Milk Thistle

Silybum marianum (L.) Gaertn.

[Fam. *Asteraceae*]

Overview

Milk thistle preparations have been used in European medicine for over 2,000 years to treat liver and biliary tract diseases. In 1998, $180 million was spent on milk thistle preparations in Germany alone. In the U.S. in 2000, milk thistle ranked 11th in sales of all herbal products sold in food, drug, and mass market outlets, reaching about $9 million in retail sales. With an estimated 50 clinical studies involving over 2,400 patients carried out using a proprietary milk thistle preparation from Germany, it is perhaps the best documented therapeutic agent available to treat various types of liver intoxication.

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Primary Uses

- Liver disease, alcoholic
- Liver cirrhosis, alcoholic
- Infectious hepatitis
- Drug-induced hepatitis

Other Potential Uses

- Liver disease secondary to diabetes mellitus
- To decrease toxicity of narcotics used in cholecystectomy surgery (gallbladder removal)
- *Amanita* mushroom poisoning (i.v. drip of purified compound silybinin)

Pharmacological Actions

Hepatoprotective; reduces serum gamma glutamyl transpeptidase (GGT) and transaminases (ALT, AST); reduces triglyceride in serum; normalizes serum-bilirubin and BSP retention; reduces malondialdehyde concentration in serum; increases superoxide dismutase (SOD) activity in erythrocytes and lymphocytes; reduces cytotoxic lymphocytes in blood; reduces procollagen-III peptide in serum.

Dosage and Administration

For chronic conditions, milk thistle must be taken over an extended period for efficacy. For acute conditions that last longer than a week or recur periodically, patients are encouraged to seek a healthcare provider's advice. The duration of use for standardized preparations depends on the severity and chronic nature of the condition. Research has suggested that standardized extracts may be used continuously for as long as 24 months.

NOTE: The crude and infusion forms are indicated only for mild dyspeptic complaints, whereas high dosage and/or standardized extract forms are required for serious liver diseases. Due to the poor water solubility of silymarin, only a small fraction (<10%) of silymarin is released into an aqueous infusion.

DRY EXTRACT (STANDARDIZED): 40–70:1 (*w/w*), 70–80% silymarin, daily equivalent to 200–400 mg of silymarin, calculated as silibinin in divided doses. Many clinical trials have used a daily dose equivalent to 420 mg of silymarin, delivered in three divided doses. The dose of 140 mg must be swallowed with sufficient amounts of fluid.

NOTE: Most clinical studies on milk thistle have employed the concentrated, standardized extract.

Contraindications

None known.

PREGNANCY AND LACTATION: No known restrictions.

Adverse Effects

Crude Preparations

None known.

Standardized Preparations

A mild laxative effect has been observed occasionally. In one case report, a more severe gastrointestinal reaction to a milk thistle product occurred, but the link to the standardized extract is unclear.

Drug Interactions

None known. Concomitant use of the purified silymarin fraction with butyrophenones or phenothiazines has resulted in the reduction of lipid peroxidation damage of the liver.

Clinical Review

In 21 clinical studies on milk thistle that included a total of 2,430 participants, all but two studies demonstrated positive effects for indications including cirrhosis and alcoholic liver disease, hepatitis, and psychotropic drug-induced liver damage. Eight double-blind, placebo-controlled (DB, PC) studies investigated cirrhosis and alcoholic liver disease, involving over 600 patients. The most recent DB, PC study did not result in statistically significant findings on liver cirrhosis. Two randomized (R), DB, PC trials investigated milk thistle extract as a treatment for acute viral hepatitis A and B (HBV) and chronic active hepatitis due to HBV and/or hepatitis C (HCV). One observational study on 998 patients showed that milk thistle extract reduces collagen fibrogenesis in patients with toxic livers. Treatment of psychotropic drug-induced hepatic damage with purified silymarin is the subject of another R, DB, PC study and one multi-center study involving 220 patients over four years, which found that intravenous purified silibin complemented standard treatment, lowering mortality rates in cases of acute *Amanita* mushroom poisoning. A recent systematic review and meta-analysis funded by the National Institutes of Health (NIH) concluded that (1) the available evidence suggests that milk thistle extract is relatively safe, associated with few, generally minor, adverse events; (2) despite substantial *in vitro* and animal research, the mechanism of action is not fully defined and may be mulitfactorial; and (3) clinical efficacy is not clearly established because interpretation of the evidence is hampered by poor study methods and/or poor quality of reporting in publications. Other problems noted by NIH researchers included heterogeneity in etiology and extent of liver disease, small sample sizes, variation in formulation (for products other than Legalon®), dosing, and duration of therapy. Possible benefits have been shown most frequently for improvement in aminotransferases and liver function tests.

Milk Thistle

Silybum marianum (L.) Gaertn.
[Fam. *Asteraceae*]

Overview

Milk thistle preparations have been used in European medicine for over 2,000 years for the treatment of liver diseases. In the U.S. in 2000, milk thistle ranked 11th in sales of all herbal products sold in food, drug, and mass market outlets, reaching about $9 million in retail sales. With numerous clinical studies involving over 2,400 patients, it is perhaps the best documented therapy available for treating liver intoxication.

Uses

Alcoholic liver disease; alcoholic liver cirrhosis; infectious hepatitis; drug-induced hepatitis.

Dosage

For chronic conditions, milk thistle must be taken over an extended period for efficacy. For acute conditions that last longer than a week or recur periodically, patients are encouraged to seek a healthcare provider's advice.

Dry extract (standardized): 40–70:1 (*w/w*), 70–80% silymarin, daily equivalent to 200–400 mg of silymarin, calculated as silibinin in divided doses. Many clinical trials have used a daily dose equal to 420 mg of silymarin divided into three doses. The dose of 140 mg should be swallowed with sufficient amounts of fluid.

Contraindications

No known contraindications.

Pregnancy and Lactation: No known restrictions.

Adverse Effects

The standardized preparation has occasionally caused a mild laxative effect.

Drug Interactions

None known. Ingesting silymarin at the same time as psychopharmaceutical drugs, butyrophenones, or phenothiazines has produced the benefit of decreased lipid peroxidation damage of the liver.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Milk Thistle

Silybum marianum (L.) Gaertn.

[Fam. *Asteraceae*]

Overview

Milk thistle preparations have been used in European medicine for over 2,000 years to treat liver and biliary tract diseases (Der Marderosian and Liberti, 1997; Flora *et al*., 1998; Foster, 1991). In 1998, $180 million was spent on milk thistle preparations in Germany alone (McCaleb *et al*., 2000). In the U.S. in 2000, milk thistle ranked 11th in sales of all herbal products sold in food, drug, and mass market outlets, reaching about $9 million in retail sales (Blumenthal, 2001). With an estimated 50 clinical studies involving over 2,400 patients carried out using a proprietary milk thistle preparation from Germany (Blumenthal *et al*., 2000), it is perhaps the best documented therapeutic agent available to treat various types of liver intoxication (Morazzoni and Bombardelli, 1995).

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Description

Milk thistle preparations consist of the dried fruits (also known as achenes) of *Silybum marianum* (L.) Gaertn. [Fam. *Asteraceae*], freed from the pappus. The U.S. *National Formulary* requires that milk thistle preparations contain no less than 20% silymarin, calculated as silybin (USP, 2002). Silymarin is the collective name for the flavonolignans silibinin (silybin), silydianin, and silychristin. The *German Pharmacopoeia* requires that preparations made of the crude milk thistle fruits, contain at least 1.5% silymarin (DAB, 1999). The semi-purified standardized dry extract, which has been the subject of numerous clinical studies, has a drug-to-extract ratio range of 40–70:1 (*w/w*) and contains no less than 70% silymarin (Blumenthal *et al*., 1998).

Primary Uses

Liver Disorders

- Liver disease, alcoholic (Bunout *et al*., 1992; Deák *et al*., 1990; Müzes *et al*., 1990; Fehér *et al*., 1989; Salmi and Sarna, 1982; Fintelmann and Albert, 1980)
- Liver cirrhosis, alcoholic (Ferenci *et al*., 1989; DiMario *et al*., 1981)
- Infectious hepatitis (Buzzelli *et al*., 1993; Magliulo *et al*., 1978; Hammerl *et al*., 1971; Poser, 1971; Sarre, 1971)
- Drug-induced hepatitis (Palasciano *et al*, 1994; Kurz-Dimitrowa, 1971)

Other Potential Uses

- Liver disease secondary to diabetes mellitus (Velussi *et al*., 1997)
- To decrease toxicity of narcotics used in cholecystectomy surgery (gallbladder removal) (Fintelmann, 1973)
- *Amanita* mushroom poisoning (Hruby *et al*., 1984; Serne *et al*., 1996)

Combinations

- The German Commission E has approved a fixed combination of milk thistle seed (crude), peppermint leaf (*Mentha* x *piperita*), and wormwood (*Artemisia absinthium*) for treatment of dyspeptic discomfort, especially functional disorders of the biliary tract (Blumenthal *et al*., 1998)

Dosage

Internal

Crude Preparations

POWDERED SEED: 12–15 g daily for making infusions and other oral galenical preparations (Blumenthal *et al.,* 1998).

DECOCTION: 3–4 times daily, 3 g seed is placed in 150 ml cold water, boiled, simmered for 20–30 minutes, and strained (Wichtl and Bisset, 1994).

INFUSION: 150 ml boiling water is poured over 3.5 g crushed seed and steeped for 10–15 minutes, 3 to 4 times per day, one-half hour before meals, for mild digestive disorders (Braun *et al*., 1996). A small amount of peppermint leaf may be added to improve efficacy and flavor (Weiss and Fintelmann, 2000).

NOTE: The infusion form is indicated only for mild dyspeptic complaints, whereas high dosage and/or standardized extract forms are required for serious liver diseases. Due to the poor water solubility of silymarin, only a small fraction (<10%) of silymarin is released into an aqueous infusion (Foster and Tyler, 1999; Meyer-Buchtela, 1999; Wichtl, 1989).

Standardized Preparations

DRY EXTRACT: 40–70:1 (*w/w*), 70–80% silymarin, daily equivalent to 200–400 mg of silymarin, calculated as silibinin (Blumenthal *et al.,* 1998) in divided doses. Many clinical trials have used a daily dose equivalent to 420 mg of silymarin, delivered in three divided doses. The dose of 140 mg is swallowed with sufficient amounts of fluid (Blumenthal *et al.,* 2000). NOTE: Most clinical studies on milk thistle have employed the extract concentrated and standardized to 70% silymarin.

Duration of Administration

Crude Preparations

For chronic conditions, milk thistle must be taken over an extended period for efficacy. For acute conditions that last longer than one week or recur periodically, consult a healthcare provider (Braun *et al*, 1996).

Standardized Preparations

The duration of use depends on the severity and chronic nature of the condition. Research has suggested that standardized extracts may be used continuously for as long as 24 months (Ferenci *et al.*, 1989; Parés, 1998), although longer periods are possible.

Chemistry

Milk thistle seed contains 1.5–3.0% flavonolignans including silybin, silydianin, and silychristin collectively referred to as silymarin; 20–30% fixed oil, of which approximately 50–60% is linoleic acid, approximately 30% is oleic acid, and approximately 9% is palmitic acid; 25–30% protein; 0.038% tocopherol; 0.63% sterols, including cholesterol, campesterol, stigmasterol, and sitosterol; and some mucilage (Morazzoni and Bombardelli, 1995; Wichtl and Bissett, 1994).

Pharmacological Actions

Internal

Human

Standardized Preparations

Hepatoprotective (BHP, 1996). Reduces serum gamma glutamyl transpeptidase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST), reduces triglyceride in serum, normalizes serum-bilirubin and BSP retention, reduces malondialdehyde concentration in serum, increases superoxide dismutase (SOD) activity in erythrocytes and lymphocytes, reduces cytotoxic lymphocytes in blood, and reduces procollagen-III peptide in serum (Leng-Peschlow 1996a, 1996b).

Animal

Isolated silymarin has anti-inflammatory and anti-arthritic actions (Gupta *et al.*, 1999); increases bile flow and bile salt secretion (Crocenzi *et al.*, 2000); increases secretion of bile into duodenum and exerts gastroprotective effect to prevent ischemic mucosal injury (Alarcon de la Lastra *et al.*, 1995); is prophylactic and antidotal for *Amanita*/deathcap mushroom poisoning (Desplaces *et al.*, 1975; Schriewer *et al.*, 1975; Vogel *et al.*, 1984); protects against sawfly (*Arge pullata*) larvae-induced ruminant hepatotoxicosis (Thamsborg *et al.*, 1996); reduces activity level of GGT, ALT, and AST (Wang *et al.*, 1996); increases glutathione level (Vatenzuela *et al.*, 1989); inhibits synthesis of liver lecithin (Montanini *et al.*, 1977); and protects against thioacetamide damage (Schriewer *et al.*, 1973).

In vitro

Isolated silymarin is hepatoprotective (Farghali *et al.*, 2000; Mereish and Solow, 1990); antioxidant (Müzes *et al.*, 1991); inhibits alpha-amanitin uptake in hepatocyte membrane (Tongiani *et al.*, 1977); stimulates RNA-polymerase I (Morazzoni and Bombardelli, 1995); enhances human polymorphonuclear leukocyte (PMN) motility (Kalmar *et al.*, 1990); and has anticarcinogenic effects in human prostate carcinoma DU145 cells (Zi *et al.*, 1998).

External

Animal

Isolated silymarin inhibits benzoyl peroxide-induced tumor promotion, oxidative stress and inflammatory responses in skin (Zhao *et al.*, 2000); reduces skin tumor (Katiyar *et al.*, 1997).

Mechanism of Action

Milk thistle's hepatoprotective mechanism of action is not clearly understood, though it can be attributed mainly to its flavonolignan content (Der Manderosian and Liberti, 1997). Isolated silymarin acts as an antagonist in preventing liver-damage: phalloidin and amanitin (death-cap toxins), lanthanides, carbon tetrachloride, galactosantine, thioacetamide, and the hepatotoxic virus FV3 of cold-blooded vertebrates (Blumenthal *et al.*, 1998).

- Anti-inflammatory: Anti-inflammatory and anti-arthritic actions may be due to silymarin's inhibition of 5-lipoxygenase (Gupta *et al.,* 1999).
- Antioxidant: Silymarin scavenges pro-oxidant free radicals, increases glutathione production by the liver, intestines and stomach; increases intracellular concentration of glutathione in rats (Valenzuela *et al.*, 1989; Valenzuela and Garrido, 1994). Semi-purified extract of milk thistle increases activity of SOD and glutathione peroxidase in human erythrocytes *in vitro*, which may explain its protective effect against free radicals and its stabilizing effect on red blood cell membrane (Altorjay *et al.*, 1992).
- Cholagogic and choleretic: Silymarin may increase biliary excretion and endogenous pool of bile salts by stimulating synthesis of hepatoprotective bile salts such as beta-muricholate and ursodeoxycholate (Crocenzi *et al.*, 2000).
- Regenerative: Silymarin stimulates the action of nucleolar polymerase A, resulting in an increase in ribosomal protein synthesis, thereby stimulating regenerative ability of the liver and formation of new hepatocytes (Blumenthal *et al.*, 1998). Based on molecular modeling, silibinin appears to initiate a steroid hormone by binding competitively to RNA-polymerase I, resulting in enzyme activity stimulation (Sonnenbichler *et al.*, 1998).
- Protective and regulatory: Silymarin alters the structure of the outer cell membrane of the hepatocytes in such a way as to prevent penetration of the liver toxin into the interior of the cell (Blumenthal *et al.,* 1998; Leng-Peschlow, 1996b). Stabilizes cell membranes by decreasing phospholipid turnover rate and blocking penetration of liver toxins (such as phalloidin, alpha-amanitin) into the cell (Montanini *et al.,* 1977). Isolated silibinin selectively inhibits leukotriene formation by Kupffer cells of the liver (Dehmlow *et al.,* 1996). Isolated silychristin (silymarin II) inhibits peroxidase and lipoxygenase (Fugmarm *et al.,* 1997). Hepatoprotective effect may be due to silymarin's inhibition of lipid peroxidation and modulation of hepatocyte Ca(2+)(i) (Farghali *et al.,* 2000).
- Anti-fibrotic actions: Animal research (Boigk *et al.*, 1997) and a human clinical trial (Shuppan *et al.*, 1999) have suggested that the hepatoprotective properties of silymarin may include anti-fibrotic activity, thereby interfering with the process that occurs in the hepatocytes secondary to inflammation when collagen invades the normal structure of the hepatocyte, which frequently is a result of alcohol abuse or chronic active viral hepatitis. The ability of silymarin to block fibrosis in the liver was first shown in studies with rats subjected to complete bile duct occlusion (Boigk *et al.*, 1997). This action was later demonstrated in an open-label, uncontrolled study with 998 patients with liver disease

resulting from a variety of factors including alcohol abuse, chronic active hepatitis B or C, drugs, and chemical exposure in the workplace (Schuppan *et al.*, 1998). Treatment with 140 mg of silymarin (equivalent to approximately 60 mg of silibinin) three times daily for three months led to a significant reduction in amino terminal procollagen III peptide (PIIINP), a marker of fibrosis, in 19% of the patients. This measure had dropped to the normal range expected for a healthy person at three months.

Contraindications

None known (Blumenthal *et al.,* 1998; Braun *et al.,* 1996; Brinker, 2001).

Pregnancy and Lactation: No known restrictions (Blumenthal *et al.,* 1998).

Adverse Effects

Crude Preparations

None known (Blumenthal *et al.,* 1998; Braun *et al.,* 1996).

Standardized Preparations

A mild laxative effect has been observed occasionally (Blumenthal *et al.,* 1998). There is one case report of a more severe gastrointestinal reaction to a milk thistle product (Adverse Drug Reactions Advisory Committee, 1999); the link to the standardized extract is unclear.

Drug Interactions

None known, according to the Commission E (Blumenthal *et al.,* 1998) and other authoritative German pharmaceutical literature (Braun *et al.,* 1996). Concomitant use of purified silymarin and butyrophenones or phenothiazines has resulted in the reduction of lipid peroxidation damage of the liver. In a clinical study where milk thistle was tested for its potential benefit in reducing the hepatotoxicity of these psychopharmaceutical agents (Palasciano *et al.,* 1994). One case report suggests possible protection from dilantin-induced hepatotoxicity (Brinker, 2001).

American Herbal Products Association (AHPA) Safety Rating

Class 1: Can be safely consumed when used appropriately (McGuffin *et al.,* 1997).

Regulatory Status

Australia: Approved as a Therapeutic Good (Medicine) by the Therapeutic Goods Administration (TGA).

Canada: Permitted as a component of OTC Traditional Herbal Medicine (THM) products and as an OTC 1X homeopathic drug, in both cases requiring pre-marketing authorization and application for a Drug Identification Number (DIN) (Health Canada, 2000).

France: Approved as a nonprescription drug.

Germany: Crude and standardized milk thistle preparations are approved nonprescription drugs of the Commission E monographs (Blumenthal *et al.*, 1998) and the tea infusion form is a non-prescription drug of the *German Standard License* monographs, with sales limited to pharmacies and drugstores (Braun *et al.*, 1996). The ripe fruit, freed from pappus, containing not less than 1.5% silymarin is official in the *German Pharmacopoeia* (DAB, 1999). The mother tincture and the ethanolic decoction of the ripe dried fruit are official preparations of the *German Homeopathic Pharmacopoeia* (GHP, 1993).

Italy: Approved as a prescription drug.

Sweden: No milk thistle-containing products are presently registered in the Medical Products Agency's (MPA) "Authorized Natural Remedies," "Homeopathic Remedies" or "Drugs" listings (MPA, 2001).

Switzerland: Positive classification (List D) by *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; WHO, 1998). 11 milk thistle-containing phytomedicines and 21 homeopathic preparations are listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2001).

U.K.: Not entered in the *General Sale List* (GSL).

U.S.: Dietary supplement (USC, 1994). Milk thistle seed and milk thistle seed powder have official monographs in the U.S. *National Formulary*, 20th edition (USP, 2002). The mother tincture 1:10 (*w/v*), 65% ethanol (*v/v*), of the fresh or dried seeds, is an OTC Class C drug official in the *Homoeopathic Pharmacopoeia of the United States* (HPUS, 1990).

Clinical Review

Twenty-one studies are outlined in the following table, "Clinical Studies on Milk Thistle," including a total of 2,370 participants. All but two of these studies (Parés *et al.*, 1998; Bunout *et al.*, 1992) demonstrate positive effects for indications including cirrhosis and alcoholic liver disease, hepatitis, and psychotropic drug-induced liver damage. Eight double-blind, placebo-controlled (DB, PC) studies investigated cirrhosis and alcoholic liver disease, involving over 600 patients (Deák *et al.*, 1990; DiMario *et al.*, 1981; Fehér *et al.*, 1989; Ferenci *et al.*, 1989; Fintelmann and Albert, 1980; Müzes *et al.*, 1990; Parés *et al.*, 1998; Salmi and Sarna, 1982). The most recent DB, PC study did not result in statistically significant findings on liver cirrhosis (Parés *et al.*, 1998). Two randomized (R), DB, PC trials investigated milk thistle extract as a treatment for acute viral hepatitis A and B (HBV) (Magliulo *et al.*, 1978) and chronic active hepatitis due to HBV and/or hepatitis C (HCV) (Buzzelli *et al.*, 1993). One observational study on 998 patients showed that milk thistle extract reduces collagen fibrogenesis in patients with toxic livers (Schuppan *et al.*, 1998). Treatment of psychotropic drug-induced hepatic damage with purified silymarin was the subject of another R, DB, PC study (Palasciano *et al.*, 1994), and one multi-center study involving 220 patients over four years found intravenous purified silibin complemented standard treatment, lowering mortality rates in cases of acute *Amanita* mushroom poisoning (Hruby *et al.*, 1984). A recent systematic review and meta-analysis (Mulrow *et al.,* 2000) funded by the National Institutes of Health's Agency for Healthcare Research and Quality concluded that (1) the available evidence suggests that milk thistle extract is relatively safe, associated with few, generally minor, adverse events; (2) despite substantial *in vitro* and animal research, the mechanism of action is not fully defined and may be mulitfactorial; and (3) clinical efficacy is not clearly established because interpretation of the evidence is hampered by poor study methods and/or poor quality of reporting in publications; other problems include heterogeneity in etiology and extent of liver disease, small sample sizes, variation in formulation (for products other than Legalon®, the leading standardized preparation), dosing, and duration of therapy. Possible benefits have been shown most frequently for improvement in aminotransferases and liver function tests.

Branded Products

IdB 1016 Silipide: Indena S.p.A. / Viale Ortles 12 / 20139 Milano, Italy / Tel: +39-02-57-4961 / Fax: +39-02-57-4046-20 / Email: indenami@tin.it. One capsule contains 150 mg purified dry extract of milk thistle seed standardized to 80% silymarin (120 mg).

Legalon® 35 Dragées: Madaus AG / Ostermerheimer Strasse 198 / Köln / Germany / Tel: +49-22-18-9984-76 / Fax: +49-22-18-9987-21 / Email: b.lindener@madaus.de. One tablet contains 43.25 mg–46.6 dry extract from milk thistle fruits standardized to 35 mg silymarin, calculated as silibinin. (Introduced in 1966.)

Legalon® 70: Madaus AG. One capsule contains 86.5–93.3 mg dry extract from milk thistle fruits (36–44:1) standardized to 70 mg silymarin, calculated as silibinin (extractant: ethyl acetate > 96.7%). (Introduced in 1974.)

Legalon® 140: Madaus AG. One capsule contains 173.0–186.7 mg dry extract from milk thistle fruits (36–44:1) standardized to 140 mg silymarin, calculated as silibinin (extractant: ethyl acetate > 96.7%). (Introduced in 1990.)

American equivalents, if any, are found in the Product Table beginning on page 398.

References

Adverse Drug Reactions Advisory Committee. An adverse reaction to the herbal medication milk thistle (*Silybum marianum). MJA* 1999;170:218–9.

Alarcon de la Lastra AC, Martin MJ, Motilva V, *et al*. Gastroprotection induced by silymarin, the hepatoprotective principle of *Silybum marianum* in ischemia-reperfusion mucosal injury: role of neutrophils. *Planta Med* 1995;61(2):116–9.

Allain H, Schuck S, Lebreton S, *et al*. Aminotransferase levels and silymarin in *de novo* Tacrine-treated patients with Alzheimer's Disease. *Dement Geriatr Cogn Disord* 1999;10:181–5.

Alshuler L. Milk Thistle: Goals and Objectives. *Int J Integrative Med* 1999;1(1):29–34.

Altorjay I, Dalmi L, Sari B, *et al*. The effect of silibinin (Legalon®) on the free radical scavenger mechanisms of human erythrocytes *in vitro*. *Acta Physiol Hung* 1992;80(1–4):375–80.

Angulo P, Patel T, Jorgensen RA *et al*. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. *Hepatology* 2000;32(5):897–900.

Anon. 1989. *Legalon*®. Cologne, Germany: Madaus AG.

Australian Department of Health and Aged Care. Australian Hepatitis C (HCV) Research Register. Project No: 115. Sidney, Australia: Australian Population Health Division, Commonwealth Department of Health and Aged Care. 14. December 1998.

BHP. See: *British Herbal Pharmacopoeia*.

Blumenthal M. Herb sales down 15% in mainstream market. *HerbalGram* 2001;51:69.

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS (eds.). Klein S, Rister RS (trans.). *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston: Integrative Medicine Communication; 1998;11, 169–70, 278.

Blumenthal M, Goldberg A, Brinckmann J (eds.). Milk Thistle Fruit. In: *Herbal Medicine: Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications. 2000;257–63.

Boigk G, Stroedter L, Herbst H, *et al*. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. *Hepatology* 1997;26(3):643–9.

Braun R, Surmann P, Wendt R, Wichtl M, Ziegenmeyer J (eds.). Mariendistelfrüchte. In: *Standardzulassungen für Fertigarzneimittel—Text and Kommentar,* 11. Ergänzungslieferung. Stuttgart, Germany: Deutscher Apotheker Verlag, February 1996; Zulassungsnummer 1589.99.99;1–2.

Brinker F. *Herb Contraindications and Drug Interactions*, 3rd ed. Sandy, OR: Eclectic Medical Publications. 2001.

British Herbal Pharmacopoeia (BHP, 4th ed. 1996). Exeter, U.K.: British Herbal Medicine Association. 1996;134–5.

Bunout D, Hirsch S, Petermann M, *et al*. Controlled study on the effect of silimarin in alcoholic liver disease. [in Spanish]. *Rev Med Chile* 1992;120:1370–5.

Buzzelli G, Moscarella S, Giusti A, *et al*. A pilot study on the liver protective effect of silybin phosphatidylcholine complex (IdB1016) in chronic active hepatitis. *Int J Clin Pharmacol Ther Toxicol* 1993;31(9):456–60.

Crocenzi FA, Pellegrino JM, Sanchez Pozzi EJ, *et al*. Effect of silymarin on biliary bile salt secretion in rat. *Biochem Pharmacol* 2000;59(8):1015–1022.

DAB. See: *Deutsches Arzneibuch*.

Deäk G, Müzes G, Läng I, Niederland V, *et al*. Immunomodulator effect of silymarin therapy in chronic alcoholic liver diseases. [in Hungarian]. *Orv Hetil* 1990 Jun 17;131(24):1291–2, 1295–6.

Dehmlow C, Erhard J, de Groot H. Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology* 1996;23(4):749–54.

Der Marderosian A, Liberti L. *Milk Thistle. The Review of Natural Products*. St. Louis, MO: Facts and Comparisons. Jan 1997.

Desplaces A, Choppin J, Vogel G, Trost W, The effects of silymarin on experimental phalloidine poisoning. *Arzneimittelforschung* 1975;25(1):89–96.

Deutsches Arzneibuch (DAB Ergänzungslieferung 1999). Stuttgart, Germany: Deutscher Apotheker Verlag. 1999; Mariendistelfrüchte:1–5.

DiMario F, Farini R, Okolicsanyi L, Naccarato R. The Effects of Silymarin on the Liver Function Parameters of Patients with Alcohol-Induced Liver Disease: A Double Blind Study. In: de Ritis F, Csomos G, Braatz R (eds.). *Der Toxisch-metabolische Leberschaden*. Lübeck, Germany: Hans. Verl.-Kontor. 1981;54–8.

Farghali H, Kamenikova L, Hynie S, Kmonickova E. Silymarin effects on intracellular calcium and cytotoxicity: a study in perfused rat hepatocytes after oxidative stress injury. *Pharmacol Res* 2000;41(2):231–7.

Fehér J, Deák G, Müzes G, *et al*. Hepatoprotective activity of silymarin therapy in patients with chronic alcoholic liver disease. [in Hungarian]. *Orv Hetil* 1989;130(51):2723–7.

Ferenci P, Dragosics B, Dittrich H, *et al*. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989; 9(1):105–13.

Fintelmann V. Serumcholinesterase and other liver enzymes in postsurgical conditions. [in German]. *Med Klin* 1973;68:809–15.

Fintelmann V, Albert A. The therapeutic activity of Legalon® in toxic hepatic disorders demonstrated in a double-blind trial. [in German]. *Therapiewoche* 1980;30:5589–94.

Floersheim, G.L., O. Weber, P. Tschumi, M. Ulbrich. Poisoning by the deathcap fungus (*Amanita phalloides*): Prognostic factors and therapeutic measures. [in German]. *Schweiz Med Wochenschr* 1982;112(34):1164–77.

Flora K, Hahn M, Rosen H, Benner K. Milk thistle (*Silybum marianum*) for the therapy of liver disease. *Am J Gastroenterol* 1998; 93(2):139–43.

Foster S. Milk Thistle – *Silybum marianum*. Austin, TX: American Botanical Council. No. 305, 1991.

Foster S, Tyler VA. *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies*, 4th ed. New York, NY: Haworth Herbal Press, 1999.

Fugmann B, Lang-Fugmann S, Steglich W (eds.). Silybin. In: *Rompp Lexikon: Naturstoffe*. Stuttgart, Germany: Georg Thieme Verlag. 1997;590.

German Homoeopathic Pharmacopoeia (GHP). Translation of the *Deutsches Homöopathisches Arzneibuch* (HAB 1). First edition 1978 with 5 supplements through 1991. Stuttgart, Germany: Deutscher Apotheker Verlag. 1993;821–7

GHP. See: *German Homeopathic Pharmacopoeia*.

Gupta OP, Sing S, Bani S, *et al*. Anti-inflammatory and anti-arthritic activities of silymarin acting through inhibition of 5-lipoxygenase. *Phytomedicine* 1999;7(1):21–4.

Hammerl H, Pichler O, Studlar M. The effect of silymarin on liver diseases. [in German]. *Med Klin* 1971;66(36):1204–8.

Health Canada. Drug Product Database (DPD). Ottawa, Canada: Health Canada Therapeutic Products Programme. 2000.

Hikino H, Kiso Y. Natural Products for Liver Disease. In: Wagner H, Hikino H, Farnsworth NR. *Economic and Medicinal Plant Research,* Vol. 2. New York, NY: Academic Press. 1988.

Homeopathic Pharmacopoeia of the United States (HPUS) Revision Service Official Compendium from July 1, 1992. Falls Church, VA: American Institute of Homeopathy. June 1990;2276-CDMR.

HPUS. See: *Homeopathic Pharmacopoeia of the United States*.

Hruby, C. Silibinin in the treatment of deathcap fungus poisoning. *Forum* 1984;6:23–6.

Kalmar L, Kadar J, Somogyi A, *et al*. Silibinin (Legalon® 70) enhances the motility of human neutrophils immobilized by formyl-tripeptide, calcium ionophore, lymphokine and by normal human serum. *Agents Actions* 1990;29(3–4):239–46.

Katiyar SK, *et al*. Protective effects of silymarin against photocarcinogenesis in a mouse skin model. *J Nat Cancer Inst* 1997;89:556–65.

Kelly GS. Insulin resistance: lifestyle and nutritional interventions. *Altern Med Rev* 2000;5(2):109–32.

Kurz-Dimitrowa D. Preservation of liver function in psychiatric patients receiving long-term treatment with psychopharmaceuticals. [in German]. *Z Präklin Geriatr* 1971;9:275.

Leng-Peschlow E. Alcohol-related liver diseases-use of Legalon® for therapy. *Quart*

Rev Nat Med 1996a; summer:103–11.
Leng-Peschlow E. Properties and medical use of flavonolignans (silymarin) from *Silybum marianum*. *Phytother Res* 1996b;10(supl):S25–6.
Magliulo E, Gagliardi B, Fiori GP. Results of a double blind study on the effect of silymarin in the treatment of acute viral hepatitis, carried out at two medical centers. [in German]. *Med Klin* 1978;73(28–29):1060–5.
McCaleb RS, Leigh E, Morien K. *The Encyclopedia of Popular Herbs*. Boulder, CO: Herb Research Foundation; Roseville, CA: Prima Publishing, 2000.
McGuffin M, Hobbs C, Upton R, Goldberg A (eds.). *American Herbal Products Association's Botanical Safety Handbook.* Boca Raton, FL: CRC Press, 1997;107.
Medical Products Agency (MPA). *Läkemedel; Läkemedelsnära Produkter (registrerade homeopatiska produkter); Naturläkemedel (Authorised Natural Remedies)*. Uppsala, Sweden: Medical Products Agency. 2001.
Mereish K, Solow R. Effect of antihepatotoxic agents against microcystin–LR toxicity in cultured rat hepatocytes. *Pharm Res* 1990 Mar;7(3):256–9.
Meyer-Buchtela, E. Milk thistle fruits. [in German]. In: *Tee-Rezepturen—Ein Handbuch für Apotheker und Ärzte,* 1. Ergänzungslieferung. Stuttgart, Germany: Deutscher Apotheker Verlag, 1999.
Mingrino F, Tosti U, Anania S, *et al*. A Clinical investigation into the therapeutic effects of silymarin in acute infective hepatitis in children. *Min Ped* 1979;31:451–60.
Montanini I, Castigli E, Arienti UG, Porcellati G. The Effects of silybin on liver phospholipid synthesis in the rat in vivo. *Farmaco (Sci)* 1997 Feb;32(2):141–6.
Morant J, Ruppanner H (eds.). Bioforce Boldocynara N. In: *Arzneimittel-Kompendium der Schweiz*® 2001. Basel, Switzerland: Documed AG. 2001.
Morazzoni P, Bombardelli E. *Silybum marianum* (*Carduus marianus*). *Fitoterapia* 1995;66(1):3–42.
MPA. See: Medical Products Agency.
Mulrow C, Lawrence V, Jacobs B *et al.* Milk thistle: Effects on liver disease and cirrhosis and clinical adverse effects. Evidence Report/Technology Assessment, #21. Agency for Healthcare Research and Quality, 2000.
Müzes G, Deák G, Láng I, *et al*. Effect of silymarin (Legalon®) therapy on the antioxidant defense mechanism and lipid peroxidation in alcoholic liver disease: double blind protocol. [in Hungarian]. *Orv Hetil* 1990;131(16):863–6.
Müzes G, Deák G, Láng I, *et al*. Effect of the bioflavonoid silymarin on the *in vitro* activity and expression of superoxide dismutase (SOD) enzyme. [in Hungarian]. *Acta Physiol Hungar* 1991;78(1):3–9.
Palasciano G, Portincasa P, Palmieri V, *et al*. The effect of silymarin on plasma levels of malondialdehyde in patients receiving long-term treatment with psychotropic drugs. *Curr Therapeut Res* 1994; 55(5):537–45.
Par A, Roth E, Rumi G Jr, *et al*. Oxidative stress and antioxidant defense in alcoholic liver disease and chronic hepatitis C. [in Hungarian]. *Orv Hetil* 2000;141(30):1655–9.
Parés A, Planas R, Torres M, *et al*. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double blind, randomized and multicenter trial. *J Hepatol* 1998;28(4):615–21.
Poser G. Experience in the treatment of chronic hepatopathies with silymarin. [in German]. *Arzneimittelforschung* 1971;21(8):1209–12.
Ruppanner H, Schaefer U (eds.). *Codex 2000/01 — Die Schweizer Arzneimittel in einem Griff*. Basel, Switzerland: Documed AG. 2001.
Salmi HA, Sarna S. Effect of silymarin on chemical, functional, and morphological alterations of the liver. A double blind controlled study. *Scand J Gastroenterol* 1982;17(4):517–21.
Sarre H. The clinical experience regarding Silymarin in the treatment of chronic liver diseases. [in German]. *Arneimittelforschung* 1971;21(8):1209–12.
Schriewer H, Kastrup W, Wiemann W, Rauen HM. The antihepatotoxic effect of silymarin on lipid metabolism in the rat disturbed by phalloidine intoxication. [in German]. *Arzneimittelforschung* 1975;25(2):188–94.
Schuppan D, Strösser W, Burkard G, *et al*. Legalon® lessens fibrosing activity in patients with chronic liver diseases. [in German]. *Z Allgemeinmed* 1998;74:577–84.
Serne EH, Toorians AWFT, Gietema JA, *et al*. *Amanita phalloides*, a potentially lethal mushroom: Its clinical presentation and therapeutic options. *Netherlands J Med* 1996;49:19–23.
Sonnenbichler J, Sonnenbichler I, Scalera F. Influence of the Flavonolignan Silibinin of Milk Thistle on Hepatocytes and Kidney Cells. In: Lawson LD, Bauer R (eds.). *Phytomedicines of Europe: Chemistry and Biological Activity.* Washington, DC: American Chemical Society, 1998;263–77.
Thamsborg SM, Jorgensen, Brummerstedt E, Bjerregard J. Putative effect of silymarin on sawfly (*Arge pullata*)-induced hepatotoxicosis in sheep. *Vet Hum Toxicol* 1996;38(2):89–91.
Tongiani R, Malvaldi G, Bertelli A. Effects of dibensothioline and silymarin on the dry weight of isolated hepatocytes of rats acutely poisoned with phalloidin and alpha-amanitin. *Curr Probl Clin Biochem* 1977;7:87–101.
United States Congress (USC). Public Law 103–417: Dietary Supplement Health and Education Act of 1994. Washington, DC: 103rd Congress of the United States. 1994.
United States Pharmacopeia (USP 25th Revision) *National Formulary* (NF 20th Edition). Rockville, MD: United States Pharmacopeial Convention, Inc., 1999;2481–2.
USC. See: United States Congress.
USP. See: *United States Pharmacopeia*.
Valenzuela A, Aspillaga M, Vial S, Guerra R. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. *Planta Med* 1989;55(5):420–2.
Valenzuela A, Garrido A. Biochemical bases of the pharmacological action of the flavonoid silymarin and of its structural isomer silibinin. *Biol Res* 1994;27(2):105–12.
Velussi M, Cernigoi AM, DeMonte A, *et al*. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need, and malondialdehyde levels in cirrhotic diabetic patients. *J Hepatol* 1997;26(4):871–9.
Vogel G, Tuchweber B, Trost W, Mengs U. Protection by silibinin against *Amanita phalloides* intoxication in beagles. *Toxicol Appl Pharmacol* 1984;73:355–62.
Wang M, LaGrange L, Tao J. Hepatoprotective properties of *Silybum marianum* herbal preparation on ethanol-induced liver damage. *Fitoterapia* 1996;LXVII(2):166–71.
Weiss RF, Fintelmann V. *Herbal Medicine,* 2d ed. New York: Thieme, 2000.
WHO. See: World Health Organization.
Wichtl M. Milk thistle fruits. [in German]. In: *Teedrogen*, 2. Auflage. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft. 1989.
Wichtl M, Bisset NG (eds.). *Herbal Drugs and Phytopharmaceuticals.* Stuttgart, Germany: Medpharm Scientific Publishers, 1994;121–3.
World Health Organization (WHO). *Regulatory Situation of Herbal Medicines: A Worldwide Review*. Geneva, Switzerland: World Health Organization Traditional Medicine Programme. 1998;26–7.
Zhao J, Lahiri-Chatterjee M, Sharma Y, Agarwal R. Inhibitory effect of a flavonoid antioxidant silymarin on benzoyl peroxide-induced tumor promotion, oxidative stress and inflammatory response in SENCAR mouse skin. *Carcinogenesis* 2000;21(4):811–6.
Zi X, Grasso AW, Kung HJ, *et al*. A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells. *Cancer Res* 1998;58:1920–9.

Clinical Studies on Milk Thistle (*Silybum marianum* [L.] Gaertner)

Cirrhosis and Alcohol Liver Disease

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Parés *et al.*, 1998	Cirrhosis of the liver	DB, PC, R, MC n=125 alcoholic patients with cirrhosis of liver	2 years	1 capsule, 3x/day (420 mg silymarin/day) vs. placebo	Brand not stated	Compared to placebo, milk thistle extract had no significant effect on the course of disease after 2 years of treatment. Milk thistle did not improve survival rates, liver function tests, or histological parameters in patients with severe and acute alcohol-induced cirrhosis of the liver. No significant side effects were observed.
Bunout *et al.*, 1992	Alcoholic liver disease	PC, R n=59 patients with chronic alcoholic liver disease	15 months	1 capsule, 2x/day (280 mg silymarin/day) vs. placebo	Brand not stated	Compared to placebo, milk thistle did not change the evolution of mortality of alcoholic liver disease within 15 months. 10 patients died during follow-up (5 milk thistle and 5 placebo). In milk thistle group 58% continued to drink alcohol during trial and follow-up; 65% in control group continued to drink alcohol. Authors note higher dose used in other studies gave positive results.
Deak *et al.*, 1990	Alcoholic liver disease	DB, PC (n=not available) Patients had chronic alcoholic liver disease	6 months	Silymarin (dose not available) vs. placebo	Legalon® 70	Compared with placebo, milk thistle significantly enhanced lectin-induced proliferative activity of lymphocytes, normalized the originally low T-cell percentage and originally high CD8+ cell percentage, and decreased antibody-dependent and natural cytotoxicity of lymphocytes. There were no significant changes in placebo group with the exception of moderate elevation of T-cell percentage.
Müzes *et al.*, 1990	Alcoholic liver disease	DB, PC (n=12) patients with chronic alcoholic liver disease (mean age 37±9 years)	6 months	420 mg silymarin/day vs. placebo	Legalon® 70	Milk thistle extract significantly enhanced low superoxide dismutase (SOD) expression on lymphocytes as determined by flow-cytoflourimetry. Milk thistle markedly increased glutathione activity but decreased serum malondialdehyde concentration. No significant changes reported in placebo group.
Fehér *et al.*, 1989	Alcoholic liver disease	DB, PC n=36 chronic alcoholic patients with hepatic fibromatosis or micronodular cirrhosis	6 months	2 capsules, 3x/day (420 mg silymarin/day) vs. palcebo	Legalon® 70	Compared to baseline and placebo, milk thistle significantly normalized serum bilirubin, aspartate aminotransferase (AST), and alanine-aminotransferase (ALT) values. Histological alterations improved in milk thistle group and remained unchanged in placebo group. The authors concluded a significant decrease in serum procollagen-III peptide levels combined with improved histological changes confirmed that milk thistle can be recommended as supportive therapy in chronic alcohol disease.
Ferenci *et al.*, 1987	Alcohol and non-alcohol-induced cirrhosis	R, DB, PC n=170 patients with cirrhosis (92 alcoholic; 78 non-alcoholic)	2–6 years, mean observation period 41 months (Patients were treated with silymarin for only 2 years)	2 capsules, 3x/day (420 mg silymarin/day) vs. placebo	Legalon® 70	No significant change in biochemical parameters at 2 years. However, 2-year survival rate was 82% in milk thistle group vs. 68% placebo; 4-year survival rate was 58± 9% with milk thistle and 39± 9% with placebo (p=0.036). Survival rate was higher in subgroup of patients with alcoholic cirrhosis (p=0.01) and in Child's A group classification of portal hypertension, though treatment was ineffective in Child's B and C group hypertension. No adverse effects observed.
Salmi and Sarna, 1982	Alcohol liver disease	R, DB, PC n=97 patients with slight acute and subacute liver disease	4 weeks with 3 additional re-examinations 1, 2, and 3 weeks after start of the trial (alcohol abstinence required during the trial)	2 capsules, 3x/day (420 mg silymarin/day) vs. placebo	Legalon® 70	After 4 weeks, milk thistle caused a highly significant (30%) decrease in mean serum AST levels compared to a 5% increase in placebo group. ALT levels decreased by 41% in milk thistle group and increased 3% with placebo. Histological changes normalized more significantly in milk thistle group. Milk thistle decreased serum total and conjugated bilirubin more than placebo, but not at a statistically significant level.
DiMario *et al.*, 1981	Fatty liver, alcoholic hepatitis, hepatic cirrhosis	DB, PC n=43 patients with alcohol-induced liver disease	1–2 months	420 mg silymarin/day vs. placebo	Legalon® 70	Significantly improved markers of liver function (AST ($p<0.05$); ALT ($p<0.01$); bilirubin ($p<0.05$, and prothrombin ($p<0.05$). Significantly improved clinical symptoms of weakness, anorexia, and nausea.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Milk Thistle (*Silybum marianum* [L.] Gaertner) (cont.)

Cirrhosis and Alcohol Liver Disease (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Fintelmann and Albert, 1980	Alcohol liver disease	R, DB, PC n=66 patients with acute alcoholic hepatitis	1 month	2 capsules, 3x/day (420 mg silymarin/day) vs. placebo	Legalon® 70	Treatment with milk thistle caused mean AST, ALT, and GGT levels to normalize significantly and much sooner (13 vs. 24 days) than placebo. More patients in milk thistle group experienced normalization of all 3 parameters vs. placebo. Significant differences were evident after 1 week.

Hepatitis

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Buzzelli *et al.*, 1993	Chronic active hepatitis due to HBV and/or HCV	R, DB, PC n=20 patients with HBV- and/or HCV-related chronic active hepatitis	1 week	2 capsules, 2x/day (2 hours before breakfast and dinner) (480 mg silymarin/day) vs. placebo	IdB 1016 Silipide 1 capsule contains 150 mg purified dry extract equivalent to 120 mg silymarin.	Milk thistle significantly reduced mean serum concentrations of AST and ALT ($p<0.01$), total bilirubin ($p<0.05$), and gamma-glutamyltranspeptidase (GGT) ($p<0.02$). However, there were no significant changes in malonaldehyde, copper, or zinc serum concentrations. Milk thistle improved hepatic function, mainly by reducing transaminases and other indices (GGT and total bilirubin) related to liver cell necrosis and/or hepatocyte membrane permeability.
Magliulo *et al.*, 1978	Acute viral hepatitis A and B	R, DB, PC, MC n=57 patients with acute viral hepatitis (14–66 years)	21–28 days (average 24.9 days)	2 tablets, 3x/day (420 mg silymarin/day) vs. placebo	Legalon® 70	After 5 days, mean levels of AST, ALT, and total bilirubin were significantly lower in milk thistle group compared to placebo. At 3 weeks, milk thistle group showed significant normalization of bilirubin (40% vs. 11%) and AST (82% vs. 52%) compared to placebo. Milk thistle did not influence the course of the immune reaction in hepatitis B surface antigen (HbsAg). Milk thistle extract caused accelerated regression of pathological markers, and authors concluded that it can be indicated for use in the treatment of acute viral hepatitis.
Hammerl *et al.*, 1971	Chronic hepatitis, cirrhosis and toxic damage to liver	O, U n=43 (14 chronic hepatitis, 22 cirrhosis, 7 toxico-metabolic liver damage)	more than 1 year	First 3 weeks: 3 tablets, 3x/day (315 mg silymarin/day) reduced to 2 tablets, 3x/day (210 mg silymarin/day)	Legalon® 35	Milk thistle showed significant changes in all test parameters including bromsulphalein test (liver excretion function), albumin/globulin quotient (mesenchymal reaction), serum, bilirubin, transaminase, and serum triglycerides (metabolic performance of liver) and a preponderant trend towards normalization. Authors concluded that milk thistle has a protective and curative action on liver.
Poser, 1971	Chronic liver disease	O, U n=67 out-patients with toxic metabolic liver damage, chronic hepatitis, and cholangitis (4–64 years)	3 months	3–5 tablets, 3x/day (315–525 mg silymarin/day) depending on severity of condition	Legalon® 35	Milk thistle significantly improved SGOT, SGPT, and glutamate-dehydrogenase (GLDH), but there was no statistically significant difference in bilirubin level. After 3 months, chronic-persisting hepatitis was bioptically cured and conditions associated with bile duct inflammation improved. Patients with cholangitic hepatopathies (bile duct inflammation) responded especially well to milk thistle treatment.
Sarre, 1971	Chronic persisting hepatitis and other hepatopathies	E n=67	3 months	3–5 tablets, 3x/day (315–525 mg silymarin/day) depending on severity of condition	Legalon® 35 Dragées	Significantly decreased SGOT, SGPT, and GLDH. No effect on bilirubin levels. Bioptically cured chronic-persisting hepatitis. Toxic-metabolic and cholangitic hepatopathies responded well to silymarin treatment. Effective in treating both young (4 years) and old (64 years) patients without adverse side effects.

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Clinical Studies on Milk Thistle (*Silybum marianum* [L.] Gaertner) (cont.)

Psychotropic Drug-Induced Liver Damage

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Palasciano *et al.*, 1994	Heptatic damage caused by psychotropic drugs (variety of xenobiotic compounds)	DB, PC, R n=60 female psychiatric patients receiving chronic psychotropic drug therapy (40–60 years)	90 days, examined at baseline, days 15, 30, 60, and 90, and again at 30 days after completion	Group 1A & B: psychotropic drugs with either 400 mg silymarin, 2x/day or placebo Group 2A & B: suspension of psychotropic drugs with either 400 mg silymarin, 2x/day or placebo	Purified silymarin (brand not stated)	Silymarin reduced lipoperoxidative hepatic damage resulting from treatment with butyrophenones and phenothiazines. Effect of silymarin was greater when treatment with psychotropic drugs was suspended. Serum levels of malondialdehyde decreased, and indices of hepatocellular damage improved with silymarin. Using ANOVA test for repeated measures, a significant treatment-time interaction was observed for silymarin ($p=0.005$). Study suggests that silymarin treatment for lipoperoxidative hepatic damage may be beneficial in cases of long-term psychotropic drug treatment.
Kurz-Dimitrowa, 1971	Psychoactive or anti-convulsant drug therapy	n=66 psychiatric patients	61 days	1–3 tablets, 3x/day (105–315 mg silymarin/day)	Legalon® 35	Normalized bromsulphalein levels in 54% of patients, normalized or improved GOT levels in 68% of patients, and improved vitality and mood in patients receiving psychoactive drugs.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Schuppen *et al.*, 1999	Fibrosis in chronic liver disease	OL (drug monitoring study) n=874 men and women (average age 55)	3 months	140 mg, 3x/day	Legalon®	Primary test parameter was amino terminal procollagen-III peptide (PIIINP) readings, as an indicator of fibrogenesis, with this factor dropping to normal range in 19% of patients. Total score of symptom scale showed definite and a clinically relevant decrease in subjective symptoms during treatment (e.g., lack of appetite, nausea, upper abdominal pressure). Of the subjects, 98% confirmed that Legalon® was well-tolerated; 2% reported moderate or poor tolerability (e.g., diarrhea, flatulence, gastrointestinal fullness, gastrointestinal pain).
Allain *et al.*, 1999	Aminotransferase levels in tacrine-induced liver transaminase elevation	R, DB, PC n=217 patients with mild to moderate Alzheimer's dementia	12 weeks	420 mg/day silymarin, and 40 mg/day tacrine for 6 weeks, then increase to 80 mg/day tacrine or tacrine (same dose), and placebo	Legalon® (silymarin) Cognex® (tacrine)	Silymarin does not prevent tacrine-induced ALAT elevation but does reduce rate of gastrointestinal and cholinergic side effects without impact on cognitive status. Silymarin can be used to improve tolerability of tacrine in initial phases of Alzheimer's treatment.
Velussi *et al.*, 1997	Diabetic patients with cirrhosis	R, O, C, Cm n=60 cirrhotic patients	1 year	2 capsules, 3x/day (420 mg silymarin/day) plus standard therapy vs. standard therapy	Legalon® 70	After 4 months, milk thistle significantly decreased ($p<0.01$) fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels. Authors conclude that treatment with milk thistle may reduce lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and need for exogenous insulin administration.
Fintelmann, 1973	Narcotic use in cholecystectomy surgery	C, Cm n=83 patients undergoing cholecystectomy	12 days (2–4 days pre-operative; 1–8 days post-operative)	2 tablets, 3x/day (210 mg silymarin/day) or 4 tablets, 3x/day (420 mg silymarin/day)	Legalon®	Pre- and post-operative administration of 4 tablets, 3x/day appeared to decrease toxicity of narcotics used in cholecystectomy surgery. Compared to control, milk thistle did not have a significant effect on enzyme parameters. Authors caution that their study is inconclusive due to a small patient population, a duration of pre-operative dosing that was too short, and research conditions that were not optimal.

Amanita Mushroom Poisoning

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Hurby *et al.*, 1984	Acute *Amanita* poisoning	U, MC n=220 patients with *Amanita* poisoning	4 years (1979–82)	20 mg/kg weight i.v.	Purified silibin i.v. infusion (brand not stated)	Mortality rate of 12.8% in silybin group. Authors conclude that use of silybin i.v. as an adjunct to standard treatment methods lowers mortality rates below previously known levels.

KEY: **C** – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.