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File: ■ Hawthorn (*Crataegus* spp.)
■ Heart Disease
■ Adjunctive Therapy

HC 041166-430

Date: August 15, 2011

RE: Hawthorn Extracts Show Clinical Benefits as Adjuncts for Cardiovascular Disorders

Koch E, Malek FA. Standardized extracts from hawthorn leaves and flowers in the treatment of cardiovascular disorders - preclinical and clinical studies. *Planta Med*. July 2011;77(11):1123-1128.

Hawthorn (*Crataegus* spp.) is native to Europe, and the leaves and flowers have been extensively studied for the treatment of heart disease.[1] In particular, numerous randomized trials have found hawthorn extract efficacious in treating mild chronic heart failure.[2] In this review of the pharmacological and clinical data behind hawthorn's bioactivity, the authors summarize the large amount of research conducted on this plant.

The authors focus their review on the leaves and flowers of hawthorn and provide an overview of the diverse active compounds therein. For example, the authors relate that the most important compounds include flavonoids such as vitexin, rutin, and hyperoside, along with catechin/epicatechin-derived oligomeric proanthocyanidins (OPC). Hawthorn leaves and flowers also contain active triterpenic acids such as ursolic, oleanolic, and crataegolic acids, in addition to chlorogenic acid, caffeic acid, and amines. Particular preparations of hawthorn have been extensively researched, and the authors highlight hydroalcoholic extractions made with a minimum of 45% alcohol and standardized to active constituents. In particular, WS®1442, manufactured by Dr. Willmar Schwabe GmbH & Co. KG in Karlsruhe, Germany, is a 45% ethanol extraction with a 4-7:1 herb to solid extract ratio standardized to 18.75% OPC. A second well-studied product according to these authors is LI 132, manufactured by MCM Klosterfrau Vertriebsgesellschaft GmbH in Köln, Germany. [Editor's Note: Other research papers identified LI 132 as being Faros 300 made by Lichtwer Pharma GmbH of Berlin, Germany.] This 70% methanol extract is standardized to 2.2% flavonoids. The authors focus most of their review on studies involving these two products and address their effect on pharmacology, vascular endothelium, lipid metabolism, pharmacokinetics, toxicity, clinical efficacy, and adverse effects and drug interactions.

In terms of pharmacology, LI 132 positively influenced contraction in vitro similar to the pharmaceuticals isoprenaline and ouabain. Though the mechanism of action has been suggested to be similar to that of cardiac glycosides, which are plant-derived compounds

used to treat heart failure, hawthorn extract effects are distinctive. WS 1442 impacts the contractions of muscle cells from failing human hearts in a concentration-dependent manner. Hawthorn extracts have been found to have antiarrhythmic activity by prolonging the refractory period, and further fractionation of the extracts point to a variety of compounds as being responsible. LI 132 and WS 1442 have both been reported as protecting the heart against ischemic reperfusion or tissue damage caused by the restoration of blood flow to an area following limited access to blood. One study found that feeding rats WS 1442 for 7 days reduced arrhythmia, death, and hypotension associated with heart ischemia. Also, results in vitro indicate that WS 1442 may help reduce cardiac hypertrophy in hypertension by inhibiting calcineurin's phosphatase activity.

When investigated on the vascular endothelium, vasorelaxation from hawthorn extracts has been shown to increase coronary blood flow. Evidence from rat models points to preventative activity of WS 1442 towards post-angioplasty atherosclerosis, and restenosis (narrowing of blood vessels). WS 1442 is also suspected to have strong antioxidant activity; in the presence of endotoxin, the preparation staved off reduced cardiac output and increased peripheral resistance with no effect on heart rate.

The authors also address berry extract effects on lipid metabolism. A hawthorn berry tincture lowered the total cholesterol, low-density lipoprotein, very low-density lipoprotein, and high-density lipoprotein levels in rats fed an atherogenic or high-fat diet. In addition, hawthorn berry extract lowered cholesterol and triglycerides in high-cholesterol diet-fed hamsters.

In studies on the pharmacokinetics of hawthorn, radio-labeled OPC and catechins showed measurable absorption in 1 hour with rates ranging from 16-40%. However, lower bioavailability was detected for vitexin rhamnoside (3.6%), similar to vitexin glucoside. A wide range of dosages has been tested for hawthorn toxicity on dogs, mice, rats, and rabbits, and no evidence of it has been reported. The adverse effects reported in clinical trials have been mild to moderate, but rare, with 166 reports out of 5,577 patients from 24 clinical studies, mostly using WS 1442 and LI 132.

Hawthorn has been investigated extensively in clinical settings. Double-blind, placebo-controlled studies and open-label studies have shown hawthorn extract to be effective in treating New York Heart Association (NYHA) stage II (mild) heart failure. In particular, improvements were observed in patient discomfort, cardiac efficiency, and physical stress tolerance. In a randomized, double-blind, placebo-controlled trial of 2,681 patients, WS 1442 at 900 mg daily as an adjunctive therapy in NYHA stage II or III (moderate) heart failure significantly reduced cardiac mortality overall and sudden cardiac death in a subgroup. A separate trial in NYHA stage III patients also showed significant improvement in workload during a bicycle exercise test in patients taking 1800 mg daily of WS 1442, while both 900 mg and 1800 mg doses reduced heart failure symptoms. Patients with type 2 diabetes mellitus in a trial taking 1200 mg daily of LI 132 as an adjunctive therapy showed significantly reduced diastolic blood pressure. Lastly, in an open-label cohort study with 711 patients, WS 1442 as an add-on treatment significantly improved the quality of life in NYHA stage II coronary heart disease patients, as well as leading to significant reductions in hospitalization costs from heart failure.

The authors describe bioactive cardiac compounds present in hawthorn flowers and leaves; a plethora of studies investigating the extracts' pharmacological effects confirm a

wide range of activity. Also, extracts WS 1442 and LI 132 are consistently shown to alleviate the symptoms of chronic cardiovascular disorders when used as add-on therapies in clinical trials. These particular extracts are well-tolerated, show no toxicity, and have not been associated with many adverse effects. Despite the large number of studies reporting positive results when using hawthorn to treat heart diseases, this review only briefly mentions bioactivity seen with hawthorn berries and is mostly limited in scope to the hawthorn flower and leaf extracts WS 1442 and LI 132; however, the review does present a substantial body of medical research evidence supporting a strong role for hawthorn in treating heart problems of varying severity, often together with conventional medications.

—Amy C. Keller, PhD

References

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[2]Pittler M, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. *Am J Med*. June 1, 2003;114(8):665-674.

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