Herbal Extract Series

Hawthorn Extract

For the Treatment of Cardiac Insufficiency
Introduction

EUROMED is a company specialized in botanical extracts and active ingredients to be used as phytomedicines within the pharmaceutical field. EUROMED devotes itself to the development and production of these therapeutically active raw materials.

The botanical raw materials are subjected to strict selection and controls, and the products are manufactured following production methods developed by the EUROMED company, which include controls to assure a standard quality according to the latest knowledge of the state of art in different fields: R&D, analysis, processes and facilities, therapeutical usage on a scientific basis.

EUROMED assures the quality of their products with a background of broad phytochemical know-how.
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1 Hawthorn Extract
General Information

1.1 Description
Hawthorn extract (as available from EUROMED) is a standardized herbal extract from Crataegus oxyacantha L. leaf with flower.

Crataegus extract is an herbal preventive and therapeutic agent for cardiac insufficiency. It improves the efficiency of the heart by increasing blood supply to the heart muscle so the heart is able to pump more blood to the body. Hawthorn lowers the resistance to blood flow in peripheral vessels.

Hawthorn extract does not interact with other drugs.

1.2 Indications
The primary indication for hawthorn leaf with flower based on available pharmacological data is the treatment of class I and II cardiac insufficiency [1, 63]. Hawthorn can be used alone or in conjunction with other conventional or botanical drugs for a wide variety of mild cardiac disturbances, including palpitations from various origins such as hyperthyroidism and menopause, tachycardia, angina, cardiomyopathy, and cardiac insufficiency [63].

1.3 Extract Specifications

Crataegus preparations usually contain 70-2000 mg Hawthorn extract.
1.4 Dosage and Methods of Administration
A daily oral dose of 160-900 mg is common practice. Table 1 shows a survey of popular German hawthorn preparations on the market.

1.5 Contraindications and Interactions
Hawthorn has no known interactions with usually prescribed drugs.

1.6 Side-effects
Hawthorn extract is generally well tolerated.
Tab. 1: German Herbal Preparations containing hawthorn extract.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of Extraction</th>
<th>Content of Hawthorn Extract [mg]</th>
<th>Total Extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiofort forte</td>
<td>Methanolic</td>
<td>130-198</td>
<td>520-792</td>
</tr>
<tr>
<td>Cardiofort forte</td>
<td>Ethanolic</td>
<td>1420-1700</td>
<td>1500-1875</td>
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<tr>
<td>Cardiofort</td>
<td>Ethanolic</td>
<td>107</td>
<td>963</td>
</tr>
<tr>
<td>Chronogard N</td>
<td>Ethanolic</td>
<td>80</td>
<td>240-480</td>
</tr>
<tr>
<td>Cordapur novo</td>
<td>Ethanolic</td>
<td>300</td>
<td>600-900</td>
</tr>
<tr>
<td>Corocrat forte Tr.275</td>
<td>Ethanolic</td>
<td>71-375</td>
<td>1000-3000</td>
</tr>
<tr>
<td>Craegium 100</td>
<td>Methanolic</td>
<td>100</td>
<td>300-600</td>
</tr>
<tr>
<td>Craegium 240</td>
<td>Ethanolic</td>
<td>240</td>
<td>480-720</td>
</tr>
<tr>
<td>Crataegus STADA</td>
<td>Ethanolic</td>
<td>240</td>
<td>480-720</td>
</tr>
<tr>
<td>Crataegutt 80mg</td>
<td>Ethanolic</td>
<td>80</td>
<td>240-480</td>
</tr>
<tr>
<td>Crataegutt Tropfen</td>
<td>Ethanolic</td>
<td>94</td>
<td>300-600</td>
</tr>
<tr>
<td>Crataegutt novo 450</td>
<td>Ethanolic</td>
<td>450</td>
<td>900</td>
</tr>
<tr>
<td>Crataegysat F Bürger</td>
<td>Ethanolic</td>
<td>1007</td>
<td>375-1750</td>
</tr>
<tr>
<td>Crataepas 100</td>
<td>Ethanolic</td>
<td>100</td>
<td>300</td>
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<tr>
<td>Crataepas 100 Tropfen</td>
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<td>100</td>
<td>500</td>
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<tr>
<td>Cratecor</td>
<td>Ethanolic</td>
<td>80</td>
<td>240-480</td>
</tr>
<tr>
<td>Esbericard novo</td>
<td>Ethanolic</td>
<td>175</td>
<td>350-700</td>
</tr>
<tr>
<td>Faros 300 mg</td>
<td>Methanolic</td>
<td>300</td>
<td>900</td>
</tr>
<tr>
<td>Herz-Tropfen EuRho</td>
<td>Ethanolic</td>
<td>800-1000</td>
<td>750-1000</td>
</tr>
<tr>
<td>Kytta-Cor forte</td>
<td>Ethanolic</td>
<td>140-194</td>
<td>280-582</td>
</tr>
<tr>
<td>Kytta-Cor novo</td>
<td>Ethanolic</td>
<td>300</td>
<td>600-900</td>
</tr>
<tr>
<td>Orthangin novo</td>
<td>Ethanolic</td>
<td>117.9-168.5</td>
<td>335.7-505.5</td>
</tr>
<tr>
<td>Poikilocard Mono</td>
<td>Ethanolic</td>
<td>160</td>
<td>780</td>
</tr>
</tbody>
</table>
Tab. 1: German Herbal Preparations containing hawthorn extract (ctd.)

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of Extraction</th>
<th>Content of Hawthorn Extract [mg]</th>
<th>Total Extract/day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulacor POS</td>
<td>Methanolic</td>
<td>200</td>
<td>600</td>
</tr>
<tr>
<td>Senicor N</td>
<td>Ethanolic</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>Senicor</td>
<td>Ethanolic</td>
<td>1000</td>
<td>1875</td>
</tr>
<tr>
<td>Steigercorton</td>
<td>Ethanolic</td>
<td>189</td>
<td>378-567</td>
</tr>
<tr>
<td>Steigercorton Fluidextreakt</td>
<td>Ethanolic</td>
<td>75.53</td>
<td>2250</td>
</tr>
<tr>
<td>SX Crataegus</td>
<td>Ethanolic</td>
<td>300</td>
<td>600-900</td>
</tr>
<tr>
<td>Valverde Kapseln</td>
<td>Methanolic</td>
<td>224-274</td>
<td>672-822</td>
</tr>
<tr>
<td>Vitalin Dragees</td>
<td>Methanolic</td>
<td>200</td>
<td>600</td>
</tr>
<tr>
<td>Weissdorn-Phyton</td>
<td>Ethanolic</td>
<td>1000</td>
<td>500-750</td>
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<td>Weissdorn-Phyton</td>
<td>Methanolic</td>
<td>42.32</td>
<td>253.92</td>
</tr>
<tr>
<td>Weissdorn-ratiopharm</td>
<td>Ethanolic</td>
<td>240</td>
<td>480-720</td>
</tr>
</tbody>
</table>
2 From Plant to Extract

2.1 Hawthorn (Crataegus)

Botanical Data

Crataegus belongs to the family of Rosaceae. The two primary Rosaceae species, *C. laevigata* and *C. monogyna*, are known to hybridize in northern Europe.

The name *Crataegus* derives from the Greek *krataios*, meaning strong, referring to the hardness of its wood, or *kratos*, meaning “always having been there”. Common names are hawthorn, Weissdorn, Hagedorn, Meidorn and harthorne. The English name hawthorn derives from the Old English *hagadorn*. References to its beauty have been made since ancient times, and some believe that the crown of thorns placed upon the head of Christ was made of hawthorn. The species names of the two primary species included in the official compendiums are *laevigata* and *monogyna*, mean “smooth” and “single pistilled”, respectively [63].

*Crataegus* species most often occur in disturbed sites or serial communities such as old fields, thickets, forest edges, or open, second-growth forests. The delineation of the species in this genus is complicated by the occurrence of hybridization, polyploidy, aneuploidy, and apomixis [11]. There is extensive morphological variation within, and intergradation between, recognized species. 150-1200 species are recognized, most of which are distributed in northern temperate regions worldwide [11].

Hawthorn leaf with flower consists of a mixture of the fresh or dried flowering tops of *Crataegus laevigata* (Poir.) DC. Syn. *Crataegus oxyacyntha* L., *Crataegus monogyna* Jacq. (Lindm.), their hybrids, or other *Crataegus* species containing not less than 1.5% flavonoids, calculated as hyperoside as determined on a dry weight basis [63].
2.2 Historic use

The medical properties of hawthorn were first documented by a military physician in the time of Nero (1st century AD). While ancient medical writers such as Dioscorides (ca. AD 40-80), Pliny, and Galen (ca. AD 131-208) noted it in their respective works, they provided little data concerning its medicinal use. Most of the historical data refer to use of the fruit, although some reports also include the leaves, flowers, and even the seeds. According to Leclerc, the use of hawthorn as a heart medicine dates back to the 17th century. Ammon and Kaul [2] report that syrup prepared from hawthorn fruit was used as a heart medicine by Quercetanus (1544-1609), the private physician of King Henry IV of France. In the late 16th century, Parkinson already reported on the use of hawthorn fruits and seeds as a primary remedy for kidney stones and as a diuretic. In 1733 Alleyne, in his *New English Dispensatory*, similarly recommended a tea made from hawthorn flowers for
treating stones. Its popularity as a heart medicine appears to have begun in 1894, after which it became one of the most popular of all the botanical cardiovascular medicines [25].

There were differing reports on the efficacy of hawthorn among eclectic physicians. The eclectic Harvey Wickes Felter reported the earlier use of hawthorn bark, root, and leaves as astringent tonics and hawthorn’s primary use as a cardiovascular medication. He reported that it was used for symptoms associated with an aging heart, although he considered that its positive effects had yet to be proven [18]. Another renowned eclectic, Finley Ellingwood (1919), provided numerous reports from physicians convinced of the effectiveness of hawthorn for a wide range of conditions in addition to its effects on the cardiovascular system. The indications cited by Ellingwood closely resemble the use of hawthorn in modern botanical therapy, including its ability to positively effect mental well-being. It has also been reported that the Cherokee tribe of Native Americans used a species of hawthorn as a heart tonic [35].

2.3 Chemistry

Flavonoids (0.5-1.5%) and the oligomeric procyanidins (OPC’s, 2.2-3.3%) are regarded as active constituents of hawthorn for the described therapeutic properties. The primary flavonoid in the leaves is vitexin-2”-O-rhamnoside or occasionally acetyl-vitexin-2”-O-rhamnoside, in the flowers it is hyperoside. The flavonoids are composed of flavanol aglycones and flavanol O-glycosides (quercetin, kaempferol, hyperoside, isoquercitrin, spirein, rutin among others), flavone-O-glycosides (luteolin-7-O-glucoside), flavone-C-glycosides (vitexin, isovitexin, orientin and isoorientin), flavone-C-O-glycosides (vitexin-2”-O-rhamnoside and acetyl-vitexin-2”-O-rhamnoside among others) and flavone-di-C-glycosides. The procyanidin fraction is composed of 2 to 8 (+)-catechin and (-)-epicatechin units. The dimeric procyanidin B-2 and the trimeric procyanidin C-1 are the main constituents. Some procyanidin tetramers are present.

Aromatic carbonic acids, mainly chlorogenic acid and caffeic acid are also found. Pentacyclic triterpenoid acids
such as oleanolic acid, ursolic acid, crataegolic acid as well as nitrogen-containing compounds such as choline, acetychloine, alkylamines, isoamylamine, isobutylamine, ethylamine, dimethylamine, ethanolamine, phenethylamine, o-methoxyphenethylamine, tyramine, N-tricoumaroylspermidine, a polyamine, adenosine, adenine, guanine, noradrenaline, adrenaline, uric acid, dopamine and L-dopamine were cited in older literature as components of the drug [2,34,42].

![HPLC fingerprint chromatogram](image)

Fig. 2: A typical HPLC fingerprint chromatogram of hawthorn leaf with flower [63].

### 2.4 Preparation of the Extract and Quality Control

The plant material used for **EUROMED Crataegus oxyacantha** 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 \textit{Crataegus oxyacantha L.} is maintained.

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

Furthermore \textit{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.

Pesticides: in compliance with the limits established in Ph. Eur. 3\textsuperscript{rd} ed., 2.8.13

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. 3\textsuperscript{rd} ed., 5.1.4 (category 4B)

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

\textit{EUROMED} applies a unique extraction process to obtain the extract. It provides a high yield of valuable constituents and a high-grade extract in a careful way.

The \textit{EUROMED} hawthorn extract meets the highest quality standards. This way it is possible to satisfy the requirements for an effective and safe herbal medicinal product.

\section*{2.5 Standardization}

The consistent batch to batch quality of the \textit{EUROMED} hawthorn extract is guaranteed by a standardized production process.
The analytical specifications of the Euromed hawthorn extract are:

* Aspect | Fine powder, brown greenish colour, characteristic odour
* Identification | TLC (Ph. Fr. Xe ed.)
* Solubility | Soluble in hydroalcoholic solutions
* Loss on drying | Max. 5.0% (Ph. Eur. 3rd ed., 2.2.32)
* Assay | Vitexin-2-rhamnoside and hyperoside min. 1.8% (HPLC)
          | Total flavonoids expressed as hyperoside min. 1.2% (DAB-10)
* Microbiology | Acc. Ph. Eur. 3rd ed., 5.1.4, category 3B
3 Heart Dysfunction

3.1 The Human Heart

The heart is a continuously working hollow muscle with a high demand for oxygen. The oxygen extraction from coronary blood is about 70% during resting. Thus the only way to meet an increased oxygen demand of the heart is by increasing the myocardium perfusion. The coronary blood flow depends upon the transcardial gradient of blood pressure and coronary resistance. This is defined by the tonus of the coronary vessels and by the intramuscular pressure of the ventricle walls. 75-85% of the coronary blood flow occurs during diastole, when the ventricle is relaxed. An increase in the preload (end diastolic ventricular pressure) also increases the resistance of the coronary vessels and subsequently decreases the coronary perfusion. The preload may be altered as a result of an increased diastolic blood pressure of the capacity vessels or of extreme dilatation and filling of the ventricle (especially in insufficient hearts with decreased compliance). The afterload is defined as the resistance to be surmounted by the ventricle to reach the ejection of blood during the contraction. The afterload is determined by the preload combined with the resistance of the aorta and peripheral blood vessels. Both, preload and afterload are parameters determining the ejection fraction and the working economy of the insufficient heart in regard to its energy and oxygen demands. Thus the main factors determining the myocardial oxygen demand are the following parameters, which directly affect the ATP turnover in the contractile system: myocardium mass, tension of the myocardium (intramyocardial wall pressure), preload and afterload, inotropism (contractility) and heart rate. The heart-time-volume network plays only a secondary role [59].

Heart performance can be improved in the following ways:
positive inotropic effect (enhanced contractility of the heart resulting in an increase of the ejection fraction with unchanged end diastolic filling volume of the ventricle),

increase in the refraction time that can be reached by faster contraction and faster relaxation (positive lusitropic effect) of the myocardium,

relative decrease of the heart rate (it can be observed after hyperpolarization of the excitation center and results in an increase in the effective refraction time),

decrease in the systolic and the diastolic blood pressure of patients with hypertension (due to simultaneous intake of diuretic medication),

decrease of preload and afterload by dilatation of capacity vessels of the total peripheral resistance (ACE-inhibitors and introvaso dilators) and

direct vasodilation of the coronary vessels.

3.2 Cardiac Insufficiency

15 million people suffer from cardiac insufficiency worldwide; in Europe degenerative heart diseases are the main cause of death. These diseases are mainly related to age and have shown an increasing incidence over the last few decades [46]. Most fatal cardiovascular diseases are caused by arteriosclerotic changes in the blood vessels. Arteriosclerosis gives rise to angina pectoris, heart insufficiency, cardiac infarction, cardiac arrhythmia and to apoplectic stroke and peripheral thrombosis [53].

Prevention and early therapy are of special importance for the slight heart dysfunction stages defined by the New York Heart Association (NYHA) as stage I (heart disease but no reduction in physical performance capacity, no typical complaints) and stage II (complaints only during unusual
performance, e.g. dyspnoea, anxiety and tachycardia) because the prognosis of advanced stages defined by the class III (complaints already at usual performance, free of complaints only during resting) or IV (complaints also during resting) of cardiac insufficiency are, despite therapeutic progress, still malign with a 5-year mortality of 50%. Support and protective therapy for the cardiovascular system should enhance energy and oxygen supply to the heart. Early and preventative treatments require a long therapeutical application time. Since synthetic medications generally have a considerable risk to provoke undesirable side effects their long-term use is not recommended for prophylactic purposes or treatment of only slight but chronic manifestation of disorders or vegetative complaints. Due to their low risk in regard to toxicity, side effects, and addiction, herbal drugs often are appropriate remedies to support health and well-being and to slow down degenerative processes during aging and convalescence.

Cardiac insufficiency is characterized by an imbalance of the oxygen demand of the body and the oxygen supply (transport) capacity of the heart. It is mainly caused by a reduced contractility and/or reduced perfusion of the myocardium, as a consequence of coronary disease. Pathogen symptoms such as hypertensive blood pressure, increased heart rate, arrhythmia and tachycardia affect the effectiveness of heart performance and its oxygen balance resulting in progressive heart damage. Reduced perfusion of the heart can result in myocardial oxygen deficiency.
4 Pharmacology

4.1 Pharmacodynamics

Various hawthorn preparations have been researched for their pharmacological activity, primarily focusing on the cardiovascular activity. The majority of the most recent clinical studies have been conducted with proprietary preparations prepared from the leaves and flowers [63].

4.1.1 Active Ingredients

A positive inotropic action has been attributed to some flavonoid compounds. It is known that flavonoids possess antioxidant activity [2, 63]. Regarding the procyanidins, the oligomeric procyanidins (OPC) are more readily absorbed by the gastrointestinal tract and skin. Higher polymers are not absorbed and exert only local effects. There is evidence that the OPC fraction is the most important class of active constituents in hawthorn, since they generally have similar effects as the flavonoids. But they have a higher bioactivity and bioavailability and therefore can be administered at lower doses. They show a more pronounced positive inotropic effect than the flavonoids. A slight negative chromotropic effect and an enhancement of coronary blood flow after administration of OPC has also been described. The OPC dimer B-2 in Crataegus is considered as a very active substance [2, 34, 63].

In general the effects of hawthorn extract are not based on an isolated component or mechanism. Although various tests and trials with single constituents have been done, they could not fully explain the observed biological activities of hawthorn extract in total. So far a presumably combined action of all the ingredients of hawthorn extracts is assumed for its pharmacological and clinical effects [2, 34, 63].
4.1.2 Special Pharmacodynamics

The main and most observed pharmacodynamic effect of hawthorn is increased coronary blood flow [33, 47]. On one hand this increase is thought to be due to the relaxation of coronary arteries, which directly increases the flow. On the other hand it is also due to an increase in contraction and relaxation velocities, which enlarges the diastolic interval and allows more time for perfusion [27, 57]. The most often proposed mechanism for the enhancement of coronary blood flow by hawthorn extract is the inhibition of the enzyme phosphodiesterase. The enzyme catalyses the degradation of intracellular cyclic adenosine monophosphate (cAMP). The inhibition of the enzyme leads to an increase of the biologically active cAMP in the cells. It is assumed that the intracellular cAMP lowers the tonus of the smooth vessel muscle [60].

Summarizing the results of some in vitro experiments, an enhancement of coronary blood flow between 22 and 186% by hawthorn preparations standardized on flavonoids or OPC could be seen, whereby a stronger effect was shown by the OPC compared to the flavonoids or to the whole fraction [2].

Hawthorn extract is supposed to be a cardiotonic because of its positive inotropic and dromotropic effect. It therefore enhances the contraction force and nerve conductivity of the heart [31, 44].

Hawthorn extract seems to inhibit the sodium/potassium ATPase in the cardiomyocytes. This enzyme is responsible for the transportation of sodium ions out of the cell against the ionic concentration gradient and for the following influx of potassium ions into the cell. The decreased concentration gradient of sodium at the cell membrane indirectly leads to an increase in intracellular Ca$^{2+}$. Enhanced intracellular Ca$^{2+}$ has been seen to enhance the contraction force of the myocytes [60].
The use of hawthorn extract produces a prolongation of the effective refractory period and thus reduces the arrhythmogenic risk for the heart. At the same time hawthorn extract acts negatively chromotropic and bathmotropic, thus it decreases the contraction rate of the heart and the reaction of cardiac tissue to external stimuli [63]. Hawthorn significantly differs in its pharmacological profile from other inotropic and dromotropic substances regarding the observed prolongation of the effective refractory period. Other inotropic principles generally shorten this parameter [27]. The refractory time is important to coronary perfusion since perfusion only occurs in diastole [63].

Since the prolongation of the effective refractory period caused by hawthorn extract is thought to be due to an effect on the action potential duration, this effect was studied in an in vitro experiment using isolated guinea pig papillary muscle. Hawthorn extract, standardized to 2.2% flavonoids at a dosage capable of inducing an inotropic effect of 2%

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Fig. 3: The effect of hawthorn extract [60].

Prolongation of the effective refractory period and negative chromotropic and bathmotropic effect
(10 mg/l), significantly increased the action potential duration and increased the recovery time of the action potential from 8.8 to 22.6 ms, indicating a weak class I-like anti-arrhythmic action [36].

An important effect attributed to hawthorn extract lies in its ability to minimize cardiac damage due to myocardial infarction.

It was shown that hawthorn extract acts economically, which is particularly interesting for the treatment of the aging or weak heart. An extract of hawthorn (2.2% flavonoids), which increased contractile output in isolated rat myocytes, has been seen to act significantly more economically regarding the energetic balance of the cells. The energy requirement of the myocytes was measured by oxygen consumption during the administration of the extract in a concentration capable of inducing a 50% positive inotropic effect on the contraction amplitude of the myocytes. The oxygen consumption was compared with oxygen consumption when equipotential inotropic acting doses of isoprenaline and ouabain were administered or when extracellular Ca$^{2+}$ was elevated until causing the same inotropic effect. During the application of hawthorn extract, oxygen consumption in myocytes increased only about 70% whereas it increased about 120% during the application of other substances or methods. [40].
Fig. 4: Effect of the hawthorn extract (cra; 60 and 120µl/ml) on contraction amplitude (upper) and apparent refractory period (t ref) (lower) during b-stimulation with isoprenaline (iso; 10-8mol/l) [40].
4.1.3 General Pharmocodynamics

The antioxidative properties of hawthorn were described in numerous recent *in vitro* and *in vivo* investigations.

Antioxidative activities of hawthorn, which are primarily associated with the flavonoid and OPC content, are reported by numerous authors [4, 7, 9]. In an *in vitro* study a special hawthorn extract (18.75% OPC), administered to sarcoma-180-cells at dosages of 5, 10, and 20 µg/ml, significantly lowered the damaging effect of free radicals caused by doxorubicin by approximately 20%, 8% and 4%, respectively, compared to the control without disturbing antitumoral activity [7].

Based on some *in vitro* and *in vivo* experiments with the extract of hawthorn, it was suggested that the OPC fraction is mainly responsible for the scavenging of oxygen radicals. A nearly flavonoid free extract consisting of 57.8% OPC showed significantly higher inhibition of lipid peroxidation and inhibition of human neutrophil elastase (HNE) than the whole extract of hawthorn. The OPC content in the fractions was correlated with the inhibitory action. There was no correlation of flavone content and inhibition of lipid peroxidation and HNE activity. Radical scavenging and HNE inhibitory activities are thought to decisively contribute to the observed cardioprotective effects when 20 mg/kg/day of an OPC rich fraction hawthorn or 100 mg/kg/day of a whole hawthorn extract was given orally to rats. The OPC fraction is thought to be the main active constituent regarding antioxidant activity [10].

Hexanoic extracts of *Crataegus monogyna*, of *Crataegus monogyna* parasitised with *Viscum cruciatum* and of *Viscum cruciatum*, with or without enrichment of triterpenes, demonstrated a significant cytotoxic activity against cultured Hep-2 cells from a human epidermoid carcinoma of the larynx *in vitro*. Regarding the non-triterpene enriched fractions, the extract of the parasite *Viscum cruciatum* had the highest activity on inhibition with 63.1% compared to control, although the other extracts showed similar cell growth inhibition activity (parasitised extract 61.5%, non-parasitised extract 57.5%). The
triterpene-enriched fractions showed a significantly higher activity in cell growth inhibition with more than 80% inhibition compared to control in all cases (triterpene enriched *Viscum cruciatum* extract 92%, parasitised *Crataegus* extract 83.3%, non-parasitised *Crataegus* extract 93.2%) [48]. Triterpenic fraction are also present in the *Crataegus* species.

A hydroalcoholic extract of *Crataegus oxyacantha* flowers was seen to inhibit thromboxane $A_2$ activity and to stimulate prostacyclin activity in rabbit cardiac tissue. The activities of the two mediators are opposed regarding platelet aggregation where thromboxane $A_2$ has a stimulating and prostacyclin inhibiting effect. Platelet aggregation leads to blood clot formation. A methanolic fraction of total extract in a concentration of 29 µg/l did not affect thromboxane $A_2$ production by rabbit heart microsomes, but stimulated the prostacyclin synthesis 50% more than in the control. [65]. Suggesting vitexin-2''-O-rhamnoside and hyperoside as probably being responsible for a thromboxane $A_2$ inhibition the authors performed another study with horse platelet microsomes. However, the inhibitory effect on thromboxane $A_2$ by the 2 substances was shown only at concentrations too high to be clinically relevant (ID$_{50}$ value for vitexin-2''-O-rhamnoside 0.4 mg/l and for hyperoside 0.48 mg/l) [66]

4.2 Pharmacokinetics

In a study of four hawthorn extract fractions, $^{14}$C marked catechins (29.2 mg/kg), trimer procyanidin (43.2 mg/kg), higher OPC (41.2 mg/kg), and a whole OPC fraction (33.8 mg/kg) were administered orally to mice. After one hour the trimeric fraction was absorbed to 65% in blood, catechins were present to 18%, higher OPC to 3% and the total OPC fraction to 12%. After 7 hours the presence of OPC in the blood decreased (catechins 10%, trimer procyanidins 6%, total OPC 5%) except the higher OPC fraction which increased to 5%. In such organs as the brain,
liver, lung, kidney, and spleen the opposite effect occurred. The four labeled fractions were quickly absorbed after one hour (catechins to 40%, trimer OPC to 40%, higher OPC to 16%, total OPC fraction to 31%) with an increase in the organs after 7 hours in most fractions (catechins 74%, trimer OPC 81%, higher OPC 42%) except the total OPC fraction, which showed a decrease to 18%. In the urine most fractions increased for 1 to 7 hours (catechins from 1.3 to 4.5%, trimer OPC from 0.4 to 1.8%, higher OPC from 1.3 to 1.8%) except the total fraction, which decreased from 9.5 to 6.4%. A general increase of the labeled fractions was registered in the exhaled air from one hour to 7 hours. Generally the shorter OPC were absorbed faster and in higher quantity in blood and organs [24].

After feeding mice for 7 days with hawthorn extract the concentrations of the extract compounds in the organs were 2-3 times higher than after a single dose, which indicates accumulation. An enrichment of OPC in the myocardial and also in other organs has been found. While continuous feeding, the excretion was first found in the feces [24].

Regarding the starting time and duration of effects after oral and injected administration (subcutaneous, intravenous and intraperitoneal administration) of hawthorn important differences were observed. Minutes after injection of the extract an enhancement of coronary blood flow occurred which lasted only a few minutes. With orally administered doses the enhancement of coronary blood flow was seen after 1-2 hours and lasted several hours [1]

The effect of orally administered doses of 1.5-2.4 g hawthorn extract on coronary blood flow was seen after 1 to 2 hours [33]. In another study an enhancement in coronary blood flow was seen 1 hour after orally administered OPC doses to dogs (20-25 mg/kg). An accumulative effect, regarding the enhancement of coronary blood flow, has been observed when 2 successive doses (35 and 50 mg/kg) of an OPC fraction were administered orally within 6 hours to dogs. Intravenous administration of extract to cats in doses from 3 to 7 ml/kg resulted in an enhancement of coronary blood flow up to the maximum within 4 minutes after administration and a decrease within
the following 6 minutes. The diminution was more significant at lower dosages [47].
5 Toxicology

The toxicity of hawthorn is generally very low.

**Acute Toxicity**

Based on numerous toxicity studies, the toxic dosage of hawthorn extract was calculated to be 500 to 1000 times than that of the therapeutic dosage for humans [1].

The LD$_{50}$ value of an unspecified flavonoid mixture from hawthorn was reported to be 1650 mg/kg in mice [13].

**Chronic Toxicity**

No toxic effects were observed in rats and dogs after oral administration of the same hawthorn extract at 30, 90 and 300 mg/kg/day over a period of 26 weeks. 300 mg/kg/day could be considered a “no effect” level for the extracts in the rat and dog [50].

**Reproduction Toxicity**

*Crataegus* does not influence the fertility and does not show embryotoxic, perinatal or postnatal toxic effects. An undefined mixture of flavonoids obtained from hawthorn extract administered at a dosage of 100 mg/kg daily to pregnant mice for 1 month did not produce any abnormal events. Offspring were normal and displayed no changes in blood and physical development [32]. Oral dosages of hawthorn extract of up to 1.6 g/kg revealed no teratogenic effects in rats and rabbits. In rats, the extract showed no peri- or postnatal toxicity and no effects on the F1 generation or their fertility [17].

**Genotoxicity /Carcinogenicity**

**Fertility, Embryotoxicity and Perinatal/Postnatal Toxicity**

**Mutagenic Activity**
No evidence for mutagenicity or clastogenicity of hawthorn extract was seen when using standard tests.

*Carcinogenicity*

No carcinogenic risk is to be expected [13, 17].
6 Clinical Pharmacology

Various *in vitro* studies have indicated possible mechanisms of action for hawthorn:

- inhibition of cAMP-phosphodiesterase activity [28, 38, 56],
- inhibition of Na⁺-K⁺-ATP-ase activity [8]
- inhibition of thromboxane (TXA₂) synthesis and stimulation of prostacyclin (PGI₂) synthesis [64, 65, 66],
- antioxidative activities [4, 3, 10] and
- inhibition of human neutrophil elastase [10].

In a placebo controlled cross-over study on 12 healthy subjects the effects of 900 mg hawthorn extract LI 132 on the cutaneous microcirculation was compared to those of 0.3 mg methylpredigoxin, a commonly used digitalis glycoside. Immediately before as well as 1 hour, 3 and 6 hours after taking the medications as a single dose the parameters hematocrite, erythrocyte aggregation, plasma viscosity, erythrocyte pre and post ischemic flow rate in the nail bed capillaries as well as heart rate and blood pressure were measured. Six hours after taking digoxin the erythrocyte aggregation had a mean increase of 19%, whereas, the hawthorn preparation decreased hematocrite by a mean of 3.2%. Changes of hematocrite might be due to effects of hawthorn on vasodilatation. No significant changes were recorded for the remaining parameters, possibly due to the single application of the drugs [19].

Simultaneous administration of hawthorn extracts with cardiac glycosides was found to potentiate the effect of the glycosides on isolated guinea pig hearts [62]. This glycoside saving effect was also observed in patients when administering *Crataegus* spp. extract with strophantin or digitalis [43]. For patients with coronary insufficiency treated with theophylline or nitroglycerin preparations, the
dosage of these medications could be reduced when *Crataegus* spp. extract was administered simultaneously [43].

In a study with 3,664 patients with cardiac disorders receiving a hawthorn preparation 2 patients suffered from severe nausea, both of them took diuretics. This might indicate a decreased tolerance of hawthorn when administered simultaneously with some diuretics [52].

![Graph showing heart frequency over weeks](image)  

**Fig. 5:** Heart frequency – mean – (beats per minute) reception, 4th week and 8th week [52].
7 Proof of Clinical Effectiveness

7.1 Efficacy

The therapeutic administration of hawthorn extracts is based on a long tradition of use as a heart supportive herbal remedy and several decades of clinical experience of therapy for cardiac insufficiency as well as further extensive scientific information. As it combines several physiological effects that result in an improved perfusion and oxygen balance of the heart, positive inotropism, decreased arrhythmia and heart rate, it is suitable for the treatment of declining cardiac performance corresponding to Functional Capacity Class II as defined by the New York Heart Association (NYHA). The German Commission E and the ESCOP monograph both acknowledge the suitability of hawthorn to strengthen the heart and circulatory function at early stages of cardiac insufficiency. The beneficial effects on heart performance of some isolated compounds of hawthorn, especially the flavonoids or OPC, are well documented.

During the last few decades, the efficacy of hawthorn preparations were tested in a great number of clinical studies. The results of the most recent placebo-controlled and non-controlled studies listed in this report are based on information obtained from more than 4,000 patients with cardiac disorders corresponding to Classes I and II (NYHA). In these studies the positive effect of hawthorn on the ergometric performance capacity and on the pressure-heart rate product was established. Both parameters are indicators of an economic heart performance and improved cardiac oxygen balance. The enhanced oxygen absorption of patients during ergospirometry and the prolongation of the time interval to reach the anaerobic threshold as well as the reduction of angina pectoris confirm these positive effects of hawthorn on the heart activity. Furthermore, a significant decrease in blood pressure and heart rate was reported.
Beside these objective parameters the improvement of subjective ones such as state of health and well-being due to hawthorn medication is reported in most of the studies. The treatment of patients with hawthorn extracts suppresses typical symptoms of heart diseases like arrhythmia, tachycardia, hypertension, nycturia and oedema as well as vegetative disorders such as anxiety, depression, irritability and decreased sleep quality. Since the heart and the cardiovascular system play a central role in the distribution of energy donors and oxygen to the whole body, cardiovascular supportive and protective therapies, which have few side effects and risks, are beneficial for the physical and concentration capacities of elderly persons or persons with a reduced stress tolerance.

In an eight-week multi-center double-blind placebo-controlled study the effect of the hawthorn extract LI 132 (Faros®; 3 x 200 mg/day) was tested on 78 patients (30 male and 48 female; average age 61.3 years) with NYHA class II heart failure. The primary test parameter was maximum work capacity on an ergometric bicycle, measured as work output (in watts) over a three-minute exercise with an increasing load. Secondary parameters were blood pressure, heart rate and subjective well-being of the patients. The work capacity of the verum group increased from 79 watts at the beginning to 99 watts after 4 weeks and further to 107 watts after 8 weeks. This result was statistically significant (p < 0.001), as the placebo group did not improve their work capacity. As systolic blood pressure and heart rate (and pressure rate product) decreased significantly, the secondary parameters were also significantly improved. These results of the objective parameters corresponded with the improvement of subjective well-being criteria (p < 0.001). No severe side effects were observed from the medication. All positive effects of LI 132 were more pronounced after 8 weeks than after 4 weeks, indicating the favorable effects of long-term administration of hawthorn preparations [52].

In another multi-center placebo-controlled double-blind clinical study on 136 patients, with symptoms according to NYHA class II cardiac insufficiency, the positive effect of hawthorn extract could be proved. One capsule of
Crataegus Special Extract WS 1442 (containing 80 mg dry extract standardized to 15 mg oligomeric procyanidins) twice a day over a period of 8 weeks caused a significant decrease (approximately 5.6) of the pressure-heart rate product monitored during standardized exercises at 50 watt on an ergometric bicycle. After 8 weeks of placebo administration a deterioration of this primary parameter was observed (about 4.2). Within the secondary parameters the subjective state of health was improved after eight weeks within the verum group compared to the placebo group, but without reaching statistical significance. Furthermore, the primary complains, typically produced by heart failure such as nycturia, oedema, beginning hypertrophy of the left ventricle and venous congestion, were determined by patient's subjective assessment. After 8 weeks the relief of these primary complain was statistically better for patients treated with hawthorn extract than in those of the placebo group (p < 0.05). The general tolerance of the medication was rated as very good [67].

![Graph showing change of main complaints (%) after 8 weeks of therapy.](image)

Fig. 6: Change of main complaints (%) after 8 weeks of therapy [67].

A randomized, double-blind cross-over study was carried out on 36 multi-morbid patients (average age 74) with stenocardiac conditions and class II (NYHA) heart insufficiency the effects of the administration of
Crataegutt® novo (1 coated tablet three times daily, each containing 60 mg of standardized hawthorn extract). After the first 6 weeks the verum and placebo medications were exchanged between the two groups and the study was repeated for another 6 weeks. During exercise and after 2 minutes of recovery all objective parameters systolic and diastolic blood pressure, the heart rate and the pressure/heart rate product were significantly decreased \((p < 0.001)\) in the verum group compared to the placebo group. Furthermore the therapeutic success, graded into six levels on the basis of the clinical parameters, was improved under verum administration. The effect of the hawthorn preparation on the psychological state of the patients was analyzed applying two different rating scales [NOSIE, CIPS 1978 and BPRS, CIPS 1977]. Both assessments documented the significant improvement in the mental state of the patients, considering such factors as depression, irritability, anxiety and ability to sleep [37].

In a further randomized, double-blind, placebo-controlled study on 72 patients with class II heart failure according to the NYHA and an average age of 51 ± 10 the effect of the hawthorn extract LI 132, 3 x 300 mg/day was tested, over 8 weeks. The primary parameters were the oxygen absorption under performance and the time interval to reach the anaerobic threshold at constant performance on ergospirometric test equipment. Under verum therapy, the improvement of these parameters was statistically significant \((p < 0.05)\). Oxygen absorption was increased from 15 to 17 mO2/kg/min and the time to reach the anaerobic threshold was prolonged by about 30 sec. Under placebo these parameters did not change. At the end of the study the subjective well-being was significantly better in the verum group \((p < 0.01)\). These results indicate an increase in oxygen supply to the heart and to the peripheral muscles and an economizing effect on heart load yielded by therapy with the hawthorn preparation [20].
Fig. 7: Patients working capacity measured by using an ergometer bicycle [5].

Radionuclide angiocardiography was used to investigate haemodynamic effects of the hawthorn preparation Crataegutt forte in 20 patients with mild congestive heart failure and decreased left ventricular ejection fraction. Daily dosage was 480 mg, standardized to 18.75% oligomeric procyanidins. After four weeks of treatment, an increase of the ejection fraction by 3.2% during resting and by 5.0% during exercise was found. Blood pressure decreased both at rest and under stress. Corresponding to a 10% increase of ejection fraction the stress tolerance was also improved by approx. 10% after 4 weeks. The heart rate did not change [15].

Recently in a large-scale open surveillance study concerning desired and undesired effects of high dosages of hawthorn preparations the data of 3,664 patients receiving 300 mg of a hawthorn extract (Faros 300; standardised to 2.2% flavonoids) 3 times a day over eight weeks were documented by 940 physicians. Clinical symptoms of 66% of the patients could be related to heart insufficiency class II (NYHA). The data of 1,476 patients, who received the hawthorn extract as the only medication, were analyzed. A rating list with 9 symptoms typical for cardiac
insufficiency and a three-step graduation were prepared, the sum of all scales was used as general score of severity of the symptoms. The general score decreased from the initial 9.0 points to 4.8 points after 4 weeks and to 2.6 points after 8 weeks. Although the class I patients were nearly symptom free at the end of the treatment the relative improvement was higher in the class II patients. The systolic and the diastolic blood pressure were decreased as well. This study emphasizes the very good tolerance of hawthorn extract, its capacity to also improve symptoms in advanced stages and the continuous improvement over the eight weeks of the treatment. Comparing these results with those of other clinical studies the author proposes the therapeutic advantage of using high dosages hawthorn therapy [52].

Fig. 8: Frequency of the important symptoms before and after therapy. After 56 days a larger decrease under verum [52].
7.2 Safety

Generally the tolerance of the hawthorn preparations has been proven to be good or very good, even at dosages of up to 900 mg extract per day over several weeks. Nevertheless some undesirable effects have been observed during the studies. However, the relationship of these undesirable effects to the hawthorn preparations could not be confirmed in the majority of cases.

No side effects were reported in an open study on 20 patients taking 480 mg/day hawthorn dry extract corresponding to 90 mg/day OPC (3 x 2 coated tablets each 80 mg standardized to 15 mg OPC) [15].
### Tab.2: Summary of other clinical trials

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of subjects</th>
<th>Diagnosis</th>
<th>Duration of treatment</th>
<th>Dosage</th>
<th>Efficacy</th>
</tr>
</thead>
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<tr>
<td><strong>I. PLACEBO CONTROLLED STUDIES</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Schmidt U, Kuhn U, Ploch M, Hübner W-D, 1994 [51]</td>
<td>78</td>
<td>NYHA class II</td>
<td>8 weeks</td>
<td>600 mg</td>
<td>Significant increase in working capacity. Reduction of systolic blood pressure, heart rate and pressure/rate product</td>
</tr>
<tr>
<td>Hanak T, Brückel M-H, 1983 [23]</td>
<td>60</td>
<td>angina pectoris NYHA classes I - II</td>
<td>3 weeks</td>
<td>180 mg</td>
<td>Significant rise in ergometric tolerance. Improvement of ECG findings</td>
</tr>
<tr>
<td>Leuchtgens H, 1993 [30]</td>
<td>30</td>
<td>Cardiac insufficiency NYHA class II</td>
<td>8 weeks</td>
<td>160 mg</td>
<td>Significant reduction of heart rate, pressure/rate product and B-L-score</td>
</tr>
<tr>
<td><strong>II. CONTROLLED STUDIES WITH REFERENCE THERAPIES</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tauchert M, Ploch M, Hübner W-D, 1994 [61]</td>
<td>132</td>
<td>Cardiac insufficiency NYHA class II</td>
<td>8 weeks</td>
<td>900 mg or Captopril 37.5 mg</td>
<td>Significant reduction of performance tolerance, pressure/rate product and symptoms in both groups</td>
</tr>
<tr>
<td><strong>III. NON-CONTROLLED STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Loew D, Albrecht M, Podzuweit H, 1996 [31]</td>
<td>147</td>
<td>NYHA classes I - II</td>
<td>4 - 8 weeks</td>
<td>900 mg</td>
<td>Significant reduction of pressure/rate product</td>
</tr>
</tbody>
</table>
8 Summary

*Efficacy*

The therapeutic administration of hawthorn extract is based on a long traditional use as a heart supportive herbal remedy and of several decades of clinical experience in the therapy of cardiac insufficiency of classes I and II (NYHA) and of further extensive scientific information. As it combines several physiological effects that result in improved perfusion and oxygen balance of the heart, positive inotropism, decreased arrhythmia and heart rate, it is equally suitable for the treatment of angina pectoris and heart insufficiency caused by infarction. The German Commission E monograph acknowledges the suitability of the hawthorn leaf with flower to strengthen the heart and circulatory function at early stages of heart insufficiency. The beneficial effects on heart performance of some isolated compounds of hawthorn, especially the flavonoids or OPC, are well documented.

*Safety*

Hawthorn preparations are generally well or very well tolerated even at high dosages of up to 900 mg per day. The most frequently observed undesirable effect has been slight or medium strong gastrointestinal irritation. Interactions with other heart active substances may occur with hawthorn preparations. Thus persons who receive other cardiovascular treatments should consult their supervising physician before hawthorn preparations are used.
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