MEDI HERB
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No. 221 July 2016

Major Therapeutic Activity of the Flavonolignans of St Mary's Thistle Seed

Key Points at a Glance

St Mary's Thistle

- traditional use of St Mary's Thistle: liver and gallbladder conditions, poor liver function; galactagogue
- concentrated extract of 'seeds' consists mainly of the flavonolignans
- the mixture of flavonolignans is known as silymarin

Indications & Safety

- To improve liver function; liver and gallbladder diseases.
- Adjunctive treatment for diabetes, PCOS and conditions where inflammatory or oxidative processes occur.
- Chemical, food or drug intolerances; fat intolerance, nausea or chronic constipation due to poor liver function; for iron chelation.
- Low toxicity and well tolerated; may cause mild laxation.

Concentrated Extract

- some confusion over name in early trials and inaccurate analytical method used prior to 2000 means doses are approximate
- clinically demonstrated to:
  - improve liver enzymes and symptoms in alcoholic liver disease (420 mg/day)
  - provide benefit in NAFLD or NASH (mixed results; 210-280 mg/day)
  - resolve biliary symptoms in acute hepatitis (420 mg/day)
  - improve liver enzymes in primary sclerosing cholangitis (420 mg/day)
  - improve liver enzymes in those exposed to chemicals or drugs including chemotherapy (200-800 mg/day)
  - improve liver enzymes in type 2 diabetics (600 mg/day)
  - improve blood glucose parameters in type 2 diabetics (mixed results; 200-750 mg/day)
  - decrease C-reactive protein levels in type 2 diabetics (420 mg/day)
  - improve blood glucose parameters in insulin-treated diabetics (400-600 mg/day)
  - improve/increase antioxidant enzymes and decrease lipid peroxidation in patients with alcoholic liver disease, cirrhosis, acne and those undergoing surgery or chemotherapy (210-450 mg/day); some positive effects in type 2 diabetics and those with kidney disease (420 mg/day)
  - improve lipids in hyperlipidaemia (600 mg/day) and NASH (420 mg/day); decrease adverse liver effects of statin in dyslipidaemia (400 mg/day)
  - have an iron-chelating effect in haemochromatosis (single dose) and beta-thalassaemia (420 mg/day)
  - provide benefit in patients with kidney disease (mixed results; 210-420 mg/day)
  - improve kidney function in diabetic nephropathy (420 mg/day) and osteoarthritis patients treated with NSAIDs (200 mg/day)
  - provide benefit for ulcerative colitis, in vitro fertilization, PCOS, acne, allergic rhinitis, chemotherapy-induced oral mucositis, neonatal hyperbilirubinaemia
  - improve biliary function in patients with cholelithiasis undergoing surgery and gallstone and cholecystectomised patients (280-420 mg/day)
  - improve cytokine levels in osteoarthritis patients and heart disease patients undergoing surgery (300-420 mg/day)
  - improve glycaemic control and lipid profile in dyslipidaemia, diabetes, PCOS when combined with a berberine-containing plant extract

Flavonolignans were first discovered in the seeds of *Silybum marianum* (common name: St Mary's thistle). The milled or pressed seeds are extracted to produce the flavonolignans. (To be botanically correct, the fruits are extracted. The fruit however, contains only one seed, so 'seed' is often used to denote the plant part.) Lipids and some impurities are removed from the extract and the resulting dry mixture of flavonolignans is called silymarin.[1] The major flavonolignans in this dry mixture are silybin A, silybin B, silydianin, silychristin A, silychristin B, isosilybin A and isosilybin B.[2] The seeds also contain 20 to 30% fixed oil which can give liquid extracts a milky colour.

Traditional Use

St Mary's Thistle seed has been used in traditional western herbal medicine for liver and gallbladder problems,[3] for digestive disorders due to reduced liver function,[4] and migraine.[5] It was also used by the Eclectic physicians for splenic, hepatic and renal congestion and for fatigue.[6] In addition to its liver tonic activity, St Mary's Thistle is regarded as a (mild) bitter tonic, and used as a choleretic and galactagogue.[7,8]

Clinical Studies

Studies reported up to the year 2000 used a spectrophotometric method to determine the quantity of flavonolignans in concentrated extracts. This type of analytical method gave higher values than the more accurate method which uses high performance liquid chromatography (HPLC).[9] The term 'silymarin' has been used imprecisely, particularly in the early trials. For example, silymarin sometimes may refer to the concentrated extract of St Mary's Thistle, in other cases to the flavonolignans which may range from 40% to 80% of the concentrated extract. The clinical trial doses outlined below have been expressed as silymarin, generally as published without definition. Considering these factors and unless more recently defined using HPLC methodology, the doses may therefore be considered an approximation.

The following abbreviations are used: ALT (alanine aminotransferase) = GPT (glutamic-pyruvic transaminase); ALP (alkaline phosphatase); AST (aspartate aminotransferase) = GOT (glutamic oxaloacetic transaminase); GGT: gamma-glutamyltransferase; GSH: glutathione; GPX: glutathione peroxidase; IL: interleukin; MDA: malondialdehyde; SOD: superoxide dismutase; tumour necrosis factor-alpha: TNF-alpha.

Liver Diseases & Effects on Liver Enzymes

Three placebo-controlled trials found that treatment with silymarin (420 mg/day) significantly improved liver enzymes and symptoms in patients with **alcoholic liver disease**.[10]

Some benefit has been observed in controlled clinical trials investigating the effect of silymarin treatment on **non-alcoholic fatty liver disease** (NAFLD) or non-alcoholic steatohepatitis (NASH). Of the three placebo-controlled trials, two demonstrated that silymarin (210 mg/day and 280 mg/day, taken for 8 and 24 weeks, respectively) significantly improved ALT and AST levels. In other trials, silymarin (140 mg/day for 8 weeks) caused a more significant change in liver enzymes compared to pioglitazone and metformin; and silymarin (210 mg/day for 12 weeks) was significantly better at normalising AST levels than vitamin E.[10] An additional trial involving patients with NAFLD conducted in Iran found treatment with silymarin (280 mg/day) taken for 6 months significantly reduced liver enzymes and improved steatosis as verified by sonography, compared to placebo.[11]

A placebo-controlled trial that used a very high dose of silymarin (2100 mg/day taken for 48 weeks) in patients with NASH found some beneficial results for silymarin treatment (*as follows*), although there was no difference between the groups for improvement in symptoms or disease activity.[12]

- Significantly more patients in the silymarin group experienced resolution of the disease.
- There was a significant decrease in the fibrosis stage in the silymarin group.

Liver cirrhosis is a frequent final outcome of non-alcoholic or alcoholic fatty liver disease and chronic hepatitis. Several controlled trials have studied the effect of silymarin treatment for **cirrhosis**. Total mortality was lower in the silymarin-treated patients in two of five trials, similar in two, with no mortality reported in the fifth trial. The results were pooled without correction for duration of trial. Silymarin was prescribed in the range 280-600 mg/day for 3 to 24 months.[13]

- The overall difference for total mortality was not statistically significant: 16.1% with silymarin versus 20.5% with placebo.
- Liver-related mortality was 10.0% with silymarin versus 17.3% with placebo ($p = 0.01$).
- Overall non-liver related mortality was non-significantly higher in the silymarin-treated patients (6.7%) than in those who received placebo (3.4%).

Use of silymarin among patients with advanced hepatitis C-related liver disease was associated with reduced progression from fibrosis to cirrhosis, but had no impact on clinical outcomes.[14]

A meta-analysis of randomised placebo-controlled trials to 2014 found that treatment with silymarin (332-2100 mg/day, for 12 weeks to 12 months) did not improve serum levels of ALT or serum HCV RNA titer in chronic hepatitis C virus- (HCV-) infected patients.[15] A substudy of one of these trials investigated immunological aspects of silymarin treatment (1260-2100 mg/day) in patients with chronic hepatitis C unsuccessfully treated with interferon. Blood was provided before and after treatment and was analysed for T-cell proliferation and cytokine responses *in vitro*. No effect on HCV-specific T cell proliferation, interferon-gamma production or IL-10 secretion was observed. Silymarin produced modest nonspecific suppression of T-cell proinflammatory effects (as evidenced by suppression of Candida-specific T-cell interferon-gamma production and PHA-induced T-cell proliferation).[16] A randomised, double-blind, placebo-controlled trial conducted in Nigeria found that treatment with silymarin (420 mg/day) for 4 weeks significantly

improved serum ALT and AST levels as well as mental health scores from baseline values in patients with chronic hepatitis B infection. Serum bilirubin and ALP were unchanged. Changes in the placebo group were not significant.[17] Patients with **acute hepatitis** who received silymarin (420 mg/day) for 4 weeks in a randomised trial had significantly quicker resolution of symptoms related to biliary retention (dark urine, jaundice, scleral icterus) than the placebo group. Seventy-five percent of patients had hepatitis of viral aetiology. Silymarin treatment also resulted in a reduction in indirect bilirubin, but direct bilirubin, ALT and AST were not significantly reduced.[18]

Treatment with silymarin (420 mg/day) for one year resulted in a positive response in 34% of patients with **primary sclerosing cholangitis**. A positive response to treatment was defined as a decrease in serum ALP, total bilirubin or AST by greater than or equal to 50%, or a return to normal status without an increase of greater than or equal to 25% in other values. Serum levels of AST and ALP were also significantly reduced.[19]

Silymarin treatment:

- significantly improved serum transaminases in patients who had long-term exposure to toluene and xylene vapours (420 mg/day);[20]
- significantly reduced serum levels of AST, ALT and ALP, in workers who had been occupationally exposed to hydrogen sulfide for at least 5 years (420 mg/day for 1 month);[21]
- improved serum transaminases in patients who received halothane anaesthesia and those treated with neuroleptic drugs, although the results are not regarded as robust;[13]
- resulted in a non-significant decrease in serum transaminases in patients treated with the psychotropic drugs butyrophenones or phenothiazines (800 mg/day for 90 days);[22]
- did not prevent tacrine-induced ALT elevation in Alzheimer's disease patients, but did reduce the rate of gastrointestinal and cholinergic side effects from the drug (420 mg/day for 13 weeks);[23]
- significantly reduced liver enzymes, leading to marked improvement in liver-related symptoms and increased quality of life after 2 months in patients with **drug-induced elevated transaminase levels**; analgesics and anti-inflammatory drugs were used most frequently (45.8%), and had been administered for a median period of 2.8 years; (324 mg/day for 2-3 months);[24]
- significantly reduced the elevation in AST, ALT and ALP caused by treatment with the non-steroidal anti-inflammatories piroxicam and meloxicam in osteoarthritis patients (200 mg/day for 8 weeks);[25]
- significantly reduced serum levels of AST, ALT and GGT, in children with anticonvulsant-induced elevations of transaminases (tablets at 5 mg/kg/day for 1 month);[26]
- significantly reduced the elevation in AST and ALT caused by CAF chemotherapy (210 or 420 mg/day)[27] and taxane **chemotherapy** (210 mg/day);[28]
- did not improve liver function in patients undergoing transcatheter hepatic arterial chemoembolization (a surgical and chemotherapy treatment for unresectable hepatocellular carcinoma; 280 mg/day + B vitamins for 2 weeks).[29]

The benefit of silymarin treatment to reduce the liver toxicity of antituberculosis drugs has not been conclusively demonstrated. In two randomised, placebo-controlled trials silymarin (420 mg/day for 4-8 weeks) reduced the number of patients who developed drug-induced liver injury or reduced the increase in liver enzymes caused by drug treatment.[30,31] There was no difference in the frequency of drug-induced liver injury or frequency of mild elevation of liver enzymes in another randomised, placebo-controlled trial (420 mg/day for 2 weeks).[32] A longitudinal study found silymarin (231 mg/day) did not reduce the risk of drug-induced liver injury.[33] A randomised trial that compared St Mary's Thistle extract to vitamin C found no difference in the risk of developing probable drug-induced liver injury, but a higher risk of developing possible drug-induced liver injury in the herb group. (Possible drug-induced liver injury had less strict criteria than probable drug-induced liver injury.)[34]

Examples of the effect of silymarin on liver enzymes from placebo-controlled clinical trials is outlined in Table 1.

Diabetes & Improved Insulin Sensitivity

Four placebo-clinical trials have assessed the effect of silymarin in diabetics.[35-38] All patients were also taking oral hypoglycaemic drugs or insulin. Significant improvements were found for fasting blood glucose and glycosylated haemoglobin (HbA1c) in the three trials involving type 2 diabetes treated with silymarin (200-600 mg/day for 3 to 4 months),[35-37] but not in the type 2 diabetes with overt nephropathy (420 mg/day for 6 months).[38] For example, silymarin prescribed at 420 mg/day for 3 months changed fasting blood glucose levels from 14.0 to 9.0 mmol/L and HbA1c from 10.4% to 8.5%. The levels in the placebo group increased.[37] *See also Table 1 and Dialysis section below.*

Lipids significantly improved in two trials with diabetics,[35,37] but not in those also with nephropathy.[38] Blood insulin levels improved in one trial,[37] but not the other.[35]

Dose	Liver Enzymes	Silymarin		PLacebo		Ref
		Before	After	Before	After	
alcoholic liver disease						
420 mg/day for 1 month	GOT (U/L)	89.8	38.2	73.9	51.2	39
	GPT (U/L)	152.3	57.5	107.5	90.2	
non-alcoholic fatty liver disease						
280 mg/day for 24 weeks	ALT (U/L)	113.54	73.14	104.54	89.92	40
	AST (U/L)	71.42	49.66	73.02	66.16	
	number of patients (%) with normal ALT	0	26 (52%)	0	9 (18%)	
	number of patients (%) with normal AST	0	31 (62%)	0	10 (20%)	
non-alcoholic steatohepatitis*						
210 mg/day for 8 weeks	ALT (U/L)	91.3	38.4	84.6	52.3	41
	AST (U/L)	62.8	30.5	70.4	36.2	
taxane chemotherapy						
210 mg/day§	ALT (U/L)	24.54	49.94	23.94	55.44	28
	AST (U/L)	24.42	44.46	22.0	48.04	
type 2 diabetes						
600 mg/day for 4 months‡	GOT (U/L)	22	17	22	20	35
	GPT (U/L)	19	12	17	18	

Table 1. Examples of serum levels of liver enzymes in patients treated with silymarin in placebo-controlled trials.

Abbreviations: AST: aspartate aminotransferase (= GOT); ALT: alanine aminotransferase (= GPT); GOT: glutamic oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase

Notes: Normal range for liver enzymes: ALT (= GPT): less than 40 U/L; AST (= GOT): less than 40 U/L; * All patients were recommended to change their diet, lose weight and have daily physical activity. § Results presented are for after the fourth dose of chemotherapy; patients received the taxane (paclitaxel or docetaxel) once every 3 weeks for 4 times plus either silymarin or placebo. ‡ All patients were also taking oral hypoglycaemic drugs.

There are some results available for other placebo-controlled trials involving type 2 diabetics. Fasting blood glucose and HbA1c were significantly reduced in two trials (600-750 mg/day for 2-4 months).[42,43]

Peripheral nerve conduction velocity improved in 14 type 2 diabetics treated with silybin (231 mg/day) for 4 weeks. Symptoms of **peripheral neuropathy disappeared** in many patients. Blood glucose was unchanged, but the erythrocytic sorbitol level was significantly reduced.[44]

There was a significant reduction in high-sensitivity C-reactive protein (hs-CRP) levels of 26.83% in type 2 diabetics treated with silymarin (420 mg/day for 45 days) compared to those who received placebo (in which the levels increased). Fasting blood glucose levels were also significantly decreased by silymarin.[45] In one of the placebo-controlled trials mentioned above, CRP was significantly reduced in those treated with silymarin (420 mg/day for 3 months).[37]

In a controlled study with type 1 diabetics, treatment with silymarin (400 mg/day for 60 days) produced significant reductions in fasting blood glucose and Hb1Ac, significant increase in C-peptide (hence endogenous insulin secretion) and significant improvement in total cholesterol, LDL-cholesterol and HDL-cholesterol, compared to placebo. Silymarin significantly reduced the level of microalbuminurea compared to placebo.[46]

A 12-month study was conducted in two groups of insulin-treated diabetics with alcoholic cirrhosis: those who received silymarin (600 mg/day) plus standard therapy, and a control group who received standard therapy alone. There was a significant decrease in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels after 4 months of treatment in the silymarin group. In addition, there was a significant decrease in fasting insulin levels and mean exogenous insulin requirements in those treated with silymarin, while in those not treated with silymarin both were significantly increased.[47]

Sixty-six patients with NAFLD were randomly assigned to receive silymarin (140 mg/day), pioglitazone (15 mg/day) or metformin (500 mg/day) for 8 weeks. Only a small reduction in fasting blood glucose and serum insulin levels occurred for silymarin.[48]

Antioxidant Enzymes & Lipid Peroxidation

Silymarin treatment:

- increased the activity of GPX, increased SOD activity of red blood cells and lymphocytes and decreased serum MDA in patients with alcoholic liver disease (420 mg/day for 6 months);[49]
- increased GSH and decreased lipid peroxidation in peripheral blood cells in patients with alcoholic liver cirrhosis (450 mg/day for 6 months);[50]

- significantly alleviated the decline in plasma SOD level compared to placebo in patients receiving antituberculosis drugs; no effect on MDA or GSH (420 mg/day for 4 weeks);[30]
- decreased serum MDA in patients treated with the psychotropic drugs butyrophenones or phenothiazines; the decrease was significantly greater than occurred in the placebo group when the drugs were discontinued (800 mg/day for 90 days);[22]
- significantly reduced serum MDA and increased GSH levels compared to placebo in patients with papulopustular acne (420 mg/day for 8 weeks);[51]
- significantly reduced plasma MDA and increased GSH compared to untreated controls in patients undergoing coronary artery bypass grafting surgery (420 mg/day, given 3 days before surgery);[52]
- significantly alleviated the detrimental effect on serum MDA and GSH levels in breast cancer patients treated with CAF chemotherapy (210 and 420 mg/day for 9 weeks);[53]
- significantly increased red blood cell GPX compared to controls, did not significantly decrease serum MDA (420 mg/day for 3 weeks),[54] but increased catalase in red blood cells compared to controls (420 mg/day for 2 months)[55] in patients with end-stage renal disease;
- did not produce a significant decrease in urinary F2-isoprostane levels in healthy volunteers (525 mg/day for 28 days).[56]

In two of three trials with type 2 diabetics, silymarin (420 mg/day for 3 and 4 months) significantly decreased serum MDA levels compared to placebo.[37,38] In the trial that produced no significant effect on MDA levels compared to placebo, treatment with silymarin (420 mg/day for 45 days) significantly increased blood levels of SOD and GPX.[45] MDA levels were also significantly decreased in insulin-treated diabetics who also had cirrhosis after silymarin treatment (600 mg/day for 12 months) compared to controls.[47]

Hypolipidaemic Effects

There was greater improvement in lipid levels when silymarin was added to simvastatin in patients with coronary heart disease. Results for silymarin (120 mg/day) plus simvastatin (10 mg/day) were similar to that of simvastatin prescribed at the higher dose of 20 mg/day. The treatment period was 8 weeks.[57]

A controlled trial with 20 hyperlipidaemia patients found significant reduction from baseline levels in triglycerides, cholesterol, LDL-cholesterol, VLDL-cholesterol and significant increase in HDL-cholesterol after silymarin treatment. Levels were unchanged in those treated with placebo. Placebo and silymarin (600 mg/day) were taken for 2 weeks.[58]

Treatment with silymarin alone (400 mg/day) for 2 months significantly improved the lipid profile of dyslipidaemic patients. This trial also investigated the effect of lovastatin (20 mg/day) and a combination of silymarin (200 mg/day) plus lovastatin (10 mg/day) on lipids and liver enzymes. Serum GOT and GPT significantly increased in the lovastatin group, but did not increase in the combination group. The lipid profile improved to the greatest extent for those treated with silymarin alone. Lovastatin alone was better than the combination for total cholesterol and LDL-cholesterol. Addition of silymarin may **reduce the adverse effects** on liver enzymes caused by statin drugs.[59]

Patients who were diagnosed with NASH and hyperhomocysteinaemia were treated with silymarin (420 mg/day) for 2 months. They experienced significant reduction in plasma homocysteine, cholesterol, triglycerides and fasting blood glucose from baseline values.[60]

Iron Chelation & Thalassaemia

Ten hereditary **haemochromatosis** patients consumed 13.9 mg of iron via a vegetarian meal with either 200 mL of water, 200 mL of water and 140 mg of flavonolignans calculated as silybin, or 200 mL of black tea (containing 170 mg of polyphenols as gallic acid equivalents) on 3 separate occasions. Consumption of silymarin resulted in a significant reduction in the postprandial increase in serum iron compared with water and tea.[61]

Five placebo-controlled trials have assessed the effect of silymarin added to iron chelators in reducing serum ferritin levels in beta-thalassaemia patients.[62,63,64,65,66] In three trials the results were significant.[63,65,66] Silymarin reduced the elevated levels of two immunosuppressive cytokines, TGF-beta and IL-10, and the pro-inflammatory cytokine, IL-23 in these patients.[64] Silymarin was prescribed at 420 mg/day for 12 to 36 weeks (most often 24 to 36 weeks).

In other trials of the same design, treatment with silymarin (420 mg/day for 6 months) reduced the soluble apoptosis marker sTNFR1 which may indicate an anti-inflammatory effect. There was no change in sTNFR1 levels in placebo-treated patients.[67] Silymarin treatment did not produce an effect on iron levels in the liver, although the method used may not be accurate when liver iron levels are higher than 300 micromol/g, as occurred with some patients.[68]

Silymarin (420 mg/day for 12 weeks) administered to beta-thalassaemia patients significantly decreased serum TNF-alpha and increased IL-4 and interferon-gamma from activated T cells. This suggests silymarin stimulates cell-mediated immune response in these patients, possibly

through direct action on cytokine-producing mononuclear cells.[69]

Dialysis & Effects on Kidney Function

Treatment with silymarin (420 mg/day for 2 months) improved haemoglobin and albumin levels in patients with end-stage renal disease undergoing peritoneal dialysis.[55] In 15 peritoneal dialysis patients treated with silymarin (210 mg/day for 2 months), serum TNF-alpha was not significantly reduced. However, in patients who showed at least a 20% decrease in TNF-alpha from baseline (defined as 'responders') the decrease in TNF-alpha was significant. In the entire group of patients, the effect on haemoglobin was not significant, but in the responders, haemoglobin concentration significantly increased.[70]

Treatment with silymarin (420 mg/day for 3 weeks) improved haemoglobin levels in patients on haemodialysis.[54]

A clinical trial suggested that treatment with silymarin (280 mg/day taken 7 days prior to drug) may prevent cisplatin nephrotoxicity in cancer patients,[71] however a more robust trial found it was not effective.[72] In the latter trial, 420 mg/day of silymarin was started 24-48 hours before drug administration and continued to the end of three 21-day cycles of chemotherapy.

Single dose of silymarin (280 mg) prior to administration of contrast media in patients with chronic stable angina referred for elective coronary angiography showed a trend toward preventing contrast-induced nephropathy (CIN) compared with placebo. The patients selected for this trial were at low to moderate risk for CIN.[73]

Silymarin (420 mg/day for 6 months) **reduced proteinuria in type 2 diabetics** with overt nephropathy who were also treated with renin-angiotensin system inhibitors. The effect, as measured by the significantly higher reduction in urinary albumin-creatinine ratio compared to that of placebo, was not due to better glycaemic control. Urinary levels of TNF-alpha were significantly decreased in the silymarin group compared to placebo.[38]

Silymarin (200 mg/day for 8 weeks) significantly reduced the elevation in serum levels of urea and creatinine caused by treatment with the non-steroidal anti-inflammatories piroxicam and meloxicam in osteoarthritis patients.[25]

Other Conditions

Silymarin treatment:

- significantly decreased the disease activity index and produced a higher rate of complete remission compared to placebo in patients with **ulcerative colitis** (140 mg/day for 6 months);[74]
- significantly reduced the proportion of early apoptosis and total apoptosis of granulosa cells in women undergoing **in vitro fertilization**, compared to the results for the placebo group (210 mg/day);[75]
- significantly improved blood glucose, insulin, progesterone and insulin resistance in women with **polycystic ovary syndrome**; 4 of the 20 women ovulated (750 mg/day for 3 months); the effects were greater in women treated with silymarin and metformin combined;[76]
- significantly reduced the lesion count and serum IL-8 levels in patients with papulopustular **acne** (420 mg/day for 8 weeks);[51]
- produced significantly greater improvement in symptom severity than placebo in patients with **allergic rhinitis** (420 mg/day for 1 month);[77]
- significantly decreased serum levels of the cytokines IL-1alpha, IL-8 and complement proteins C3 and C4 when prescribed alone or in combination with non-steroidal anti-inflammatories piroxicam or meloxicam in patients with knee **osteoarthritis** (300 mg/day for 8 weeks);[78]
- significantly reduced the elevation in inflammatory cytokines (IL-1beta, IL-6, TNF-alpha) and C-reactive protein compared to untreated controls in patients undergoing **coronary artery bypass grafting surgery** (420 mg/day, given 3 days before surgery);[52]
- significantly reduced the severity of **chemotherapy-induced oral mucositis** compared to indomethacin and placebo (420 mg/day for 14 days);[79]
- significantly reduced cholesterol in bile, increased bile acid level and reduced the postoperative inflammatory response compared to untreated controls in patients with **cholelithiasis** undergoing surgery (280 mg/day);[80]
- reduced the biliary cholesterol concentration and bile saturation index in **gallstone** and cholecystectomised patients compared with placebo (420 mg/day for 30 days);[81]
- along with phototherapy was more effective than phototherapy alone in treating full-term, healthy neonates with unconjugated **hyperbilirubinaemia** (3.75 mg/kg, orally twice daily).[82]

Combined with Berberine

A proprietary product combining *Berberis aristata* root, containing a known quantity of berberine, and concentrated *Silybum marianum* seed extract containing a minimum quantity of flavonolignans has been evaluated in several clinical trials. Silymarin was added initially to the berberine-containing herb extract to improve the bioavailability of berberine (on the basis that silymarin inhibits of P-glycoprotein activity, and P-glycoprotein contributes to the poor intestinal absorption of berberine),

although changes in absorption by combining silymarin with berberine have not been verified in humans. The effect may instead be additive, although the dosage of silymarin is low in comparison to most clinical trials using silymarin alone.

Trials have used a dosage that provides 1000 mg/day of berberine and at least 126 mg/day of flavonolignans from concentrated extract of *Silybum marianum*. In controlled trials, this combination **improved glycaemic control and lipid profile** compared to those treated with placebo in patients with dyslipidaemia,[83,84] including those intolerant to statins,[85,86] type 2 diabetics[87] and type 1 diabetics.[88] It was also a beneficial treatment for polycystic ovary syndrome.[89]

One trial compared the effect of the combination and the berberine-containing herb extract. Fifty-seven patients with type 2 diabetes completed the study in which they received either tablets that contained *Berberis aristata* root, providing 1000 mg/day of berberine and concentrated *Silybum marianum* seed extract providing at least 126 mg/day of flavonolignans, or tablets that contained *Berberis aristata* root, providing 1000 mg/day of berberine. The group who received the combination had a significantly greater reduction in HbA1c from baseline than the berberine group: reduction of 12.35% versus 7.17%, respectively ($p < 0.05$). Fasting blood glucose decreased by nearly 20% in both groups.[90]

Safety

Clinical studies indicate silymarin has a very good safety profile,[91] and chronic toxicity studies in rodents have confirmed that silymarin has very low toxicity.[10]

A review of trials of patients with alcoholic liver disease and/or cirrhosis found the incidence of adverse events was slightly lower in the silymarin group than in the placebo group. The incidence was very low and within the range of placebo values. In comparative studies, the side effects with an incidence of greater than or equal to 1%, were headaches and pruritus. The side effects in open trials evaluating silymarin showed a predominance of digestive symptoms (diarrhoea 0.2%, irregular stools 0.1%, nausea 0.13%, dyspepsia 0.08%). Rare cases of allergic skin rashes have been reported.[13] A mild laxative effect has been observed.[92,93]

A dose-escalation, phase I study in noncirrhotic patients with chronic hepatitis C study found oral doses of silymarin up to 2100 mg/day were safe and well tolerated.[94]

Drug monitoring studies to 1995 involving more than 3500 patients found excellent tolerability, with adverse effects seen in 1% of patients which were mainly gastrointestinal and were mild.[95]

Silymarin has been used in pregnant women with intrahepatic cholestasis at doses of 560 mg/day for 16 days, with no toxicity to the patient or the foetus.[96]

Silymarin is not expected to be harmful in pregnancy or lactation.[97]

Actions

Hepatoprotective, hepatic trophorestorative, antioxidant, choleretic, galactagogue.

Indications

- To improve liver function, specifically when exposed to alcohol, chemicals or drugs including environmental toxins and chemotherapy.
- Liver and gallbladder diseases.
- Adjunctive treatment for diabetes, polycystic ovary syndrome and kidney disease, as well as conditions with inflammatory or oxidative processes occur such as ulcerative colitis, allergic rhinitis, in vitro fertilization.
- Chemical, food or drug intolerances.
- Fat intolerance, nausea, headaches or chronic constipation due to poor liver function.
- For iron chelation e.g. haemochromatosis, thalassaemia.

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