Health Effects of Hawthorn

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Hawthorn medicinal extract has long been a favored herbal remedy in Europe. The active components of this slow-acting cardiotonic agent are thought to be flavonoids and oligomeric procyanidins. The most studied hawthorn extracts are WS 1442 and LI 132. Reviews of placebo-controlled trials have reported both subjective and objective improvement in patients with mild forms of heart failure (New York Heart Association classes I through III). Other studies of hawthorn in patients with heart failure have revealed improvement in clinical symptoms, pressure–heart rate product, left ventricular ejection fraction, and patients' subjective sense of well-being. However, there is no evidence of a notable reduction in mortality or sudden death. Hawthorn is well tolerated; the most common adverse effects are vertigo and dizziness. Theoretic interactions exist with antiarrhythmics, antihypertensives, digoxin, and antihyperlipidemic agents. Proven conventional therapies for heart failure are still recommended until the safety and effectiveness of hawthorn has been proven in long-term studies. (*Am Fam Physician*. 2010;81(4):465-468, 469. Copyright © 2010 American Academy of Family Physicians.)

▶ **Patient information:** A handout on hawthorn, written by the authors of this article, is provided on page 469.

Hawthorn, a *Crataegus* species, is part of a genus of spiny shrubs and trees native to temperate regions in the Northern Hemisphere in Europe, Asia, and North America. Depending on the taxonomic interpretation, between 200 and 1,000 species of *Crataegus* have been recognized. Hawthorn is the oldest known medicinal plant in European medicine; its actions on the heart were first described by Dioscorides in the first century.[1] Hawthorn is also a popular herbal supplement in the U.S. market.[2]

Hawthorn extracts have historically been derived from the flowers, leaves, and fruits of the plant. However, most of the data supporting the cardiac activity of hawthorn are based on evaluation of the dried flowering tops of the plants (specifically from *Crataegus monogyna* or *Crataegus laevigata*). There are fewer clinical studies on the extract of hawthorn berry alone.[3,4] The dried fruits are traditionally used in Chinese medicine as a digestive aid and are often made into jam, jelly, candies, or wine.

Pharmacology

The leaves, flowers, and berries of hawthorn contain an abundance of oligomeric procyanidins and flavonoids, which are thought to be responsible for its pharmacologic effect. The most studied hawthorn extracts, WS 1442 and LI 132, are standardized to oligomeric procyanidins and flavonoids, respectively. The majority of the pharmacologic studies on hawthorn extract are in vitro and animal studies; however, several in vivo studies have also demonstrated its physiologic effects.

Damage to the myocardium during ischemia may be related to free radical effects and the release of human neutrophil elastase from neutrophils. Oligomeric procyanidins in the leaves and flowers of hawthorn inhibit human neutrophil elastase and act as a free-radical scavenger, which may attenuate damage to the myocardium caused by ischemia.[5] Oligomeric procyanidins have also been shown in animal studies to lead to an increase in coronary blood flow.[6,7] One in vivo study of the WS 1442 formulation of hawthorn demonstrated a positive inotropic effect, along with an ability to improve the force-frequency ratio in failing human myocardium.[8]

Flavonoids activate endothelium-derived relaxing factor and inhibit phosphodiesterase, thereby increasing vasodilation.[5] Flavonoids have been studied as part of a compound that possesses antioxidant properties that inhibit the oxidation of low-density lipoprotein cholesterol in vitro,

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Hawthorn, in the form of a standard extract (LI 132 or WS 1442), can be used as an adjunct to standard therapy to relieve symptoms of New York Heart Association classes I through III chronic congestive heart failure. There is no evidence of a decrease in mortality.	A	1, 4, 14-16, 23, 24, 27, 28	Based on a systematic review of 14 RCTs[14] and a meta-analysis of 13 RCTs[15]; studies were short-term, and long-term data are lacking.

RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

which may explain the antiatherogenic properties of hawthorn extract.[9,10] Flavonoids have also been shown to inhibit platelet aggregation and adhesion.[11,12]

Uses and Effectiveness

Hawthorn has traditionally been used to treat anxiety, asthma, hypertension, dyslipidemia, hypotension, angina, arrhythmias, heart failure, and indigestion. The most substantial evidence for clinical benefits of hawthorn is its use in chronic congestive heart failure (CHF). Limited evidence is available for other traditional uses; therefore, a more in-depth review of these conditions will not be included here.[13]

CHRONIC CONGESTIVE HEART FAILURE

Results of two meta-analyses, including a 2008 Cochrane systematic review, found that when used as an adjunct to conventional treatment in patients with chronic CHF (New York Heart Association [NYHA] classes I through III), hawthorn substantially increased maximal workload tolerance, increased exercise tolerance, decreased the pressure–heart rate product (an index of cardiac oxygen consumption), and improved symptoms of fatigue and shortness of breath as compared with placebo.[14,15] The duration of the randomized controlled trials (RCTs) in these reviews ranged from three to 16 weeks, with most between six and eight weeks. The RCTs in these reviews used specific standardized leaf and flower extracts of hawthorn: LI 132 and WS 1442. Hawthorn extract WS 1442 is standardized to 18.75 percent oligomeric procyanidins. Hawthorn extract LI 132 is standardized to 2.2 percent flavonoids. The authors concluded that the results suggest a marked benefit in symptom control and physiologic outcomes when hawthorn extract is used as an adjunctive treatment for chronic CHF.[14]

In another study, hawthorn was pitted against the angiotensin-converting enzyme (ACE) inhibitor captopril (Capoten) in comparable groups of patients with NYHA class II heart failure. By the end of the trial, both groups had improved exercise capacity compared with baseline measurements, with no statistically significant differences between the two treatment arms. However, the investigators used a relatively low daily dosage of captopril (37.5 mg taken orally).[16]

A recent trial sponsored by the National Center for Complementary and Alternative Medicine found that WS 1442 given for six months had no apparent effect on six-minute-walk distance in the Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB-CHF) trial.[17] Another recent long-term placebo-controlled study, Survival and Prognosis: Investigation of *Crataegus* Extract WS 1442 in CHF (SPICE), hinted that WS 1442 may protect against cardiac death and sudden death, but failed to show a statistically significant benefit when given along with standard drug therapy to more than 2,600 patients with NYHA class II or III heart failure and a left ventricular ejection fraction (LVEF) of 35 percent or less.[18]

Contraindications, Adverse Effects, and Interactions

The only absolute contraindication for the use of hawthorn is known hypersensitivity to *Crataegus* products. Its use is not recommended during pregnancy because of potential uterine stimulation. One publication recommends against use in pregnancy based on results of animal studies and human case reports.[19] Scientific evidence for the safe use of *Crataegus* during lactation or in young persons is not available. It is therefore not currently recommended for children or breastfeeding mothers.

The majority of studies indicate that oral hawthorn is well tolerated; vertigo and dizziness are the most common adverse effects.[14] Less common adverse effects include nausea, fatigue, sweating, palpitations, headache, dizziness, dyspnea, sleeplessness, agitation, and epistaxis.[14,20] Adverse effects were reported in 1.3 percent of patients participating in a post-marketing study that evaluated daily treatment with 900-mg hawthorn extract for eight weeks (n = 3,664).[15] Adverse effects were reported to be rare in a meta-analysis that included eight double-blind, placebo-controlled, randomized clinical

trials evaluating hawthorn extract as an adjunctive treatment for chronic CHF in dosages ranging from 160 to 1,800 mg daily.[14]

As many as one third of patients with heart failure are taking complementary and alternative medicine supplements, several of which may interact negatively with typical heart failure medications.[20] Despite the low adverse effect profile of hawthorn, patients taking the supplement should be followed closely, especially because the majority will be taking other medications and supplements. Hawthorn should be used with caution when combined with other herbs and supplements that have cardiovascular effects (e.g., danshen, epimedium, ginger, *Panax* ginseng, turmeric, valerian).[19] There are theoretic interactions with antiarrhythmics, antihypertensives (vasodilators, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers), cardiac glycosides (digoxin), vasodilators (phosphodiesterase type 5 inhibitors), and antihyperlipidemic agents.[13,21] Recent data suggest no notable interaction between hawthorn and digitalis glycosides and standard therapy for chronic CHF, but caution is still advised until more definitive data are available.[18,22]

Dosage and Standardization

Hawthorn is usually standardized to its content of flavonoids (2.2 percent) or oligomeric procyanidins (18.75 percent). The daily dosage as reflected in the literature ranges from 160 to 1,800 mg, but most physicians believe there is greater therapeutic effectiveness with higher dosages (600 to 1,800 mg in two or three divided doses daily).[15,21,23-25] Standardized extracts are also available and generally provide 30 to 169 mg of procyanidins, calculated as epicatechin, or 3.5 to 19.8 mg of flavonoids, calculated as hyperoside and taken in two or three individual doses.[1] A trial of at least four to eight weeks should be completed to determine if a patient will benefit from the use of hawthorn.[13]

Bottom Line

The German Commission E specifically recommends hawthorn leaf and flower as the parts of the plant to be used therapeutically.[21] Reviews of placebo-controlled trials have reported both subjective and objective improvement in patients with chronic CHF (NYHA classes I through III).[1,15,26] Other studies of hawthorn in patients with heart failure have revealed improvement in clinical symptoms, pressure–heart rate product, LVEF, and subjective sense of well-being, without a marked reduction in cardiac mortality.[4,18,23,24,27,28]

Despite the supported clinical benefits, any treatment for symptomatic heart failure with claims of inotropic activity should be studied for a long period to rule out any potential increase in mortality. This has been the case with several synthetic inotropic drugs.[29] Considering the existence of other proven therapies for chronic CHF,[25] we recommend that physicians encourage conventional treatments until the safety and effectiveness of hawthorn have been proven in long-term studies. In addition, because these products are not regulated by the U.S. Food and Drug Administration, patients who insist on using hawthorn should be given a trial of at least four to eight weeks with a reputable supplement.

Table 1 summarizes the key points about hawthorn.

Table 1. Key Points About Hawthorn

Effectiveness	New York Heart Association classes I through III chronic congestive heart failure: effective for symptom control based on short-term studies, but no evidence of decrease in mortality
Adverse effects	Well tolerated overall; vertigo and dizziness are the most common adverse effects
Interactions	May enhance the activity of digitalis; theoretic interactions with antiarrhythmics, antihypertensives, antihyperlipidemic agents
Contraindications	Known hypersensitivity to *Crataegus* products; insufficient reliable information for safety of use in children and in women who are pregnant or breastfeeding
Dosage	Most effective dosage not currently known; recommended dosages range from 160 to 1,800 mg per day in two or three divided doses
Cost*	$3 to $25 per month, based on 160- to 1,800-mg daily dosage
Bottom line	Hawthorn should not be used in place of proven conventional therapies for heart failure; may be effective for symptom improvement when used as an adjunct to conventional therapies; use should be carefully considered and monitored

**—Average retail cost (rounded to the nearest dollar) based on a search of common Internet vitamin stores, including http://www.vitacost.com and http://www.vitaminshoppe.com. Product quality may vary.*

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