

# Hawthorn

*Crataegus monogyna* Jacq., *C. laevigata* (Poir.) DC. (syn. *C. oxyacantha* auct)

[Fam. *Rosaceae*]

## OVERVIEW

Hawthorn is the name for bushes and small trees in the genus *Crataegus*, of which there are approximately 280 species native to northern temperate zones in East Asia, Europe, and eastern North America. The fruit has been used as food and medicine in Europe for centuries. Hawthorn preparations are among the most popularly prescribed botanical medicines in central Europe, particularly in Germany, Austria, and Switzerland, with the primary approved indication being treatment of declining cardiac performance, according to Stage II New York Heart Association (NYHA) classification. Over the past 20 years, several different commercially available preparations of hawthorn have been investigated in double-blind, placebo-controlled (DB, PC) clinical studies.



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## PRIMARY USES

- Congestive heart failure, NYHA Stages I and II

NOTE: The NYHA functional classification is most often used to characterize patients' limitations due to failure of the left ventricle. The classification has a strong association with mortality that is independent of left ventricular ejection fraction.

STAGE I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.

STAGE II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue or dyspnea.

## OTHER POTENTIAL USES

- Feeling of pressure and tightness in the cardiac region
- Nervous heart complaints including palpitations, sharp pain in the chest, rapid pulse, or vertigo

## PHARMACOLOGICAL ACTIONS

Improves subjective parameters of cardiac insufficiency (as NYHA Stage II); increases cardiac work tolerance; decreases pressure/heart rate product; increases the ejection fraction; raises anaerobic threshold.

## DOSAGE AND ADMINISTRATION

### Hawthorn leaf with flower (internal)

INFUSION: Pour about 150 ml boiling water over approximately 1.5 g dried herb, steep for 10–15 minutes, squeeze tea bag over cup, 3–4 times daily, during or after meals.

DRY EXTRACT (STANDARDIZED): 160–900 mg, in 2–3 individual doses per day, corresponding to 30–168.7 mg procyanidins, calculated as epicatechin, or 3.5–19.8 mg flavonoids, calculated as hyperoside [4–7:1 (*w/w*) with defined flavonoid or procyanidins content, ethanol 45% (*v/v*) or methanol 70% (*v/v*)].

### Hawthorn fruit (internal)

NOTE: According to Kneipp®, a properly prepared tea infusion will yield over 90% into solution of the active principles from the flavonoid and oligomeric procyanidin groups and compares dose for dose with solid-form preparations (Kneipp-Werke, 1996). Other sources report that after a 10-minute infusion, 35% of the *O*-glycoside bound flavonoids, and 40% of the *C*-glycoside bound flavonoids are released into solution (Meyer-Buchtela, 1999).

FLUID EXTRACT: 1:1 (*w/v*) in 25% alcohol (*v/v*), 0.5–1.0 ml, 3 times daily.

TINCTURE: 1:5 (*w/v*), in 45% alcohol (*v/v*), 1–2 ml, 3 times daily.

TINCTURE: 1:3.2 (*w/v*) in 49% alcohol (*v/v*), 30 drops diluted in water, 3 times daily, one-half hour before meals.

TINCTURE: 1:10 (*w/v*), 5–10 drops, 1–3 times daily.

SOLID EXTRACT: 0.25–0.50 teaspoon daily.

SYRUP: 1 teaspoon, 2–3 times daily.

## CONTRAINDICATIONS

HAWTHORN LEAF WITH FLOWER: No known restrictions.

HAWTHORN FRUIT: No known restrictions.

PREGNANCY AND LACTATION: No known restrictions, but systematic, scientific safety studies have not yet been conducted.

**ADVERSE EFFECTS**

HAWTHORN LEAF WITH FLOWER: None known.

HAWTHORN FRUIT: None known.

**DRUG INTERACTIONS**

HAWTHORN LEAF WITH FLOWER: No known interactions, according to German Commission E monograph. Hawthorn may potentiate the effects of digitalis drugs (e.g., digoxin), and it may potentiate the coronary artery dilating effects of theophylline, caffeine, papaverine, sodium nitrate, adenosine, and epinephrine (although these are not considered clinically significant interactions). A healthcare provider should be consulted before combining hawthorn with any heart medications.

HAWTHORN FRUIT: No known interactions.

**CLINICAL REVIEW**

In fourteen clinical studies on hawthorn conducted on 6,900 participants, all but one showed positive effects for cardiac insufficiency. Eight are DB, PC studies, four are open studies, one is a

large multi-center observational study, and one is a DB study comparing hawthorn to standard treatment. Most clinical studies have been conducted using a dry extract of hawthorn leaf with flower standardized to a daily dose of 9 mg or more oligomeric procyanidins. A major international randomized, DB, PC study is currently investigating the influence of the standardized extract of hawthorn leaf with flower on the mortality of patients suffering from congestive heart failure. In this trial (involving approximately 120 investigation centers in seven European countries), up to 2,300 patients with congestive heart failure, NYHA Stage II and III, and markedly impaired left ventricular function will be enrolled and treated over 24 months. The primary outcome variable is the combined end point of cardiac death, non-lethal myocardial infarction, and hospitalization due to progression of heart failure. Secondary outcome variables are total mortality, exercise duration, echocardiographic parameters, and quality of life, as well as pharmaco-economic parameters. The first patient was enrolled in October 1998. The trial is expected to be completed at the end of 2002.



# Hawthorn

*Crataegus monogyna* Jacq., *C. laevigata* (Poir.) DC. (syn. *C. oxyacantha* auct.)

[Fam. *Rosaceae*]

## OVERVIEW

Hawthorn fruit has long been used as a food and medicine in Europe; particularly in Germany, Austria, and Switzerland, where it ranks as one of the most popularly used botanical medicines, especially for treating declining heart function. Many clinical studies have been conducted on hawthorn over the past 20 years.

## USES

**NOTE:** Patients should not attempt to self-medicate for suspected or properly diagnosed cardiac conditions, but should seek the advice of a healthcare provider for appropriate treatment.

Congestive heart failure, based on the New York Heart Association (NYHA) functional classification for Stage I, no limitation of physical activity, and Stage II, slight limitation of physical activity, causing fatigue or shortness of breath.

## DOSAGE

### Hawthorn leaf with flower (internal)

**INFUSION:** Pour about 150 ml boiling water over approximately 1.5 g dried herb, steep for 10–15 minutes, squeeze tea bag over cup, 3–4 times daily, during or after meals.

**DRY EXTRACT (STANDARDIZED):** 160–900 mg, in 2–3 individual doses, corresponding to 30–168.7 mg procyanidins, calculated as epicatechin, or 3.5–19.8 mg flavonoids, calculated as hyperoside [4–7:1 (*w/w*) with defined flavonoid or procyanidins content, ethanol 45% (*v/v*) or methanol 70% (*v/v*)].

### Hawthorn fruit (internal)

**NOTE:** Hawthorn fruit products have *not* been tested for effectiveness in recent clinical research. Most of the published studies have been conducted on standardized extracts of hawthorn leaf with flowers.

**FLUID EXTRACT:** 0.5–1.0 ml, 3 times daily [1:1 (*w/v*) in 25% alcohol (*v/v*)].

**TINCTURE:** 5–10 drops, 1–3 times daily [1:10 (*w/v*)]

**TINCTURE:** 1–2 ml, 3 times daily [1:5 (*w/v*), in 45% alcohol (*v/v*)].

## Comments

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



## CONTRAINDICATIONS

No known contraindications for hawthorn leaf, flower, or fruit.

**PREGNANCY AND LACTATION:** No known restrictions. Scientific studies are lacking, however, so consult with a healthcare provider before using hawthorn during pregnancy or while breast-feeding.

## ADVERSE EFFECTS

No known adverse effects for hawthorn leaf, flower, or fruit.

## DRUG INTERACTIONS

**HAWTHORN LEAF WITH FLOWER:** Hawthorn may increase the effects of the heart drug digoxin and mildly increase the coronary artery dilating effects of substances like caffeine, theophylline in tea, and papaverine in opium-containing products (such as cough medicines). Consult with a healthcare provider before combining hawthorn with any heart medications.

**HAWTHORN FRUIT:** No known interactions.



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# Hawthorn

*Crataegus monogyna* Jacq., *C. laevigata* (Poir.) DC. (syn. *C. oxyacantha* auct)

[Fam. *Rosaceae*]

## OVERVIEW

**H**awthorn is a bush or small tree that includes approximately 280 species native to northern temperate zones in East Asia, Europe, and eastern North America (Hobbs and Foster, 1990). The fruit has been used as food and medicine in Europe for centuries. Over the past 20 years, several different commercially available preparations of hawthorn have been investigated in double-blind, placebo-controlled (DB, PC) clinical studies. Hawthorn preparations are among the most popularly prescribed botanical medicines in central Europe, particularly in Germany, Austria, and Switzerland. The primary approved indication is treatment of declining cardiac performance according to Stage II of the New York Heart Association (NYHA) classification. Hawthorn has become increasingly popular as a dietary supplement in the U.S., ranking 20th in sales in mainstream retail stores in 2000 (Blumenthal, 2001). Separate *United States Pharmacopoeia-National Formulary* botanical monographs are presently under development for hawthorn leaf with flower and its preparations including extract, powder, and tablet (USP, 2002).



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## DESCRIPTION

Hawthorn leaf and flower preparations consist of whole or cut, dried, flower-bearing branches of *Crataegus monogyna* Jacq. or *C. laevigata* (Poir.) DC. (syn. *C. oxyacantha* auct.), their hybrids, or other *Crataegus* species including *C. piperi* Britton (syn. *C. columbiana* T.J. Howell var. *piperi* [Britt.] Egglest) and *C. rivularis* Nutt. (syn. *C. douglasii* Lindl. var. *rivularis* [Nutt.] Sarg.) [Fam. *Rosaceae*]. Various species of hawthorn leaf and flower are recognized as official by different compendia: the *German Pharmacopoeia* recognizes up to five species, and the *Pharmacopoeia Europa* recognizes two. The *American Herbal Pharmacopoeia* (unofficial) recognizes *C. laevigata*

(*C. oxyacantha*) and *C. monogyna*, or their hybrids, and other species (Upton, 1999a, 1999b).

The *Pharmacopoeia Europa* requires that hawthorn preparations contain not less than 1.5% flavonoids, calculated as hyperoside (Ph.Eur., 2001). Both the *Austrian Pharmacopoeia* and the *German Pharmacopoeia*, however, require not less than 0.7% flavonoids (DAB, 1999; ÖAB, 1994). The *Pharmacopoeia Europa* requires a flavonoid content of 1.5% based on a spectrophotometric method, while the 0.7% flavonoid concentration of the *German Pharmacopoeia* is based on a high-performance liquid chromatography method. Thus, the apparent differences in value are based on different analytical methods, not on differences of raw material.

Hawthorn fruit consists of the dried pome of *C. monogyna* Jacq. or *C. laevigata* (Poir.) D.C. (syn. *C. oxyacantha* auct.), or hybrids or combinations of these species. The dried fruit contains not less than 1.0% of procyanidins calculated as cyanidin chloride (DAC, 1992; Ph.Eur., 2001).

## PRIMARY USES

### Hawthorn leaf with flower (internal)

- Congestive heart failure NYHA Stage I and II (Tauchert *et al.*, 1999; Blumenthal, *et al.*, 1998; Loew *et al.*, 1996; Weigl *et al.*, 1996; Bödigerheimer and Chase, 1994; Förster *et al.*, 1994; Schmidt *et al.*, 1994; Tauchert *et al.*, 1994; Leuchtgens H, 1993; Weigl and Noh, 1992; Eichstädt *et al.*, 1989; O'Conolly *et al.*, 1986; Hanak and Brückel, 1983; Iwamoto *et al.*, 1981)

NOTE: NYHA functional classification is most often used to characterize patients' limitation from left ventricular failure. The classification has a strong association with mortality independent of left ventricular ejection fraction.

STAGE I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.

STAGE II: Slight limitation of physical activity.

Comfortable at rest, but ordinary physical activity results in fatigue or dyspnea.

## OTHER POTENTIAL USES

- Feeling of pressure and tightness in the cardiac region (Morant and Ruppner, 2001; Braun *et al.*, 1996)
- Nervous heart complaints such as palpitations, sharp pain in the chest, rapid pulse, or vertigo (Morant and Ruppner, 2001; Pfister-Hotz, 1997; van Hellemont, 1988; Wichtl, 1997)

## DOSAGE

### Hawthorn leaf with flower (internal)

#### Crude Preparations

INFUSION: About 150 ml boiling water poured over approximately 1.5 g dried herb, steeped for 10–15 min., tea bag

squeezed over cup, 3–4 times daily, during or after meals (Morant and Ruppanner, 2001; Braun *et al.*, 1996).

NOTE: According to Kneipp®, a properly prepared tea infusion will yield over 90% into solution of the active principles from the flavonoid and oligomeric procyanidin groups and compares dose for dose with solid-form preparations (Kneipp-Werke, 1996). Other sources report that after a 10-minute infusion, 35% of the *O*-glycoside bound flavonoids, and 40% of the *C*-glycoside bound flavonoids are released into solution (Meyer-Buchtela, 1999).

FLUID EXTRACT (DAB, 2000) [1:1 (*w/v*), 45% ethanol (*v/v*), ≥1.0% flavonoids calculated as hyperoside ethanol]: The German Commission E requires that a single- or daily-dose phytoequivalence to the native dry extract dosage must first be confirmed by a clinical-pharmacological experiment or clinical study before a dosage recommendation can be made (Blumenthal *et al.*, 1998).

#### Standardized Preparations

DRY EXTRACT [4–7:1 (*w/w*) with defined flavonoid or procyanidins content, ethanol 45% (*v/v*) or methanol 70% (*v/v*): 160–900 mg, in 2–3 individual doses, corresponding to 30–168.7 mg procyanidins, calculated as epicatechin, or 3.5–19.8 mg flavonoids, calculated as hyperoside, according to Commission E (Blumenthal *et al.*, 1998).

#### Hawthorn fruit (internal)

##### Crude Preparations

NOTE: The following doses for hawthorn *fruit* preparations are *not* approved by Commission E and do not correlate to clinical trials summarized in the table in this monograph. These doses are presented as guides for non-official uses of hawthorn fruit preparations that are not documented by recent clinical research but are nevertheless published in the literature as potentially useful in NYHA Stage I and possibly Stage II (Upton, 1999).

FLUID EXTRACT [1:1 (*w/v*) in 25% alcohol (*v/v*): 0.5–1.0 ml, 3 times daily (BHP, 1983; Karnick, 1994).

TINCTURE [1:5 (*w/v*), in 45% alcohol (*v/v*): 1–2 ml, 3 times daily (BHP, 1983).

TINCTURE [1:3.2 (*w/v*) in 49% alcohol (*v/v*): 30 drops diluted in water, 3 times daily, one-half hour before meals (Morant and Ruppanner, 2001).

TINCTURE [1:10 (*w/v*): 5–10 drops, 1–3 times daily (Hänsel *et al.*, 1992–94).

SOLID EXTRACT: 0.25–0.50 teaspoon daily (Upton *et al.*, 1999a).

SYRUP: 1 teaspoon, 2–3 times daily (Upton *et al.*, 1999a).

#### DURATION OF ADMINISTRATION

##### Internal

The Commission E reports that a healthcare provider should be consulted in cases where symptoms continue unchanged for more than six weeks or in case of swelling of the legs. Medical diagnosis is absolutely necessary when pain occurs in the region of the heart, spreading out to the arms, upper abdomen, or the area around the neck, or in cases of respiratory distress (dyspnea) (Blumenthal *et al.*, 1998).

#### CHEMISTRY

NOTE: Fully validated methods for determining procyanidin content are lacking. Therefore, the findings provided should be taken as relative values (Upton, 1999b).

#### Hawthorn leaf with flower

Constituents considered most important and primarily responsible for the pharmacological activity of hawthorn include flavonoids and procyanidins. The oligomeric procyanidins with a lower degree of polymerization appear to be more active than those with a higher degree of polymerization. Various concentrations are found in different plant parts and vary from species to species (Upton, 1999b). All species and parts studied contain a wide array of flavonoids (0.5–1.5%). The primary flavonoids are hyperoside (quercetin-3-*D*-galactoside), vitexin-2''-*O*-rhamnoside, and acetylvitexin-2''-*O*-rhamnoside. The primary flavonoid in the flowers is hyperoside, although in the leaves, vitexin-2''-*O*-rhamnoside and, occasionally, acetylvitexin-2''-*O*-rhamnoside dominate (Rehwald, 1995).

The leaf and flower contain to 1.78% total flavonoids (flavones and flavonols) of which approximately 0.53% are vitexin-2''-*O*-rhamnoside, 0.28% hyperoside, 0.17% rutin, and 0.02% acetylvitexin-2''-*O*-rhamnoside (Hänsel *et al.*, 1992–94; Wagner and Tittel, 1983); 1.0–2.4% oligomeric procyanidins; 0.6% triterpene acids including ursolic, oleanolic, and crataegolic acids; and phenolic acids such as caffeic acid, chlorogenic acid, and related phenolcarboxylic acids (Hänsel *et al.*, 1992–94).

#### Hawthorn fruit

The fruits contain relatively low levels of flavonoids and consist primarily of oligomeric and polymeric procyanidins (Rehwald, 1995; Tittel and Wagner, 1981). The procyanidins contained in the fruit reportedly have a higher degree of polymerization than the procyanidins in the leaves and flowers. The pulp contains the highest concentration of procyanidins followed by the skin and stalks and procyanidin content is reportedly highest in unripe fruits (decreasing from 6.9% to 0.9% to the end of summer) (Rohr, 1999).

The fruit contains up to 2.96% total procyanidins of which approximately 1.9% are oligomeric procyanidins; 0.42–0.45% triterpene acids including ursolic, oleanolic, and crataegolic acids; and flavonoids (flavone glycosides and *C*-glycoside flavones), mainly hyperoside (Hänsel *et al.*, 1992–94). A small amount of quercetin derivatives and rutin are also present (Rohr, 1999).

#### PHARMACOLOGICAL ACTIONS

##### Hawthorn leaf with flower

###### Human

The Commission E reported that in cases of cardiac insufficiency classified as NYHA Stage II, hawthorn leaf with flower improves subjective findings, increases cardiac work tolerance, decreases pressure/heart rate product, increases the ejection fraction, and raises the anaerobic threshold (Blumenthal *et al.*, 1998).

###### Animal

The Commission E reported positive inotropic effect, positive dromotropic effect, negative bathmotropic effect, increases in coronary and myocardial circulatory perfusion, and a reduction in peripheral vascular resistance (Blumenthal *et al.*, 1998). These actions are confirmed in recent reviews (Loew, 1997; Upton, 1999a, 1999b).

###### *In vitro*

The extract standardized to procyanidins blocks beta-adrenoceptors (Rácz-Kotilla *et al.*, 1980), and has inotropic effects in isolated heart cells (Bratman and Kroll, 1999), exerts direct positive inotropic *ex vivo* effect in human myocardium taken from patients with congestive heart failure, increases force of contraction in human myocardium 3', 5'-cyclic adenosine



monophosphate (cAMP)-independently (Schwinger *et al.*, 2000) and increases antioxidant activity (Da Silva *et al.*, 2000).

### Standardized Preparations

The extract standardized to procyanidins blocks beta-adrenoceptors (Rącz-Kotilla *et al.*, 1980), lowers plasma lipids (Rajendran *et al.*, 1996), and blocks repolarizing potassium currents in ventricular cardiac myocytes (Müller, 1999).

### Hawthorn fruit

#### Human

Cardiotonic (BHP, 1996).

#### Animal

Alcoholic tincture is a hypolipidemic agent (Rajendran *et al.*, 1996; Shanthi *et al.*, 1994).

NOTE: Since hawthorn fruit contains many of the same procyanidins as the leaf and flower extract, albeit in lower concentrations, the antioxidant effect (and presumably others) are presumed to be similar (Upton, 1999b).

### MECHANISM OF ACTION

The mechanism of hawthorn's vasodilating effect remains unclear (Loew, 1997). Based on animal studies, increases in coronary blood flow do not appear to be due to the action of a single group of constituents (e.g., flavonoids) but rather to interactions between various different groups of compounds (Sticher and Meier, 1998). Because the biological activity cannot be attributed to any single substance contained in hawthorn, the entire extract must be viewed as the effective treatment (Reuter, 1994). Hawthorn's hypotensive effect is due to its vasodilating action rather than to an effect via adrenergic, muscarinic, or histaminergic receptors (Abdul-Ghani *et al.*, 1987). The hypotensive effect may be due to procyanidins inhibiting angiotensin-converting enzyme (ACE) (Sticher and Meier, 1998).

#### Human

- Based on experiments on myocardium taken from terminally failing human hearts (NYHA Class IV), it is suggested that hawthorn leaf with flower extract acts in a way similar to the cAMP-independent positive inotropic action of cardiac glycosides. Additionally, hawthorn improves the force-frequency relation in failing human myocardium (Schwinger *et al.*, 2000).

#### Animal

- Enhances LDL-receptor activity in rats. The hypocholesterolemic effect caused by the tincture may be due to up-regulation of hepatic LDL receptors (Rajendran *et al.*, 1996).

#### In vitro

- One study reports that the mechanism of hawthorn's positive inotropic effects remains elusive and the effects are not caused by phosphodiesterase inhibition or a  $\beta$ -sympathomimetic effect. In isolated guinea pig ventricular myocytes, hawthorn extract blocks repolarizing potassium currents in a way that is similar to the action of class III anti-arrhythmic drugs (Müller, 1999).
- Inhibits cAMP phosphodiesterase activity (Schüssler *et al.*, 1991, 1992, 1993, and 1995), which increases cardiac cAMP levels causing a positive inotropic effect (cardiac muscle contractility).
- Inhibits  $\text{Na}^+/\text{K}^+$  -ATP-ase activity (Brixius *et al.*, 1998; Leukel-Lenz, 1988).

- May inhibit thromboxane (TXA<sub>2</sub>) synthesis and stimulate prostacyclin (PGI<sub>2</sub>) (Vibes *et al.*, 1991, 1993, and 1994).
- Antioxidant (Bahorun *et al.*, 1994, 1996; Chatterjee *et al.*, 1997). A good correlation between hawthorn total phenolic content and antioxidant capacity has been shown (Sticher and Meier, 1998).
- Inhibits human neutrophil elastase (Chatterjee *et al.*, 1997).

### CONTRAINDICATIONS

#### Hawthorn leaf with flower

None known (Blumenthal *et al.*, 1998; Braun *et al.*, 1996; ESCOP, 1999).

#### Hawthorn fruit

None known (Meyer-Buchtela, 1999).

PREGNANCY AND LACTATION: No known restrictions (McGuffin *et al.*, 1997), but further research needs to be conducted to determine safety. The Commission E reports that no experimental data are available concerning embryonic and fetal toxicity, fertility, and postnatal development (Blumenthal *et al.*, 1998). Systematic scientific investigations have not been conducted on pregnant or lactating women. Use during pregnancy or lactation should be decided by a healthcare provider (Morant and Ruppner, 2001).

### ADVERSE EFFECTS

HAWTHORN LEAF WITH FLOWER: None known (Blumenthal *et al.*, 1998; Braun *et al.*, 1996; ESCOP, 1999).

HAWTHORN FRUIT: None known (Meyer-Buchtela, 1999).

### DRUG INTERACTIONS

HAWTHORN LEAF WITH FLOWER: No known documented interactions, according to the Commission E monograph of 1994 and later therapeutic reviews, including one by the European Scientific Cooperative on Phytotherapy (Blumenthal *et al.*, 1998; Braun *et al.*, 1996; ESCOP, 1999). Other references suggest that hawthorn preparations may potentiate drugs containing cardiac glycosides (e.g., digoxin) probably resulting from the positive inotropic and coronary vasodilating effects (Brinker, 2001). Earlier research suggested potentiation of digitalis glycosides with hawthorn (Trunzler and Schuler, 1962), and another study suggested that hawthorn preparations may potentiate the coronary artery dilating effects of theophylline, caffeine, papaverine, sodium nitrate, adenosine, and epinephrine (Hahn *et al.*, 1960). Because of the similarity in actions, one reference suggests that hawthorn should not be used with any other heart medications without the advice of a healthcare provider (Newall *et al.*, 1996).  
HAWTHORN FRUIT: None known (Meyer-Buchtela, 1999). Depending on dosage the same interactions for leaf and flower may be relevant (Upton, 1999a).

### AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 1: Herbs that can be safely consumed when used appropriately (McGuffin *et al.*, 1997).

### REGULATORY STATUS

AUSTRIA: Hawthorn leaf and flower official in the *Austrian Pharmacopoeia* (ÖAB, 1994).

CANADA: Schedule "A" drug not suitable as a non-medicinal ingredient at any level (HPB, 1993). Permitted as a component

of OTC Traditional Herbal Medicine (THM) and as a homeopathic drug monopreparation in various dilutions, in both cases requiring pre-marketing authorization and application for a Drug Identification Number (DIN) (Health Canada, 2000).

EUROPEAN UNION: Dried false fruit containing not less than 1.0% procyanidins official in the *European Pharmacopoeia*, 3rd ed. Suppl. 1998 (Ph.Eur., 2001) and dried leaf and flower containing not less than 1.5% flavonoids official in Ph.Eur. Suppl. 2001 (Ph.Eur., 2001).

FRANCE: Hawthorn leaf with flower, as well as, homeopathic mother tinctures of hawthorn fresh ripe fruit and of hawthorn fresh flowering twig tips, respectively, are official in the *French Pharmacopoeia* (Ph.Fr.X, 1982-1996). Fluid extract and tincture preparations are listed in the *Codex Fr. IX* (ESCOP, 1999; van Hellemont, 1988).

GERMANY: Hawthorn leaf with flower (DAB, 1999) and the fluid extract form (DAB, 2000) official in the *German Pharmacopoeia*. Hawthorn fruit (DAC, 1992) and hawthorn flower (DAC, 1990) are official in the *German Drug Codex* supplement to the DAB. The dry native extract of hawthorn leaf with flower is an approved drug of the Commission E monographs (Blumenthal *et al.*, 1998), and the tea infusion of hawthorn leaf with flower is an approved drug of the *German Standard License* monographs (Braun *et al.*, 1996) with sale limited to pharmacies, without prescription. The mother tincture and liquid dilutions of hawthorn fresh ripe fruit are official preparations of the *German Homoeopathic Pharmacopoeia* (GHP, 1993) and are approved drugs of the Commission D monographs (Hänsel *et al.*, 1992-1994). Thirty-three Hawthorn extract preparations are listed in the German "Rote Liste 1994" (Sticher and Meier, 1998).

ITALY: Dried leaf with flower containing not less than 0.7% flavonoids official in *Italian Pharmacopoeia IX* 1985 Supplement 1991 (Ph.Ital., 1991).

SWEDEN: Natural product (DeSmet *et al.*, 1993) As of January 2001, no hawthorn products have been listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: Hawthorn leaf with flower and standardized dry extract are official in the *Swiss Pharmacopoeia* (Ph.Helv.VIII, 1998). Positive classification (List D) by the *Interkantonale Kontrollstelle für Heilmittel* (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppner, 2001; WHO, 1998). One hawthorn Anthroposophical preparation, 27 hawthorn homoeopathic preparations and 76 hawthorn-containing phyto-medicines are listed in the *Swiss Codex 2000/01* (Ruppner and Schaefer, 2001).

UK: No licensed hawthorn products on the *General Sale List* (GSL) (Newall *et al.*, 1996).

U.S.: Dietary supplement (USC, 1994). The mother tincture 1:10 (w/v), 45% ethanol (v/v), of the fresh or dried fruit, is an Rx Class C drug official in the *Homoeopathic Pharmacopoeia of the United States* (HPUS, 1990).

## CLINICAL REVIEW

Fourteen studies are outlined in the following table, "Clinical Studies on Hawthorn," conducted on 6,900 participants. All but one of the studies (Bödiger *et al.*, 1994), demonstrated positive effects for cardiac insufficiency. Eight are DB, PC studies (Bödiger and Chase, 1994; Förster *et al.*, 1994; Hanak and

Brückel, 1983; Iwamoto *et al.*, 1981; Leuchtgens, 1993; O'Conolly *et al.*, 1986; Schmidt *et al.*, 1998; Weikl *et al.*, 1996), four are open studies (Eichstädt *et al.*, 1989; Loew *et al.*, 1996; Weikl and Noh, 1992), one is a large multi-center observational study (Tauchert *et al.*, 1999), and one is a DB study comparing hawthorn to standard treatment (Tauchert *et al.*, 1994). NOTE: Most clinical studies have been conducted using a dry extract of hawthorn leaf with flower standardized to a daily dose of 9 mg or more oligomeric procyanidins (Schulz *et al.*, 2000; Hänsel *et al.*, 1992-94).

A major international R, DB, PC study is currently investigating the influence of the standardized extract of hawthorn leaf with flower (WS 1442; Schwabe, Karlsruhe, Germany) on the mortality of patients suffering from congestive heart failure. In this trial (involving approximately 120 investigational centers in seven European countries), up to 2,300 patients with congestive heart failure, NYHA Stage II and III, and markedly impaired left ventricular function will be enrolled and treated over 24 months. The primary outcome variable is the combined end point of cardiac death, nonlethal myocardial infarction, and hospitalization due to progression of heart failure. Secondary outcome variables are total mortality, exercise duration, echocardiographic parameters, and quality of life, as well as pharmacoeconomic parameters. The first patient was enrolled in October 1998. The trial is expected to be completed at the end of 2002 (Holubarsch *et al.*, 2000).

## BRANDED PRODUCTS\*

Crataegutt® Dragees: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4 / D-76227 Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / www.schwabepharma.com / Email: melville-eaves@schwabe.de. One tablet contains 30 mg hawthorn flower, fruit and leaf hydroalcoholic dry normalized extract 5:1 (w/w), standardized to 5% (50 mg/g) oligomeric procyanidins.

Crataegutt® forte Kapseln: Dr. Willmar Schwabe Pharmaceuticals. 1 capsule contains 80 mg hawthorn leaf and flower hydroalcoholic dry normalized extract 5:1 (w/w) standardized to 18.75% (187.5 mg/g) oligomeric procyanidins (15 mg per capsule).

Crataegutt® novo Filmtabletten: Dr. Willmar Schwabe Pharmaceuticals. One tablet contains 60 mg hawthorn flower, fruit and leaf hydroalcoholic dry normalized extract 5:1 (w/w), standardized to 5% (50 mg/g) oligomeric procyanidins.

Crataegus Special Extract WS 1442: Dr. Willmar Schwabe Pharmaceuticals. One capsule contains 80 mg hawthorn leaf with flower dry extract 5:1 (w/w), standardized to 18.75% oligomeric procyanidins (15 mg per capsule). Solvent: ethanol 45%

Faros® 300 Dragées: Lichtwer Pharma AG / Wallenroder Strasse 8-14 / 13435 Berlin / Germany / Tel: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. One tablet contains 300 mg hawthorn leaf with flower dry native extract 4-7:1 (w/w) (average 5.5:1), standardized to 2.25% flavonoid content. Solvent: methanol 70% (v/v).

Faros® LI 132 Dragées: Lichtwer Pharma AG. One tablet contains 100 mg hawthorn leaf with flower dry native extract 4-7:1 (w/w), standardized to 2.25% flavonoids.

\*American equivalents are found in the Product Table beginning on page 398.

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## Clinical Studies on Hawthorn (*Crataegus* spp.)

### Cardiac Insufficiency

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Tauchert et al., 1999	Cardiac insufficiency NYHA Stage II	MC, O n=1,011 patients with cardiac insufficiency	24 weeks	80 mg tablet, 2x/day (160mg extract/day)	Crataegus Special Extract WS 1442	Hawthorn treatment associated with significant improvement in clinical symptoms (exercise tolerance, fatigue, palpitation, and exercise dyspnea); 83% decrease in ankle edema and nocturia; reduction in blood pressure, resting pulse rate, and the difference in the pressure/heart rate product (PHRP); improved ejection fraction and improvements in echocardiography.
Schmidt et al., 1998	Cardiac insufficiency NYHA Stages I and II	O, OL, MC n=3,664 with stable NYHA Stage I or II (average age 66.7 years)	8 weeks	300 mg tablet, 3x/day (900 mg extract/day)	Faros® 300 Dragées	After 8 weeks hawthorn treatment decreased average heart rate (p<0.01) from 79.9 to 75.2 beats per minute. Average pressure-rate product (PRP) scores reduced from 117 mm Hg per minute x 200 to 105.7 mm Hg per minute x 100 (p<0.05). Work tolerance, as determined by bicycle ergometry, increased from 93.5 to 109.7 watts (W) (p<0.001).
Loew et al., 1996	Cardiac insufficiency NYHA Stage I and II	OL, S n=1,476 patients with heart failure of NYHA Stages I and II	Evaluation after 1 month and 2 months	300 mg tablet, 3x/day (900 mg extract/day)	Faros® 300 Dragées	At end of surveillance period, symptom score dropped by a mean of 66.6% with NYHA Stage I patients largely symptom free. A subgroup of patients with borderline hypertension showed decreases in systolic and diastolic pressure (160 to 150 mm Hg and 89 to 85 mm Hg, respectively), a drop in heart rate from 89 to 79 beats per minute, and arrhythmias that were significantly reduced independent of heart failure.
Weickl et al., 1996	Cardiac insufficiency NYHA Stage II	DB, PC, MC n=136 patients with NYHA Stage II cardiac insufficiency (40–80 years)	2 months (after a 2 week run-in phase)	80 mg capsule, 2x/day (160 mg extract daily) vs. placebo	Crataegus Special Extract WS 1442	Hawthorn showed statistically significant superiority (p=0.018, U test, one-sided) in primary target parameter (change in pressure-rate/product [PRP] difference determined by systolic blood pressure x heart rate divided by 100) with a median decrease in PRP of 6.2 compared to +0.1 increase with placebo. Subjective complaints also decreased in hawthorn group (p<0.05).
Bödigher and Chase, 1994	Congestive heart failure, NYHA Stage II	R, DB, PC, MC n=85 patients with NYHA Stage II cardiac insufficiency	1 month	100 mg tablet, 3x/day (300 mg extract/day) vs. placebo	Faros® LI 132 Dragées	After 4 weeks there was a statistically insignificant trend towards improvement in clinical symptoms and in ergometric parameters, compared to placebo. The duration of use (only 4 weeks) and the relative low dosage (300 mg/day) may explain these results.
Förster et al., 1994	Congestive heart failure, NYHA Stage II	DB, PC n=72 patients with NYHA Stage II cardiac insufficiency	2 months	300 mg tablet, 3x/day (900 mg extract/day) vs. placebo	Faros® 300 Dragées	Oxygen uptake increased with hawthorn but not with placebo (p<0.05) based on ergospirometry. Time taken to reach anaerobic threshold during exercise increased by 30 seconds in hawthorn group and 2 seconds in placebo group. Hawthorn also showed significant improvements (p<0.001) in subjective complaint scores.
Schmidt et al., 1994	Cardiac insufficiency, NYHA Stage II	R, DB, PC, MC n=78 patients with NYHA Stage II cardiac insufficiency (men and women ages 45–73)	8 weeks with a 1 week washout period	One, 200 mg tablet, 3x/day (600 mg extract/day) vs. placebo	Faros® LI 132 Dragées containing 200mg Crataegus extract LI 132	Statistically significant (p<0.001) increase in exercise tolerance in hawthorn group by 28 watt (W) compared to 5 W in placebo group using ergometer bicycle (12.5 W). Hawthorn group showed significant reductions in systolic blood pressure (p<0.05) and heart rate (p<0.01). Subjective symptoms score also improved significantly (p<0.001).
Tauchert et al., 1994	Congestive heart failure NYHA Stage II	R, DB, MC, Cm n=132 patients with NYHA Stage II cardiac insufficiency	2 months (including a 1 week lower dosage introductory therapy period)	Three, 100 mg tablets, 3x/day (900 mg extract/day) vs. 12.5 mg, 3x/day of ACE inhibitor Captopril (37.5 mg/day)	Faros® LI 132 Dragées vs. captopril	None of the target parameters (ergometry, pressure-rate-product (PRP), score for 5 typical symptoms) showed significant differences between hawthorn and captopril groups. Both showed statistically significant increase (p<0.001) in maximum tolerated exercise performance, 83 to 97 watt (W) in hawthorn group and 83 to 99 W in captopril group. Both treatments reduced PRP and decreased incidence and severity of symptoms (shortness of breath; fatigue after exercise) by 50%.
Leuchtgens, 1993	Cardiac insufficiency, NYHA Stage II	R, DB, PC n=30 patients with NYHA Stage II cardiac insufficiency	2 months	80 mg capsule, 2x/day (160 mg extract/day) vs. placebo	Crataegus Special Extract WS 1442	Hawthorn showed statistically significant (p<0.05) improvements over placebo (hawthorn -11.6, placebo -4.9) in the pressure-rate-product (PRP) during exercise (systolic blood pressure x heart rate/100) using bicycle ergometer, in subjective complaints score (hawthorn -16.5, placebo -4, p<0.05), and in heart rate.

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

## Clinical Studies on Hawthorn (*Crataegus* spp.) (cont.)

### Cardiac Insufficiency (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Weikl and Noh, 1992	Congestive heart failure NYHA Stage II	OL n=20 patients with NYHA Stage II cardiac insufficiency and LVEF <55%	1 month	One to two, 80 mg capsules, 3x/day (240–480 mg extract/day)	Crataegutt® forte capsules	480 mg/day increased ejection fraction from 40.18% to 43.5% at rest and 41.51% to 46.56% during exercise using radionuclide angio-cardiography method. Slight decrease in blood pressure during rest and exercise. Treatment of 7 patients with 240 mg/day increased the LVEF from 29.8% to 30.45% based on nuclear resonance scanning method.
Eichstädt et al., 1989	Congestive heart failure, NYHA Stage II LVEF<55%	OL n=20 NYHA Stage II patients	1 month	Two, 80 mg tablet, 3x/day (480 mg extract/day)	Crataegus Special Extract WS 1442 (Crataegutt® forte)	Hawthorn improved exercise tolerance and cardiac performance as well as subjective symptoms using a bicycle ergometer. After 4 weeks, patients maximum exercise tolerance rose from 704 to 772 watts (W) x minute (p<0.05).
O'Conolly et al., 1986	Heart failure, NYHA Stage I or II	R, DB, PC, CO n=36 patients with Stage I or II cardiac insufficiency (average age 74 years)	6 weeks	60 mg tablet, 3x/day (180 mg extract/day)	Crataegutt® novo Filmtabletten	Patients treated with hawthorn had decreased heart rate and improved cardiac output under resting and exercise conditions. Pressure-rate-product (PRP) was significantly reduced and quality of life measurements significantly improved. Significant improvement in psychological assessment including reduction in anxiety (p<0.0001) and sleep behavior.
Hanak and Brückel, 1983	Coronary disease, NYHA Stage I and II	R, DB, PC n=60 patients with stable angina pectoris	3 weeks	60 mg tablet, 3x/day (180 mg extract/day) vs. placebo	Crataegutt® novo Filmtabletten	Electrocardiogram measures improved in hawthorn group, and blood flow and oxygen delivery to the heart muscle rose. Hawthorn patients also exercised for longer periods of time without an angina attack.
Iwamoto et al., 1981	Cardiac insufficiency, NYHA Stage II or III	DB, PC n=80 patients with NYHA Stage II cardiac insufficiency	6 weeks	Weeks 1–2: Two, 30 mg tablets 3x/day after meals (180 mg/day) Weeks 3–6: Two or three, 30 mg tablets 3x/day after meals (180 mg or 270 mg/day)	Crataegutt® Dragées 30 mg of an extract of <i>Crataegus monogyna</i> and <i>C. oxyacantha</i> per tablet	Compared to placebo, hawthorn group exhibited statistically significant improvement of cardiac function (p<0.001) and of subjective symptoms such as dyspnea and palpitations (p<0.001). No difference in improvements in ECG recordings between hawthorn and placebo groups.

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