferritin. Silymarin in combination with Desferrioxamine demonstrated a significant reduction in serum ferritin from baseline in comparison to Desferrioxamine treatment alone.[20]	Combined treatment of Desferrioxamine and silymarin is potentially beneficial, as this combination has been shown to improve clinical outcomes for patients suffering ß-thalassemia major.[27]

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DRUG CLASS	DRUG	INTERACTION	CLINICAL IMPLICATION/ PRESCRIBING RECOMMENDATION
UNLIKELY INTERACTION			
Hyperacidity, reflux, ulcers	Ranitidine (eg. Zantac)	A crossover pharmacokinetic study in healthy individuals found that 140mg of silymarin did not interact with 150mg ranitidine.[27] There was no difference in the peak or total ranitidine exposure in those treated with silymarin compared to those treated with ranitidine alone.[27]	Although an interaction is unlikely, it is advised to monitor the patient closely for signs of increased adverse reactions or reduced drug clearance when used concomitantly.[27]
Hypolipidaemic	Rosuvastatin (eg. Crestor)	A small single parallel group pharmacokinetic study investigated the possible interaction associated with the co-administration of silymarin, 140mg three times daily and rosuvastatin, 10mg daily in healthy individuals.[29] The study found no significant difference in rosuvastatin pharmacokinetics with rosuvastatin and silymarin compared to rosuvastatin alone.[29]	There appears to be no clinically significant interaction associated with the co-administration of silymarin and rosuvastatin. Although an interaction is unlikely, it is advised to monitor the patient closely when taken concomitantly.[27]
Antihypertensive agents	Nifedipine (eg. Adalat CC, Procardia)	A small crossover pharmacokinetic study found that supplementation with 280mg of silymarin twice daily in addition to 10mg of nifedipine once daily, led to a small change in drug blood concentrations, however such changes are unlikely to be clinically significant.[30]	There appears to be no clinically significant interaction associated with the co-administration of silybin and nifedipine. Although an interaction is unlikely, it is advised to monitor the patient closely when used concomitantly.[27]
CAUTION			
Antibiotic cytotoxics	Daunorubicin (eg. Cerubidine)	*In vitro* studies have suggested that *Silybum marianum* may increase tumour cell sensitivity to chemotherapy toxicity or may affect P-glycoprotein activity, and therefore result in intracellular build-up of chemotherapy drug.[27,31]	Caution is advised when prescribing *Silybum marianum* alongside daunorbicin as current evidence to support its safety has not yet been fully established. Patients need to be strictly monitored for drug efficacy and adverse reactions as a negative interaction could be clinically very serious.[27]
	Doxorubinicin (eg. Adriamycin)	*In vitro* studies have suggested that *Silybum marianum* may increase tumour cell sensitivity to chemotherapy toxicity or may affect P-glycoprotein activity, and therefore result in intracellular build-up of chemotherapy drug.[27]	Caution is advised when prescribing *Silybum marianum* alongside doxorubinicin as current evidence to support its safety has not yet been fully established. Patients should be monitored very closely with co-administration as a negative interaction could be clinically very serious.[27]
Antiviral agents	Darunavir (eg. Prezista), Ritonavir (eg. Norvir)	An open-label, fixed sequence study explored the potential interactions of silymarin 150mg three times daily with darunavir/ritonavir 600/100mg twice daily for two weeks in patients with HIV.[32] Results demonstrated co-administration led to a slight and non-significant decrease in darunavir/ ritonavir exposure.[32]	Caution is advised when prescribing *Silybum marianum* alongside darunavir/ritonavir. If used concomitantly it is advised to monitor the patient closely for reduced drug efficacy.[27]
	Indinavir (eg. Crixivan)	Clinical trials in healthy volunteers have demonstrated no effect of *Silybum marianum* on the pharmacokinetics of indivir 480-1350mg/day, however further trials in patients are needed to assess risk of interaction.	Caution is advised when prescribing *Silybum marianum* alongside indinavir. If used concomitantly it is advised to monitor the patient very closely for signs of increased adverse reactions or reduced drug efficacy. A negative interaction may be potentially very serious.[27]
Antineoplastic agents	Cisplatin (eg. Platinol)	There are currently no *in vivo* or clinical studies that investigate co-administration of *Silybum marianum* and cisplatin.[27] *In vitro* studies have suggested that *Silybum marianum* may increase tumour cell sensitivity to chemotherapy toxicity or may affect P-glycoprotein activity and therefore result in intracellular build-up of chemotherapy drug.	Caution is advised when prescribing *Silybum marianum* alongside cisplatin. If used concomitantly, patients need to be strictly monitored for drug efficacy and adverse reactions as a negative interaction could be clinically very serious.[27]
	Irinotecan (eg. Camptosar)	Studies in cancer patients have demonstrated that *Silybum marianum* 160mg silymarin three times daily did not have an effect on the pharmacokinetics of irinotecan (infusion 125mg/m^2 for 90mins) after four and twelve days.[33]	Caution is advised when prescribing *Silybum marianum* alongside irinotecan, due to differences in dose, and bioavailability of *Silybum marianum*, preparations and administration duration. If used concomitantly it is advised to monitor the patient for signs of increased adverse reactions or reduced drug clearance.[27]
Vinca Alkaloid	Vinblastine	Currently there are no human clinical studies on interactions between *Silybum marianum* and vinblastine, however *in vitro* evidence has indicated a potential affect on P-glycoprotein activity which may affect disposition *in vivo*.[27,34]	Caution is advised when prescribing *Silybum marianum* alongside vinblastine. If *Silybum marianum* is prescribed concomitantly patients should be strictly monitored for drug efficacy and adverse drug reactions as negative interactions are clinically serious.[27]
Antibiotics and anti-infectives	Metronidazole (eg. Flagyl, Filmet)	A crossover clinical trial in healthy volunteers demonstrated that co-administration of silymarin, 170mg/day and metronidazole 400mg three times daily, resulted in a slight increase in clearance of metronidazole and its major metabolite, hydroxy-metronidazole.[27] Silymarin reduced metronidazole AUC by 28%, and although this may be a small reduction, it is clinically significant in the context of pathogens with reduced sensitivity to metronidazole, and when high serum concentrations are required for optimal efficacy.[27]	Caution is advised when prescribing *Silybum marianum* alongside metronidazole. If used concomitantly it is advised to monitor the patient closely for reduced drug efficacy.[27]
Antipsychotic agents	Risperidone (eg. Risperdal, Risperdal costa)	A study conducted on rats has demonstrated that co-administration of a silymarin extract (40mg/kg), has a small effect on the pharmacokinetics of risperidone's active metabolites.[35] Human studies are required to determine is this occurs in humans.[35,27]	Caution is advised when prescribing *Silybum marianum* alongside risperidone. If used concomitantly it is advised to monitor the patient for signs of increased adverse reactions, reduced drug clearance or reduced drug efficacy.[27]