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.

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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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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.

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