Milk Thistle
Dry Extract

For the Treatment of Toxic Liver Damage
Milk Thistle Fruit Extract

Introduction

EUROMED is a company specialized in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces therapeutically active raw materials.

The botanical raw materials are subject to strict selection and inspection, and products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutical points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices, therapeutic applications on a scientific basis.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.
Milk Thistle Fruit Extract

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1 Milk Thistle Extract:
   General Information

1.1 Description
The milk thistle dry extract is a standardized herbal extract of the fruits of Silybum marianum (L.) Gaert. (Fam. Asteraeae; formerly Compositae)

The extract of Cardui Mariae Fruct. is a herbal preventive and therapeutic agent against metabolic liver diseases. The therapeutic effect is based on

- Stimulation of RNA polymerase I in liver cells
- Stabilization of liver cell membranes
- Antioxydative properties

The Milk thistle extract protects liver cells both directly and indirectly. It also possesses the unique ability to regenerate liver cells that have been injured.

There are no reports on interaction of milk thistle extract with other drugs.

1.2 Indications
The extract of milk thistle is used in the treatment of toxic liver damage and is also recommended for supportive treatment of chronic inflammatory liver diseases and cirrhosis.
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1.3 Extract Specifications

Finished preparations usually contain about 80-375 mg of milk thistle extract (as available from EUROMED). Table 1 shows a survey of popular milk thistle preparations on the market [1].

1.4 Dosage and Methods of Administration

A daily oral dose of 200-400 mg of silymarin as silibinin for 6 to 8 weeks is common practice. Once improvement begins it may be reduced to 280 mg daily. It is frequently used in combination with other plant extracts.

1.5 Contraindications and Interactions

None known up to date

1.6 Side-effects

Well tolerated

In individual cases a mild laxative effect has been observed.
**Milk Thistle Fruit Extract**

Table 1: European mono-preparations containing milk thistle dry extract

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Content of Milk Thistle Extract [mg] (Silymarin)</th>
<th>Total Extract/day [mg] (Silymarin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardeyhepan N</td>
<td>250 (100)</td>
<td>500-1000 (200-400)</td>
</tr>
<tr>
<td>Legalon 140</td>
<td>180(140)</td>
<td>360-540 (280-420)</td>
</tr>
<tr>
<td>Cefasilymarin</td>
<td>180 (140)</td>
<td>360-540 (280-420)</td>
</tr>
<tr>
<td>Durasilymarin</td>
<td>375 (150)</td>
<td>750 (300)</td>
</tr>
<tr>
<td>Hepaduran V</td>
<td>80 (40)</td>
<td>480 (240)</td>
</tr>
<tr>
<td>Hepaloges N</td>
<td>150 (63)</td>
<td>900 (378)</td>
</tr>
<tr>
<td>Hepa-Merz Sil.</td>
<td>239 (167)</td>
<td>478-717 (334-501)</td>
</tr>
<tr>
<td>Heparano N</td>
<td>170 (84)</td>
<td>510 (252)</td>
</tr>
<tr>
<td>Hepar-Pasc</td>
<td>140 (100)</td>
<td>280-560 (200-400)</td>
</tr>
<tr>
<td>Hepatorell</td>
<td>160 (110)</td>
<td>480-640 (330-440)</td>
</tr>
<tr>
<td>Hepatos Mariendisteldragees</td>
<td>240 (100)</td>
<td>480-960 (200-400)</td>
</tr>
<tr>
<td>Heplant</td>
<td>140 (84)</td>
<td>420-560 (252-336)</td>
</tr>
<tr>
<td>Silbene</td>
<td>285 (200)</td>
<td>285-570 (200-400)</td>
</tr>
<tr>
<td>Silimarit</td>
<td>200 (140)</td>
<td>400 (280)</td>
</tr>
</tbody>
</table>
Milk Thistle Fruit Extract

2 From Plant to Extract

2.1 Milk Thistle Fruits (Silybum marianum): Botanical Data

The milk thistle, a annual, mediterranean plant, which belongs to Asteraceae. It can, however, also be found in warm, dry regions of Central Europe as well as South America and South Australia.

Today all material used for extract production, comes from cultivated plant material\(^1\).

The milk thistle is about 80 to 150 cm height, with a slightly wooly stem, upright and in the upper parts branched. The leaves have toothed spiny margins and are pencilled with white veins. At the top of the stem or at the ramifications there are large, spheroidal flower heads, purple coloured, surrounded by spiny, involucral bracts resembling leaves. The tubular flowers are hermaphrodite. The ripe, 6 to 7 mm long fruits are smooth, mostly dark-brownish, and have white, silky hairs at their apex.\(^2\)
Milk Thistle Fruit Extract

Fig. 1: Milk Thistle (Silybum marianum Gaertn.)
2.2 Historic Use

The name *Silybum* is derived from the name given to edible thistles during the first century by Dioscorides. The name *marianum* comes from the legend that the white mottling of the leaves was caused by a drop of the Virgin Mary's milk.

*Silybum* was used as an officinal plant in Graeco-Roman time and the Middle Ages. Its application in the treatment of liver diseases, however, was first mentioned by Haller in 1755. Later in the 19th century, the milk thistle “seeds” were repeatedly mentioned in connection with liver, gallbladder and pancreatic disorders. Intensive research during the last 35 years into the active principle of the milk thistle fruits and pharmacological properties has led to silymarin to be one of the best documented medicinal plant compound.

Today Extractum Cardui mariae, standardized to Silymarin is one of the most important remedies for the treatment of toxic liver diseases.

2.3 Chemistry of Milk Thistle Extract
The milk thistle fruit extract contains different chemical substances like:

**Flavolignans:** 1.5 to 3% Silymarin\(^4,5\), (Fig. 2) an isomer mixture of the flavolignanes\(^6\) silybin\(^7,8\), silychristin\(^9,10\) and silydianin\(^11\) (Inn: silibinin, silichristin, silidianin). Silibinin is a 1:1 diastereomer pair in respect of the configuration of substituents on the benzodioxan ring\(^8,12\). Other flavonolignans like isosilybin\(^13\), isosilichristin\(^14\), dehydrosilibin\(^15\) and dehydrosilichristin\(^16\) in low concentrations are found.

**Flavonoids:** Apigenin, chrysoeriol\(^17\), 5,7-dihydrixchromone\(^16\), dihydrokaepferol\(^18\), eriodictyol\(^17\), isofraxidin\(^19\), naringenin\(^17\), quercetin\(^20\) and taxifolin\(^14\).

**Neolignan:** Dehydroconiferyl alcohol\(^21\)

**Aliphatic oil:** 20-30% with a high yield of linoleic acid (ca. 60%) oleic acid (20-30%) and palmitic acid (7-9%) as well as some other fatty acids and sterols together with tocopherol\(^22,23\).
MILK THISTLE FRUIT EXTRACT

Fig. 2 Silymarin Isomers

Silibinin

Silicristin

Silidianin
2.4 Preparation of the Extract and Quality Control

Milk thistle, the plant of Cardui mariae fruct. originates from material grown in Europe. From these fruits, specially identified and with a standard quality, 
EUROMED manufactures Milk thistle extract. The plant material used for Milk thistle extract is primarily cultivated. Permanent professional botanical inspections are part of the growth of the crops and ensure that conditions of cultivation, harvest, drying and storage are up to the highest standards. This way the extract quality of Milk thistle extract is maintained.

When the plant material arrives at 
EUROMED an exhaustive inspection of the raw material is carried out according to the current methods in order to guarantee the quality of the final product. Furthermore 
EUROMED evaluates the possible contamination of the drug. Only high-quality raw plant material selected according to the strictest criteria is used.

EUROMED applies an extraction process which provides a high yield of valuable constituents and a high-grade extract in a careful way.
MILK THISTLE FRUIT EXTRACT

According to the original processes EUROMED produces a dry extract from the fruits of Cardui mariae:

- **EXTR. CARDUI MARIAE FRUCT. SICCUM**
  (MILK THISTLE DRY EXTRACT)
  Fine, light brown powder, hygroscopic.

EUROMED milk thistle extract satisfies the highest quality standards. This way it is possible to meet the requirements for an effective and safe medication.

2.5 Standardization

The consistent batch to batch quality of the EUROMED milk thistle extract is guaranteed by the standardized production process.

The analytical specifications of the milk thistle extract are:

- **Aspect**
  Fine powder, light brown color, hygroscopic

- **Identification**
  TLC (DAB)

- **Loss on drying**
  Max. 2.0%

- **Assay**
  Silymarin calculated as Silybin min. 80% (Adapted spectrophotometric method DAB-10, 2.N.1993)
  @Silymarin calculated as silibinin min. 65% (HPLC DAB method)

- **Microbiology**
  Acc. Ph. Eur. 3rd ed., 5.1.4, category 3B
3 Toxic Liver Damage

Metabolic functions of the liver

The liver has many functions; this has been beautifully described by Pablo Neruda. You can look at your liver as a factory which produces many substances (synthesis) and which maintains the balance in the body of many nutrients (homeostasis). Our body makes many waste products (such as e.g. bilirubin - the degradation product of the red dye in our blood) which can be excreted only by the liver (excretory function). The liver plays a central role in the detoxification of drugs. Drugs are being taken up by the liver, degraded and excreted. The liver is placed strategically between the gut and the rest of our body; thereby it acts as a filter and prevents the passage of bacteria from the gut into the blood. Thus, the liver is also an important player in our defense mechanisms. You will find some important functions listed in the table.
The metabolic activities of the liver are:

**Homeostasis of:**

- Glucose (sugar)
- proteins
- fat and cholesterol
- hormones
- vitamins, in particular the fat soluble ones (A, D, E and K)

**Synthesis of:**

- proteins including the clotting factors
- bile acids (products of cholesterol, important in fat digestion)
- cholesterol

**Storage of:**

- vitamins
- cholesterol

**Excretion of:**

- cholesterol, bile acids, phospholipids
- bilirubin
- drugs
- poisons (e.g. pesticides, insecticides, heavy metals)
Milk Thistle Fruit Extract

Filter of:

- poisons from the gut
- nutrients such as amino acids, sugar and fat
- bilirubin, bile acids
- IgA
- Drugs

Defense against:

- Excretion of IgA (defense against bacteria in the gut)
- Special macrophages (Kupffer cells) gobble up bacteria which have crossed from the gut into the blood. Macrophage means "big eater" and so they are!
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Protein biosynthesis and biotransformation are of special relevance to the therapeutic action of silymarin.

Protein biosynthesis:

Among the fundamental processes of protein biosynthesis is the transcription of DNA into various types of RNA in the nucleus by means of DNA-dependent polymerases I, II and III. The RNA types then pass into the cytoplasm.

Biotransformation:

Biotransformation denotes the process by which foreign substances (= xenobiotics; xenos (greek) = stranger) such as environmental pollutants and drugs are transformed by means of enzyme systems into hydrophilic substances which are more readily excreted.

Biotransformation takes principally place in the liver (in the hepatocytes) and only to a minor extend in other organs (e.g. intestine, kidney, spleen, skeletal muscles, skin or blood).
3.2 Epidemiology

Toxic liver damage, an extremely common disease

The most common cause of liver disease in humans is chronic alcoholism. Depending on the period and quantity of alcohol consumption, a fibrotic restructuring of the liver cell occurs along with an impairment of liver function which can finally result in cirrhosis of the liver.

The majority of cases of toxic liver damage in Germany are related to alcohol (71%), but they also include toxic liver damage caused by drugs (18) and occupational toxins (11%). More than 30% of those patients claiming regular exposure to occupational chemicals or use of drugs also report a regular consumption of alcohol\textsuperscript{24}. 

3.3 Etiology

Modern lifestyle of western civilization is part of the reasons for liver diseases. There are several xenobiotics which effect liver function.

- Chronic Alcoholism
- Drugs
- Toxines
- Occupational Toxines

Various xenobiotics, in particular those which because of their lipid solubility persist for long periods within the liver, may act as enzyme inducer.

As a consequence of enzyme induction, there is an increase in breakdown capacity and hence in biotransformation rate. This may be of benefit if it speeds up the elimination of foreign substances or of metabolic products which can no longer be utilized.

The increased biotransformation of certain substances, however, may also lead to an increased formation of toxic metabolites, e.g. radicals, as short-lived intermediate compounds, with toxic effects.
MILK THISTLE FRUIT EXTRACT

3.4 Symptoms

Clinical symptoms of liver diseases are very diffuse. Among them are

- Anorexia
- Nausea
- Upper abdominal pain and pressure in the epigastrium
- Lassitude and general weakness
- Pruritus

Other important indicators for liver damage is an increase of hepatic enzymes. Damaged cells release more cell constituents which is shown, for example, by an increase in serum transaminases. Most of the liver damages coincides with an increased activity of hepatic enzymes in the serum.
3.5 Stages

Intoxication in the liver develops consecutively following stages.

- Incorporation of fat into the liver cells
- Fibrosation of the in parts
- Liver cirrhosis

3.7 Therapy

Therapy of toxic liver damage should at first exclude the toxic agents and then following a treatment with Silymarin. Due to its good anti-hepatotoxic effects Silymarin will rapidly normalize the liver function, particularly in cases of alcohol-induced liver damage, but also in liver damage caused by drugs and occupational toxins. Subjective complaints will also decline rapidly.
4 Pharmacology

4.1 Pharmacodynamic

The therapeutic benefit of milk thistle extract and its main constituent silymarin in the treatment of liver damage is essentially based on

- a membrane effect
- an antiperoxidative action
- regenerative effects
- an antifibrotic effect

Numerous experimental models of toxic liver damage demonstrated the anti hepatotoxic activities of Silymarin.
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4.1.1 Membrane effect

Silibinin the major isomer of silymarin was investigated in several experimental models to show the effects on membranes. One of the most important result was that silibinin is able to block binding sites and by this to hinder the uptake of xenobiotics, e.g. fungal toxins.25

Fig. 2: Uptake of amatoxin by perfused liver in relation to silbicin concentration (= controls).25 There is no interference with physiological gradient-controlled transport processes or with active transport into or out of the cell.

In experimental animals poisoned with various liver poisons (CCl₄, peraesodymium nitrate, galactosamine or paracetamol) silymarin counteracts the increased liberation of liver enzymes into the serum.26, 27, 28, 29, 30, 31, 32, 33
4.1.2 Antiperoxidative action

Several hepatotoxic substances tend to increase lipid peroxidation in the liver. Lipid peroxidation damages the cell membrane and adversely affects metabolic processes.

Due to its phenolic structure, silibinin possesses radical-capturing powers and hence acts as an antioxidative agent. Silibinin blocks the release of malondialdehyde and the increased uptake of oxygen induced by peroxidative agents. Many other investigations confirmed the antiperoxidative action.

Fig. 3: Silibinin inhibits the formation of malondialdehyde (MDA) induced by adding NADPH-Fe^{2+}-ADP.

Further research has indicated that silymarin also stimulates the activity of the antioxidant enzyme superoxide dismutase and also exerts an immunomodulating activity.
4.1.3 Regenerative effects

Silibinin raises the activity of RNA polymerase I (polymerase A) in the nucleus, specifically stimulating transcription rate and hence the rate of synthesis of mRNA in the liver cell\textsuperscript{38, 39}. Due to the accelerated synthesis of rRNA there is an increase in the numbers of ribosome in the cell and hence an increase in protein synthesis\textsuperscript{40}.

![Diagram of primary molecular processes within the cell](image)

Fig.4: Diagram of primary molecular processes within the cell

This involves both structural proteins (membrane proteins) and functional proteins (enzymes). The overall biosynthetic capacity of hepatocytes is hereby benefited and enhanced\textsuperscript{41}. Any enhancement of biosynthetic capacity of hepatocytes is of great value in the regeneration of the liver. The increases in rRNA and protein synthesis can enhance DNA synthesis and hence speed up regeneration, provided that they have been preceded by an additional stimulus.
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This stimulus may be provided by liver damage caused by hepatotoxic substances or under experimental conditions, by partial hepatectomy. The outcome is accelerated cell regeneration.

4.1.4 Antifibrotic effect
In rat secondary biliary fibrosis (induced by bile duct obliteration with ethibloc) silibinin has an antifibrotic effect, the collagen disposition slows down by more than 50%. This animal model is characterized by low inflammation, it can be supposed that direct antifibrotic effects of silymarin may be involved.
4.2 Pharmacokinetics

4.2.1 Animal pharmacokinetics

Studies in rats and dogs show that up to 50% of an oral dose of silibinin, the main active isomer of silymarin, is absorbed. This has been ascertained by measuring the amount of excreted bile. By far the greatest proportion (four–fifths) is eliminated in the bile, in rats and human beings alike\(^48\).

As the substance is sparingly soluble in water and when formed spontaneously is to appear as unabsorbable microcristals. Its bioavailability is therefore dependent on the pharmaceutical preparation, a fact that has been shown in various extract preparations\(^49\).

4.2.2 Human pharmacokinetics

Silibinin is rapidly absorbed after oral administration. The maximal plasma concentration is reached at 1.3 hours\(^50\). The half life is approx. 6 hours\(^51\). As shown by in-vitro studies, the proportion of silibinin bound to plasma protein is 90-95%. Renal elimination of silibinin is low. In the first 24 hours after oral administration of silymarin between 1 and 2.1% of the silibinin is excreted in the urine\(^50\).
5 Toxicology

Low toxicity

Acute Toxicity

In acute experiments silymarin proved practically nontoxic. Male and female mice tolerated oral doses of 0.5 to 20 g/kg body weight without symptoms. Mongrel dogs tolerated an oral single dose of 1 g silymarin/kg body weight without adverse effects.

Chronic Toxicity

Trials of the subchronic toxicity of silymarin were performed in rats of both sexes at a daily oral dose of 1 g/kg body weight for 15 days or in another study rats were given 100 mg/kg body weight daily for up to 22 weeks. In both studies the rat’s behavior was consistently normal and they gained weight. The investigations did not show any relevant differences between the treated groups and controls, and the analiticopathological findings showed no evidence of any possible target organs.
Reproduction Toxicology

Investigations of possible embryotoxic effects have been performed in rats and rabbits. Oral application of 100 mg/kg body weight given from the eighth to seventeenth days after conception, rats 1g/ kg body weight from the eighth to twelfth days after conception did not show any significant difference between the silymarin treated groups and the controls. There were no maltransformations either in the internal organs or the skeleton\textsuperscript{52}.

Genotoxicity/Carcinogenicity

There are no data available.
6 Clinical Pharmacology

6.1 Toxic liver damage

Mushroom poisoning comes in most cases (90%) from ingestion of Death cap (Amanita phalloides). The Amanitin, the toxic principle of Amanita phalloides blocks the RNA-polymerase in liver cells. After a latez period of about 12-24 hours the y die. The action of silibinin is to dislodge the amanitin competitively from the enzyme and thus set protein biosynthesis going on.

The clinical relevance was shown in several case reports. In former years, without silibinin treatment of mushroom intoxication the mortality rate was 30-50%. Among the recorded cases with Silibinin treatment, the mortality was 1 of 18 patients.
7 Proof of Clinical Efficacy

7.1 Clinical Trials with Placebos

Several randomized double-blind and placebo-controlled studies comprising a total of more than 250 patients with toxic liver damage due to alcohol showed a more rapid normalization of the transaminases GOT and GTP after treatment with silymarin (420 mg/day).

The normalization of $\gamma$-GT activity and improvement of the liver function (bilirubin, BSP-retention) were more rapid too.
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Daily doses of silymarin (420 mg/day) or placebo were given for 4 weeks to patients with toxic liver damage. A curative action was demonstrated under double-blind conditions by changes in the markers of toxic liver cell damage, the enzymes GOT, GTP and γ-GT.

Fig. 5: GTP activities (X) in patients with toxic liver damage receiving silymarin (420 mg/day or placebo)

There were significant differences between the two groups in serum transaminase and γ-GT levels measured on the 18 day period.
At the commencement of the study mean \( \gamma \)-GT levels were over 300 U/l in the placebo group and over 400 U/l in the verum group. After 14-24 days’ treatment the fall in the Silymarin group was significantly greater than in the placebo group.

In an other trial comprising 97 patients with elevated serum transaminase levels due to alcohol – induced liver damage the superiority of silymarin (420 mg/day over 4 weeks) over placebo was clearly demonstrated by a more rapid improvement in the liver enzymes GOT and GTP and in bilirubin and BSP retention\(^56\).

![Graph showing action of silymarin on GOT and GTP](image)

Fig. 6: Action of silymarin (420mg/day) on GOT and GTP as compared with placebo in patients with alcohol-induced liver damage\(^56\).

The curves of GOT and GTP showed statistically significant differences between the silymarin and placebo groups.

Histological examination, carried out before and after the therapy showed significantly superior results in the silymarin group in comparison to the control group.
These results were improved in another study in patients with alcohol-induced liver disorders. Administration of Silymarin (420 mg/day) over two months produced a significant improvement in various markers of liver function (GOT, GTP, bilirubin and prothrombin time) as compared with a placebo group.

TAB. 2: Liver function tests before and after treatment with silymarin (L) or Placebo in patients with alcohol-induced liver damage.

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOT</strong></td>
<td>L 0–12 U/l</td>
<td>41.16±</td>
<td>25.39±</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>20.20±</td>
<td>15.60±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>GPT</strong></td>
<td>L 0–12 U/l</td>
<td>40.75±</td>
<td>23.45±</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>15.42±</td>
<td>16.37±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Alkaline</strong></td>
<td>L 30–85 U/l</td>
<td>166.8±</td>
<td>165.3±</td>
<td>n.s.</td>
</tr>
<tr>
<td>phosphatase</td>
<td>P</td>
<td>66.1±</td>
<td>56.2±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>L 0.1–0.8 mg/dl</td>
<td>2.82±</td>
<td>1.42±</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.60±</td>
<td>0.53±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>L 160–260 mg/dl</td>
<td>182.7±</td>
<td>178.7±</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>71.2±</td>
<td>65.3±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Albunin</strong></td>
<td>L 3.5–5 g/dl</td>
<td>3.77±</td>
<td>4.19±</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>1.05±</td>
<td>1.16±</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Prothrombin</strong></td>
<td>L 100%</td>
<td>75.41±</td>
<td>91.56±</td>
<td>&lt;0.05</td>
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<tr>
<td>time</td>
<td>P</td>
<td>12.30±</td>
<td>8.40±</td>
<td>n.s.</td>
</tr>
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</table>

**Improvement of subjective symptoms**
MILK THISTLE FRUIT EXTRACT

Clinical symptoms such as weakness, anorexia and nausea also improved significantly in the silymarin group as compared to the placebo group.

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>p</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper abdominal pain</td>
<td>0.01</td>
<td>Silymarin</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>Placebo</td>
</tr>
<tr>
<td>Weakness</td>
<td>0.05 n. s.</td>
<td>Silymarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.01 n. s.</td>
<td>Silymarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.01 n. s.</td>
<td>Silymarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Tab.3: Clinical symptoms before and after treatment with silymarin or placebo in patients with alcohol-induced liver damage\(^57\).
36 patients with chronic alcoholic liver disease (fibrosis of the liver of the micronodular type cirrhosis) were treated over 6 months with silymarin (420 mg/day) or placebo. Although the patients reduced their alcohol-intake during the study, there was a significant reduction of γ-GT, transaminases and bilirubin in the silymarin group only. These values were much lower in the treatment group than in the placebo group. The control biopsies showed an improvement only in the silymarin group.

Fig. 7: Serum GTP, GOT and bilirubin values after 6-months treatment with silymarin or placebo

\[ \text{Fig. 7: Serum GTP, GOT and bilirubin values after 6-months treatment with silymarin or placebo}^{58} \]
Lipid peroxidation induced by free radicals harms the liver especially when the glutathione-concentration is low, and contributes much to alcoholic liver damage. Increased serum malondialdehyde (MDA) levels are regarded as a parameter for increased lipid peroxidation. The reduction of MDA during treatment with silymarin, can therefore, be considered as an evidence for an antiperoxidative effect.

Fig. 8: Serum malondialdehyde in patients with chronic alcoholic liver disease before and after treatment with silymarin (420 mg daily) or placebo.
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*Silymarin in the supportive treatment of hepatic cirrhosis*

Favourable responses to silymarin have also been observed in patients with hepatic cirrhosis. In view of the strongly progressive tendency of this disease, any retardation of its advance can be regarded as success. A placebo-controlled randomized double-blind trial was performed to answer the question whether long-term administration of silymarin can influence the course of cirrhosis. The trial comprised 170 patients with hepatic cirrhosis. The diagnosis was verified by biopsy in 70%, but the remaining 30% biopsy was not practicable because of coagulation abnormalities. The severity of the disease was assessed at the commencement of the trial by determination of Child's index and of various clinical, biochemical and immunological parameters. All parameters of liver function were checked at three month intervals.

The patients were randomly allocated to a treatment group (n=87) or a control group (n=83) and were given 420 mg Silymarin /day or placebo for at least 2 years. Therapy was continued after the end of the 2 year trial, and the mean duration of therapy was hence 41 months. After 2 years there had been 16 deaths in the treatment group (13 of them from hepatic causes) and 25 deaths in the placebo group (23 of them from hepatic causes) (p<0.05).
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Over the entire period of therapy (average 41 months) there were 24 deaths in the silymarin group (18 of them from hepatic causes) and 37 deaths in the placebo group (31 of them from hepatic causes).

The mean 4-year survival rate for patients treated with silymarin was 58±9% as compared with 39±9% for the controls (p=0.02). For the subgroup of patients with hepatic cirrhosis of alcoholic origin reciving treatment with silymarin the cumulative survival rate was higher (p=0.01).

Fig. 9: Survival curves of 170 patients with hepatic cirrhosis receiving treatment with silymarin or placebo subdivided in terms of severity grading at the commencement of the trial.
7.2 Open Studies

In a nonblind longitudinal trial 66 psychiatric or neurological patients who were receiving large doses of psychoactive drugs or anticonvulsants (mainly phenothiazine derivatives, but also diphenyl hydantoins, pyrimidines and barbiturates) were also given silymarin (105-315 mg/day) for an average of 61 days with the purpose of preventing or minimizing toxic liver damage\textsuperscript{24}
Before commencement of the study and after the period of silymarin treatment liver function assessed by checking various serum indices (GOT, GTP, bilirubin, bromsulphalein test). There were 13 patients receiving psychoactive drugs who had abnormal bromsulphalein tests (>7% retention at 45 min). After silymarin treatment BSP retention had returned to normal in 7 patients (54%), improved in 3 (23%) remained unchanged in a further 3 (23%).

Fig. 10: Abnormal bromsulphalein retention in psychiatric or neurological patients receiving psychoactive drugs or anticonvulsant therapy and the changes occurring during supplementary silymarin treatment (105-315 mg Silymarin/day for an average of 61 days)²⁴.
At the beginning of the trial there were 41 patients with GOT levels and raised GPT levels. After silymarin treatment GOT levels had returned to normal in 14 patients and had improved in further 14 patients (68%). GTP levels had returned to normal in 8 patient (58%) and had improved in a further 4 (27%). During the period of silymarin treatment – administration of psychoactive drugs being continued – the investigators noted some improvement in psychotic manifestations together with gains in vitality and elevation of mood.
Milk thistle extract is notable for its particularly high level of clinical safety. It is almost devoid of any side effects and may be used by a wide range of people. Since it does stimulate liver and gallbladder activity, it may have a mild, transient laxative effect in some individuals [65].

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