Artichoke Extract

For the Treatment of Dyspeptic Complaints
Introduction

EUROMED is a company specialized in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces these 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 its broad phytochemical know-how.
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1 Artichoke Extract: General Information

1.1 Description

The extract of artichoke is a standardized herbal extract made from the leaves of carefully selected plants of *Cynara scolymus* L.

The extract of *Cynara scolymus* L. is a herbal preventive and therapeutic agent against dyspeptic complaints. It can be used without side effects for long term treatment of disturbances of lipid metabolism. It results in relief of symptoms, such as:

− digestive complaints
− heartburn/sour belching
− chest pain
− sickness/vomiting
− intolerance against fat
− irregular bowel movements
− pain of epigastrium
− functionally caused disturbance of bile drain

The *Cynara scolymus* L. extract (as available from EUROMED) gives most patients some relief of symptoms within the first 4-6 weeks, with positive effects starting as early as after 10 days.

The extract of *Cynara scolymus* L. does not interact with other drugs.
1.2 Indications

The extracts of *Cynara scolymus* L. (as available from EUROMED) are used in the treatment of dyspeptic and digestive complaints, especially in the case of functionally caused disturbances of bile drain.

1.3 Extract Specifications

*Cynara scolymus* L. dry extract is an extract of artichoke leaves containing 5% cynarin-derivatives. It is a fine powder with brown color (hygroscopic). Finished preparations typically contain about 200 - 400 mg *Cynara scolymus* L. extract (as available from EUROMED).

1.4 Dosage and Methods of Administration

A daily oral dose of 1200 mg *Cynara scolymus* L. extract on average is common practice. Table 1 gives a survey of popular European *Cynara scolymus* L.-preparations available on the market.

1.5 Contraindications and Interactions

There are no known contraindications to the long-term use of *Cynara scolymus* L. extract. There are no known interactions with drugs usually prescribed.
1.6 Side-effects

*Cynara scolymus* L. extract is very well tolerated. Side effects are rare and relatively mild, when the standardized extract is taken. In exceptional cases there exist allergic reactions upon direct dermal contact with dried plant parts [9].

Well tolerated

Table 1: European preparations containing *Cynara scolymus* L. extract.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of extraction</th>
<th>Content of <em>Cynara scolymus</em> L. Extract [mg]</th>
<th>Total Extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carminagal® N</td>
<td>water</td>
<td>142-178</td>
<td>852-1068</td>
</tr>
<tr>
<td>Cynacur®</td>
<td>water</td>
<td>300</td>
<td>900-1200</td>
</tr>
<tr>
<td>Cynafol®</td>
<td>water</td>
<td>300</td>
<td>900</td>
</tr>
<tr>
<td>Hekbilin®</td>
<td>water</td>
<td>400</td>
<td>1600</td>
</tr>
<tr>
<td>Hepagallin N</td>
<td>water</td>
<td>220</td>
<td>1320</td>
</tr>
<tr>
<td>Hepar-POS®</td>
<td>water</td>
<td>400</td>
<td>1200-1600</td>
</tr>
<tr>
<td>Hepar-SL® forte</td>
<td>water</td>
<td>320</td>
<td>960-1920</td>
</tr>
<tr>
<td>Hewechool</td>
<td>water</td>
<td>290</td>
<td>1740</td>
</tr>
<tr>
<td>Maquil</td>
<td>water</td>
<td>200</td>
<td>1200</td>
</tr>
</tbody>
</table>
2 From Plant to Extract

2.1 Artichoke (Cynara scolymus L.): Botanical Information

The artichoke, *Cynara scolymus* L., belongs to the family *Compositae* and developed most likely from the wild form, *Cynara cardunculus* [25]. The herb with its big leaves that originate at the plant base grows up to a height of 2 meters, and is similar to thistles. *Cynara scolymus* L. flowers during summer, in blue or violet colors.

The plant is cultivated today in Middle- and Southern Europe, North Africa, South America, and California. It prefers a light warm soil and an open position in full sun.

The little leaves that surround the flower are used as a tasty vegetable [9]. The eatable bump of the flower can be as large as 15 cm in diameter. The taste is mildly bitter and it is considered to be a gourmet food. Only the base of each bract is eaten, plus the “heart” or base that the petals grow on.

The medically used parts are the big leaves that originate from the plant base.
Figure 1: Artichoke (*Cynara scolymus* L.).
2.2 Historic Use

The artichoke is one of the oldest cultivated plants. Its origin lies most probably in Ethiopia. From there it spread through Egypt to Southern Europe. The Arabic word “al-harsuf” and the Spanish “alcachofa” led to the French word “artichaut” and to the English term “artichoke” [4].

In ancient times (400 b.C.) the artichoke was used already as a remedy and it was a scholar of Aristotle, Theophrast (371 b.C., Lesbos), who gave one of the first descriptions of the plant. It is not surprising that later the Romans chose this plant as one of their favorite vegetables, as they recognized its positive effects on digestion and the gastric juices [25].

The actual rise to a medically used plant occurred in the first half of the 20th century. French and other scientists investigated the role of artichoke for the cure of gastric complaints. They found choleric, cholesterinolytic and diuretic properties of the extracts [23, 37]. Consequently it was recommended as a cure of liver and bile disorders.

After the isolation and structural identification of the putative main active principle cynarin by Italian researchers [26], its industrial synthesis became possible. The “Cynarin Era” started.
Later it was found that pure cynarin preparations did not have the full positive effects of the plant extracts and the interest in these preparations was lost [9]. Today it is generally accepted that the complex of substances contained in the whole extracts is responsible for its effectiveness [41].

2.3 Chemistry of *Cynara scolymus* L. leaf

*Cynara scolymus* L. leaves contain a complex of substances. The most important chemical components are caffeoylquinic acids (Ccs, “caffeic acid derivative”), flavonoids and sesquiterpene bitter agents. The choleretic and hepato stimulating effects of artichoke extracts have been found to depend on their Ccs content. Cynarin is genuinely contained in very low concentrations [17].

Figure 2 shows the main therapeutically relevant components contained in the extract of the leaves of *Cynara scolymus* L.
Figure 2: Therapeutic relevant components of *Cynara scolymus* L. extract
The following table gives a general review of the substances found in artichoke leaves.

Table 2: Substances found in *Cynara scolymus* L. leaves. Approximate values in brackets. [1, 3, 4, 7, 17, 36, 39].

<table>
<thead>
<tr>
<th>Active and Other Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Caffeoylquinic acid (Cs, 1 – 4 %)</td>
</tr>
<tr>
<td>• Chlorogenic acid</td>
</tr>
<tr>
<td>• 1,3-Di-0-Cs</td>
</tr>
<tr>
<td>• Cryptochlorogenic acid</td>
</tr>
<tr>
<td>• Neochlorogenic acid</td>
</tr>
<tr>
<td>• Flavonoids (0,5%)</td>
</tr>
<tr>
<td>• Glycoside</td>
</tr>
<tr>
<td>• Cynaroside</td>
</tr>
<tr>
<td>• Scolymoside</td>
</tr>
<tr>
<td>• Cynarotrioside</td>
</tr>
<tr>
<td>• Luteolin</td>
</tr>
<tr>
<td>• Sesquiterpene lactones (0 – 4 %)</td>
</tr>
<tr>
<td>• Cynaropicrin</td>
</tr>
<tr>
<td>• Dehydrocynaropicrin</td>
</tr>
<tr>
<td>• Grossheimine</td>
</tr>
<tr>
<td>• Cynaratriol</td>
</tr>
<tr>
<td>• Cynarin</td>
</tr>
</tbody>
</table>
2.4 Preparation of the Extract and Quality Control

The plant material used for EUROMED Cynara scolymus L. 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 EUROMED Cynara scolymus L. is maintained.

When the plant material arrives at EUROMED an exhaustive inspection of the raw material guarantees the quality of the final product.

Furthermore EUROMED evaluates the possible contamination of the drug. In doing so the company assures that the limits fixed by international standards or literature are not exceeded.

Aflatoxins: the contamination with these mycotoxins is controlled by legal limits world-wide

Heavy metals: the contamination with heavy metals is checked by atomic absorption spectrophotometry

Microbiology: in compliance with the limits established in Ph. Eur. 3rd ed., 5.1.4 (category 4B), (1997)

Only high-quality raw plant material, selected according to the strictest criteria, is used.
Unique extraction process

EUROMED applies a unique extraction process to obtain the extract. This procedure of EUROMED meets the indications of the Commission E monograph [20]. It provides a high yield of valuable constituents and a high-grade extract in a careful way.

EUROMED Cynara scolymus L. extract satisfies the highest quality standards of the various European regulatory systems. It meets and exceeds all European requirements for approved European medicinal use.
2.5 Standardization

The consistent batch to batch quality of the 
\textit{Cynara scolymus} \textit{L.} extract is
 guaranteed by the standardized production
 process.

The specific positive effects of \textit{Cynara scolymus} \textit{L.} extract arise only from the combination of the
 contained substances. Therefore the extract of the
 whole leaves is taken. The analytical
 specifications of the \textit{Cynara scolymus} \textit{L.} extract are:

\begin{itemize}
  \item \textbf{Aspect} \hspace{1cm} \textit{Fine powder, brown color, hygroscopic}
  \item \textbf{Identification} \hspace{1cm} \textit{TLC}
  \item \textbf{Loss on drying} \hspace{1cm} \textit{Max. 8.0 %}
  \item \textbf{Ash} \hspace{1cm} \textit{Max. 30.0 %}
  \item \textbf{pH} \hspace{1cm} \textit{4.0 – 5.5}
  \item \textbf{UV Absorption} \hspace{1cm} \textit{Max. 325, 285 nm}
  \item \textbf{Assay} \hspace{1cm} \textit{Cynarin derivatives min. 5.0 %}
\end{itemize}
3 Dyspeptic complaints

3.1 Epidemiology

About one third of the total population suffers from dyspeptic complaints. These mostly consist of functional disorders of the upper intestine tract, including the bile, liver and pancreas, but without any detectable organic cause. Often the complaints continue for several days to weeks, and tend to reoccur regularly [29, 31]. Because of their high frequency and chronic nature, dyspeptic complaints have significant socioeconomic consequences. They are therefore a threat to public health.

3.2 Symptoms

The symptoms are related to regular digestive disorders that can be painful and disturbing. Especially after meals with a high content of fat complaints occur. Table 3 gives an overview of the common symptoms.
Table 3: Symptoms of dyspeptic disorders

<table>
<thead>
<tr>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>early feeling of satiation, loss of appetite</td>
</tr>
<tr>
<td>digestive complaints</td>
</tr>
<tr>
<td>heartburn/sour belching</td>
</tr>
<tr>
<td>non-sour belching</td>
</tr>
<tr>
<td>chest pain</td>
</tr>
<tr>
<td>sickness/vomiting</td>
</tr>
<tr>
<td>flatulence</td>
</tr>
<tr>
<td>fat intolerance</td>
</tr>
<tr>
<td>irregular bowel movements</td>
</tr>
<tr>
<td>pain of epigastrium</td>
</tr>
<tr>
<td>functionally caused disturbance of bile drain</td>
</tr>
<tr>
<td>vegetal symptoms such as loss of power, sleep disorders, early fatigue, functional heart pain</td>
</tr>
</tbody>
</table>

### 3.3 Therapy

It can be expected that many patients with dyspeptic complaints that visit a doctor, suffer in fact from a disorder of the liver-bile system. This explains the often ineffective treatment with H₂-receptor antagonists and anti-acidic or prokinetic remedies [22].
Dyspeptic disorders mostly functional without organic cause

87% of all upper intestine tract complaints are of functional nature, only 13% can be attributed to organic diseases like gastric or duodenal ulcers [30].

Today it is generally accepted that an increase of bile secretion is an essential means for the treatment of dyspeptic complaints. Experimental and clinical data suggest that dyspeptic complaints do arise simply from gastric disorders, but show that bile malfunctions are involved, too [29]. Dyskinesia of bile pathways is considered as the main cause of non-ulcer dyspeptic complaints.

Relief due to increase of biliary secretion and enhanced intestinal peristaltic

The effects of choleretic remedies are twofold: they increase the biliary secretion that is important for digestive activity and they have a positive influence on intestinal motility. However, a successful therapy is dependent on a proven choleretic effect, which is only true for a few preparations, most notably artichoke extracts [19]. Figure 4 shows the main postulated modes of action for artichoke extracts.

Cynara scolymus L. is recommended in a positive monograph

Artichoke extracts have been used for many decades by thousands of patients. They have become a standard medication in the treatment of dyspeptic disorders and are well regarded by medical practitioners. In a positive monograph by the German Federal Public Health Department artichoke leaf extracts are recommended to treat dyspeptic complaints [20].
Artichoke extract

- Inhibition of cholesterol biosynthesis
- Anti-oxidative effects
- Cell-protective effects
- Choleretic effects

- Prevention of atherosclerosis
- Protection of cell membranes against noxious substances (hepatoprotective effects)
- E.g. diuresis
- Complex of dyspeptic symptoms

Figure 4: Postulated modes of actions for *Cynara scolymus* L. extracts. From [9].
4 Pharmacology

4.1 Pharmacodynamics

Artichoke leaves contain many different substances and it is not yet fully determined, which exactly are responsible for the medical effects. Hence the whole extract is considered as the effective compound. Cynarin and the sesquiterpene lactones are not responsible alone for the diverse pharmacological effects. Other caffeoylquinic-acids (Ccs) such as chlorogenic-acid and 1,3-Di-0-Ccs contribute to the effects of *Cynara scolymus* L. extract [6].

It is well known that artichoke leaves have choleretic effects. Moreover results from several studies during the last decades show that they induce a lowering of cholesterol- and lipid levels in the blood.

The therapeutic benefit of *Cynara scolymus* L. extract is based on a range of effects:

- distinct increase of choleresis
- protective effects in liver due to detoxification, antioxidative effects and promotion of regenerative processes
- normalization of cholesterol and triglyceride levels by increase of choleretic elimination and influence on biosynthesis of cholesterol
For the isolated components (e.g. Ccs, chlorogenic acid, caffeic acid and cynarin) there exists a wealth of results that show their choleretic, anti-hepatotoxic, anti-oxidative and/or positive influence on lipid metabolism [5]. But none of these substances reaches the same high efficacy as the therapeutically used extract [11, 19].

4.1.1 Increase of choleresis

In the 1950-ies several groups found positive effects of artichoke leaf extracts on choleresis [2, 16, 27, 35].

In 1957 it was shown with patients and healthy volunteers, using a duodenal sound, that artichoke extract increases specifically choleresis but not cholelkinisis. The choleretic effects began “mildly” immediately, peaked after 1/2 hour and decayed after 1 hour. Indigestion and other gastrointestinal disorders related to deficient secretion of bile were overcome. The increase in bile secretion particularly improves fat digestion [32].
Alcoholic dry-extracts (10.0 g dissolved in 40 ml) led to a 20-40 % increase of bile production in the rat [2]. Two water/alcoholic extracts, containing 19 % or 46 % caffeic acid derivatives, were given to male Sprague-Dawley rats and female Wistar rats intraperitoneally (dose: 25 or 200 mg/kg bodyweight, respectively). The volume of secreted bile increased with the dose of Ccs [24].

Figure 5: Effect of artichoke extract given intraperitoneally on choleresis of anaesthetized rats (as measured by bile dry residue). Two different concentrations of extract were tested. Filled circles: 100 mg/kg body weight, open circles: 25 mg/kg body weight, open squares: control group [24].
In-vivo experiments have shown the influence of chlorogenic acid and caffeic acid derivatives on the bile. Rats given chlorogenic acid perorally (40 mg/kg bodyweight) reacted with a 75% increase of bile secretion [8].

Experiments on the isolated, perfused liver of the rat have proven a clear dose-dependency of the choleretic effect [21].
In cell cultures of liver cells it was demonstrated that artichoke leaf extract (0.1 mg/ml) increases the secretion of characteristic bile substances. It also led to more and bigger bile secreting structures in the cells. Another consequence was the accumulation of bile containing vesicles in the liver, that could be detected by electron microscopy [14].

4.1.2 Lowering of cholesterol levels

Pathologic levels of blood cholesterol are not the cause, but consequence of metabolic disorders. It is quite probable that insufficient production of bile and a disturbed enterohepatic system have unfavorable effects on cholesterol metabolism [32].

Since 1933 it is known that the extract from artichoke leaves lowers cholesterol levels. Since 1934 the extracts are used to treat hypercholesterolemia. They improve the ability of blood plasma to keep cholesterol in solution. Pathologic levels of cholesterol could be lowered to normal values [9, 15].

Cynarin significantly reduced blood lipid levels in rabbits. In alcoholized rats, fatty acid esters were reduced by 28 % and ethanol induced hypertriglyceridemia was reduced significantly [10].
**Artichoke extract inhibits cholesterol biosynthesis**

By measuring the incorporation of $^{14}$C-marked acetate into the lipids of isolated hepatocytes, it was shown that artichoke extract can inhibit the de-novo synthesis of cholesterol. After an incubation of 2 hours the extract (0.01 – 1 mg/ml) led to a significant dose-dependent inhibition (see Figure 7). This could mean that the synthesis of cholesterol by the liver is reduced by artichoke extract *in vivo*, too [12].

![Figure 7: Inhibition of cholesterol biosynthesis by artichoke extract (as measured by the incorporation of acetate into the lipids of hepatocytes). The effect is dose-dependent (*, p<0.01; .....= control) [12].](image-url)
4.1.3 Diuretic effects

Artichoke extracts can lead to an enhancement of diuresis [9]. It is assumed that this goes along with an improved concentration of urine in the kidneys. The resulting enforced urea clearance leads to a normalization of pathological blood urea levels [28, 32].

4.1.4 Anti-hepatotoxic and anti-oxidative effects

The contents of artichoke extracts stimulate blood flow in the liver, mobilize energy resources, increase the number of binucleate hepatic cells as well as the content of RNA in liver cells and stimulate cell division [32]. Furthermore, artichoke extract is able to enhance regenerative abilities of the liver [32, 40].
The anti-oxidative effect was shown in cultured liver cells by inducing oxidation artificially. This was done by treating the cells with a peroxide (tertiary butylhydroperoxide, t-BHP). This was quantified by measuring the formation of malondialdehyde (MDA). MDA is produced naturally in small amounts only. Adding t-BHP increases MDA production significantly, which leads to increased cell death. Adding artichoke extract to the culture medium reduces cell death and MDA production in a dose-dependent manner (see Figure 8) [13].

![Figure 8: Anti-oxidative effect of artichoke extract: t-BHP induced production of MDA in cultured liver cells is reduced depending on dose of extract (*p<0.05; **p<0.01) [13].](image-url)
Artichoke extract has protective effects against the classic liver toxin carbon tetrachloride (CCl₄). Hepatocytes treated with CCl₄ produce less mitochondrial formazan and are damaged. Adding artichoke extract prevents cell death and restores formazan production almost completely (see Figure 9).

Figure 9: Artichoke extract induced inhibition of hepatocyte damage induced by CCl₄. Mitochondrial production of formazan is used as a measure of cell damage after 3 h (light bars) after 24 h (dark bars; *: p<0.01; **: p<0.001).

4.2 Pharmacokinetics
The extract of *Cynara scolymus* L. leaves is a complex compound. Therefore pharmacokinetic investigations are difficult and data is mainly available for cynarin which was long considered as the main substance.

Administering cynarin i.v. in the mouse shows a very short serum half-life of approx. 11 minutes. After 24 h about 40 % unchanged cynarin is excreted with the urine and no metabolites were found. Considering the clinical action pattern, a distribution in other compartments and excretion through feces is likely [34].
5 Toxicology

Low toxicity

The toxicity of *Cynara scolymus* L. extract (as available from EUROMED) is generally very low.

Acute Toxicity

The acute toxicity of *Cynara scolymus* L. extract has been studied in different species of animals. The LD$_{50}$ in mice with i.p. application of isolated cynarin is 3.5 g/kg body weight. In male Sprague-Dawley rats the LD$_{50}$ for artichoke extract is 1 g/kg body weight (i.p. application) [24].

Local Toxicity

Contact dermatitis was described for persons who were in direct contact with plants due to professional reasons [9]. The allergic reactions mostly derive from the substances cynaropicrin or grossheimine. There are no allergic reactions described after oral application [18].

Subacute and chronic Toxicity

No data from systematic investigations is available. For humans taking regular doses of artichoke leaves or extracts there are no known toxicological effects [32].
There is no indication for any embryotoxic, mutagenic, carcinogenic, immunotoxic or phototoxic effects of artichoke leaf extracts [34].
6 Clinical Pharmacology

A placebo-controlled, cross over double-blind study was performed to investigate the influence of artichoke leaf extract on choleresis. In this study 20 patients took part in two groups: 10 in verum group and 10 in placebo group. Their bile secretion was measured in the isolated duodenal segment. The test medication was 1.92 g artichoke leaf extract dissolved in 50 ml water, applied through a multichannel-sound. After the first test phase a wash-out phase was performed (8 days), and then, after crossing the groups, a second test phase.

30 minutes after application there was an increase of bile secretion in the verum group of 127.3 % compared to placebo (see Figure 10). After 60 minutes the increase was 151.5 % and after 90 minutes 94.3 % (all significant, p<0.01). Clinical relevant increases were found up to 3 h after application [19].
Figure 10: Effect of artichoke extract on choleresis in placebo-controlled double-blind study. Bile secretion was measured intra-duodenally after duodenal application of extract using a multichannel sound and is normalized to its value at t=0 min (*=p<0.05; **=p<0.01; n=20) [19].

The influence of choleretic active substances on the excretion of bile in feces was determined on 4 patients suffering from adiposis hepatica and two healthy volunteers. Treatment with cynarin (2 dragees, 3 times per day) led to an increase of bile acid excretion from 116.8 mg/24 h to 381.7 mg/24 h in the patient group. For the healthy volunteers it increased from 187.9 mg/24 h to 254.7 mg/24 h [33].
7 Proof of Clinical Effectiveness

7.1 Clinical Trials with Placebos

A randomized, placebo-controlled study was performed with 60 patients suffering from dyspepsia (non-ulcer dyspepsia). Symptoms like upper abdominal pain, heartburn, obstipation, fullness, sickness and vomiting were monitored. Bile acid secretion was measured using a duodenal sound. Patients were treated for 14 days with an artichoke extract containing compound (3 x 3 dragees daily, 50 mg artichoke extract per dragee). In 50 % of the patients this led to an improvement of the monitored symptoms. The increase of choleresis was measured at day 1, 4, 7 and 14 after begin of treatment. In the verum group choleresis increased significantly more than in the placebo group (see Figure 11) [22]. This study confirmed similar clinical studies from the 1950-ies [21].
Figure 11: Increase of choleresis by an artichoke extract containing compound in a placebo controlled study (**=p<0.01, n=30 per group) [22].
7.2 Drug Monitoring Trials

Artichoke leaf extract was tested in an extensive post-marketing-surveillance study with 553 patients, with respect to its effectiveness and tolerance [10]. Patients were treated for 6 weeks with a daily dose of 3-6 capsules containing 320 mg artichoke extract each. The treatment led to a significant and clinically relevant decrease of dyspeptic complaints. The scores for the respective symptoms decreased as follows: vomiting by 88.3 %, sickness by 82.2 %, abdominal pain by 76.2 %, obstipation by 71.0 %, flatulence by 68.2 %, fat intolerance by 58.8 %.

These effects occurred on average after 10 days, about one third of patients reported improvement after 7 days (in 50 % of patients symptoms improved during the first 14 days, in 17 % after 14 days). 98 % of all patients rated effectiveness better than previous therapies.

Serum lipid levels were determined for 302 patients (total cholesterol and triglycerides). Both were significantly reduced after 6 weeks (see Figure 12) [10].
Figure 12: Total cholesterol (top) and triglycerides (bottom) in serum after treatment with artichoke extract [10].
The global effectiveness of the treatment with *Cynara scolymus* L. was “excellent” or “good”, as rated by medical doctors in 87% of all patients (see Figure 13).

![Figure 13: Global efficacy of artichoke leaf extract (according to judgment of MD) [10].](image)

Similar results were obtained in another study with 50 patients suffering from hyperlipoproteinemia using an artichoke extract preparation combined with *Rhizoma Rhei*. A daily dose of 1200 mg artichoke extract (3 x 2 dragees) led after 4 weeks to a significant reduction of cholesterol and triglyceride levels [38].

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Summary

The treatment with *Cynara scolymus* L. extract is effective for dyspeptic complaints. Common symptoms as upper abdominal pain, heartburn, obstipation, fullness, sickness and vomiting are improved. Furthermore it has positive effects on serum cholesterol levels and on cholesterol biosynthesis. *Cynara scolymus* L. extract is tolerated well with minimal side effects.

7.3 Therapeutic Safety

*Cynara scolymus* L. extract is notable for its particularly high level of clinical safety. Particular emphasis should be put on the high tolerance of artichoke extract preparations leading to a high level of treatment compliance because of the almost total absence of side-effects.
8 Bibliography


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[23] Leclerc, H.: Presse Med. 36 (1928) 1540


Tixier, L.: Presse Med. 47 (1939) 880


