

## Selections from current literature: effects of Hawthorn on the cardiovascular system

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Physicians often express concerns about use of herbal therapies. Many have little or no training in herbal medicine, are not sure of their effects, adverse reactions, or interactions with other medications. Many criticize use of herbal products because they are often of poor quality, and their efficacy have not been demonstrated by sound clinical and basic science research. Others note lack of standardization of and variability between herbal products.

In the United States there has been an increase in the number of people who are using herbal products. Over 12 billion dollars were spent on natural supplements in the US in 1997, almost twice the amount spent in 1994. The consumption of herbal products has continued to increase by over 10% per year. This large increase in the use of these products makes it crucial for physicians to be aware of some of the commonly used herbs.

A Medline and EMBASE literature search was performed selecting recent articles which focused on hawthorn. Clinical studies, *in vivo* animal studies and *in vitro* studies were selected to answer the following questions:

- (i) What effects of hawthorn have been demonstrated in clinical studies?
- (ii) What mechanisms account for the effects of hawthorn on the cardiovascular system?
- (iii) What components of hawthorn are important to its action?

Hawthorn/passion flower extract and improvement in physical exercise capacity of patients with dyspnoea class II the NYHA function classification.

Von Eiff M, Brunner H, Haegeli A, Kreuter U, Martina B, Meier B, Schaffner W. *Acta Therapeutica* 1994; **20**: 47–66.

The authors used a randomized, double-blind, placebo-controlled, parallel study to analyse the effect of a hawthorn/passion flower extract or placebo on physical performance. A total of 40 patients between the ages of 53 and 86 years were evaluated; all had dyspnoea with

New York Heart Association class II function. Exercise capacity was evaluated by 6-minute walking and bicycle ergometer tests. Blood lactate levels, heart rate and blood pressure were measured during exercise, as well as symptoms and urine biochemical parameters. Patients receiving the hawthorn/passion flower extract had an increase in walking capacity. Both the hawthorn/passion flower group and the placebo group had an increase in the bicycle ergometer test of about 10% above baseline. The group receiving the extract had a slight but significant decrease in resting heart rate, mean diastolic pressure during exercise and total serum cholesterol.

### Comment

The focus of this study was the effect of the hawthorn/passion flower extract on exercise capacity; but the effect on diastolic blood pressure, heart rate and cholesterol are also significant and merit further clinical investigation. The patients were mainly women (37 versus 3 men). Additional studies are required to examine the effects in both genders. Two ml of extracts was administered three times a day to the patients. As pointed out by the author, a similar study by Schmidt *et al.*<sup>1</sup> used higher doses of hawthorn for 8 weeks and found a significant effect of hawthorn on bicycle ergometer tests compared with control. Von Eiff points out that it is difficult to compare different hawthorn preparations, since there is no standard method of extraction.

Hawthorn (Shan Zha) drink and its lowering effect on blood lipids levels in humans and rats.

Chen JD, Wu YZ, Tao ZL, Chen ZM, Liu XP. *World Rev Nutr Diet* 1995; **77**: 147–154.

Hawthorn's ability to reduce body weight, body fat and blood lipids was studied on rats and humans. The animal experiments were performed on 37 Sprague–Dawley male rats divided into three groups; one was given a hawthorn drink containing 4–6% sugar, another water containing 8% sugar and the third group received tap water. Body weights of the rats were lower in hawthorn-fed rats, but the decrease in body weight was not statistically significant (perhaps due to the small number of rats used). The hawthorn group did have significantly decreased body

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fat, total cholesterol levels and triglyceride level compared with the two control groups. The HDL level was greater in the hawthorn group than in those drinking sugar water, but was less than in the group drinking tap water. The rats drinking sugar water significantly decreased their solid food intake compared with the tap-water-fed rats. In the hawthorn-fed rats, food intake fell to a level between the two control groups.

In the human portion of the study, 30 volunteers diagnosed as hyperlipidaemic participated. After consuming hawthorn for 1 month, average cholesterol levels decreased from  $7.31 \pm 1.04$  mmol/l to  $6.19 \pm 1.56$  mmol/l ( $P < 0.001$ ). Serum triglyceride levels decreased from  $1.93 \pm 0.92$  to  $1.75 \pm 0.96$  mmol/l. Hawthorn did not raise HDL levels in the human study. Hawthorn was also shown to decrease serum levels of lipid peroxidate malonic dialdehyde levels from  $3.2 \pm 0.9$  to  $2.5 \pm 0.4$  nmol/ml, suggesting a strong antioxidative effect.

This paper concluded that 1 month of hawthorn ingestion significantly decreased serum cholesterol, LDL-C and triglycerides, and a significant MDA reduction showed an antioxidative effect.

#### Comment

Both rat and human data showed a decrease in total cholesterol, LDL cholesterol and triglycerides when hawthorn was ingested. Unfortunately, the number of humans used for this study was small, 25 women and 5 men, and the study was neither double-blind nor placebo controlled. It was noted that the patients placed on hawthorn stopped taking other medications, but the medications they stopped were not described. The patients kept their daily life, activity and diet constant, but analyses of these variables were not given. Although, this was not a double-blind placebo-controlled study, the effects on cholesterol are in agreement with the previously cited study.

In the animal study, the rats were given either a hawthorn drink containing 4–6% sugar, water with 8% sugar or tap water. The results showed a difference between the group consuming 8% sugar water and the group consuming tap water. The group consuming hawthorn fell between these two groups in some of the analysed parameters, making it difficult to establish whether some of the differences were due to the composition of the animals' diet. Perhaps an isocaloric group to compare with the hawthorn animals would have been helpful in determining its specific effects.

Effect of tincture of *Crataegus* on the LDL-receptor activity of hepatic plasma membrane of rats fed an atherogenic diet.

Rajendran S, Deepalakshmi PD, Parasakthy K, Devarj H, Niranjali Devaraj S. *Atherosclerosis* 1996; **123**: 235–241.

Extract of hawthorn has been shown to lower total and LDL cholesterol. The authors propose the hypothesis that

the decrease may be due to an increase in LDL-receptor activity of hepatic membranes. When hawthorn was administered to rats fed an atherogenic diet, there was a significant increase of binding of LDL to liver plasma membrane *in vitro*. The liver membrane bound an increased number LDL molecules compared with controls. Hawthorn extract was also shown to increase bile acid excretion and to depress hepatic cholesterol synthesis in these rats.

#### Comment

The hawthorn extract used in this study was an alcohol extract. An equivalent quantity of ethanol was not given to the control groups. This may or may not be an issue depending on the quantity of ethanol which the hawthorn experimental group consumed. Although this point was not addressed by the authors and may effect the results, the mechanism suggested may have a physiological effect in humans.

Ischaemia- and reperfusion-induced cardiac injury: effects of two flavonoid containing plant extracts possessing radical scavenging properties.

Kurcok A. *Naunyn-Schmiedeberg's Arch Pharmacol* 1992; **345** (Suppl): R81.

In this abstract, hawthorn, *Ginkgo biloba* or vehicle (controls) were administered 5 minutes prior to transient occlusion of a coronary artery. Reperfusion-induced ventricular fibrillations were observed in 88% of control animals ( $n = 25$ ), and in only 20% of two groups of hawthorn-treated animals, one treated with 0.5 mg/kg, the other with 5 mg/kg. The mean duration of the arrhythmia was also decreased. Hawthorn, however, did not effect the reperfusion-induced CPK release. *Ginkgo biloba* was noted to have an effect on reperfusion-induced ventricular arrhythmia but only with the higher dose of 3–5 mg/kg; however, the duration of the arrhythmia was not effected. *Ginkgo biloba* was effective in decreasing the ischaemia reperfusion-induced rise in CPK versus controls:  $5.7 \pm 0.4$  U/g versus  $13.1 \pm 1.15$  U/g, respectively.

#### Comments

While data from this study are interesting, the study was published as an abstract, not as a full journal article. Not all data are presented. Histological analysis of the myocardium may have contributed additional information about the extent of necrosis which CPK alone cannot address. Analysis of the extracts of hawthorn and *Ginkgo biloba* were not presented. The results may have important consequences, particularly the decrease in mortality from ventricular arrhythmias.

Experimental myocardial infarction of the rat and stimulation of the revascularization by the flavonoid drug crataemon.

Guendjev Z. *Arzneim.-Forsch./Drug Res* 1977; **27** (II): 1576–1579.

The left coronary artery of 67 female Wistar rats was ligated. Two days before and 10 days after the ligation, 34 of the experimental rats were treated with 150 mg/kg crataemon, a purified flavonoid extracted from *Crataegus monogyna* leaves. The other 33 rats were not treated. Twenty-seven of the control and 32 of the experimental rats survived the procedure and were sacrificed 10 days post-ligation. Histological sections demonstrated that the necrotic focus was smaller in the experimental rats than in the controls. It was also noted that there were significantly more capillaries, venules and arterioles in the experimental rats compared with controls. The ratio of venous vessels to arterial vessels was similar in both experimental and control animals. Deaths of animals within 2–5 days post-surgery were attributed to bronchopneumonia. The author suggests that decreased post-operative mortality in the experimental animals might be due to the capillary strengthening effect of crataemon. The high level of revascularization produced by crataemon causes an immediate high blood flow, containing many phagocytic cells, to the necrotic tissue, thus decreasing the dimension of the necrotic focus.

#### Comments

One specific compound found in hawthorn, namely the flavonoid crataemon, was analysed for its effect on reperfusion of the myocardium after ligation of a coronary vessel. In both this study and the previous one, the mortality was decreased in the treated group compared with the control group. Synergistic actions of this compound with other compounds found in extractions of hawthorn may exist. While it is important to study the effect of an individual component, comparison to the whole herbal extract is also useful. Consumption of hawthorn over a longer duration of time may have additional effects that are not noted in acute administration. If hawthorn increases vascularization of the myocardium, perhaps collateral vessels develop over the long term and have a protective effect. Hawthorn may possess anti-arrhythmic properties and increase revascularization. Neither of these studies demonstrates a decrease in revascularization injury to the myocardium.

Myocardial effects of flavonoids from *Crataegus* species. Schussler M, Holzl J, Fricke U. *Arzneim.-Forsch./Drug Res* 1995; **45** (II).

Different compounds in hawthorn were tested for their effects on coronary flow, heart rate and ventricular systolic and diastolic pressure in Langendorff perfused isolated guinea pig hearts at a constant pressure of 70 cm

H<sub>2</sub>O. An increase in coronary blood flow was caused by luteolin-7-glucoside (186%), hyperoside (66%) and rutin (66%). There was an increase in relaxation velocity by luteolin-7-glucoside (104%), hyperoside (62%) and rutin (73%). The major effects of these compounds were at 0.5 mmol/l. These compounds also had small positive inotropic and chronotropic effects. Vitexin, vitexin-rhamnoside and monoacetyl-vitexin-rhamnoside had similar actions, but to a lesser extent. Adrenergic activity of the compounds was abolished by addition of propranolol or reserpine.

#### Comment

This study analyses some of the individual components of hawthorn extracts. As expected, more than one compound accounts for the actions of hawthorn. This work is essential for optimizing the preparations of hawthorn. In addition to the actions of individual components, the interaction of the components is crucial to the understanding of this herb. The effects may be additive, or it may be that only one of the components maximizes the desired effect.

Molecular physiological effector mechanisms of hawthorn extract in cardiac papillary muscle and coronary vascular smooth muscle.

Siegel G, Casper U, Schnalke F, Hetzer R. *Phytotherapy Res* 1996; **10**: S195–S198.

Hawthorn extracts (with flavonoid concentrations of 10<sup>-7</sup> to 10<sup>-5</sup> mol/l) influence canine papillary muscle action potential. The authors noted an increase in the maximal upstroke velocity and overshoot of the action potential, indicating an enhancement of the inward fast Ca<sup>2+</sup> current. This action is similar to beta-adrenergic stimulation. The enhancement of the Ca<sup>2+</sup> channel in this case is caused by stimulation of adenylate cyclase, which in turn activates protein kinase A, which in turn phosphorylates Ca-activatable K<sup>+</sup> channels. This chain of events causes an increase in the open state probability of the channel. The effects of hawthorn differ from the beta-adrenergic stimulation in that there is also slowing of the final repolarization phase. Other ion channels must therefore be affected by hawthorn which are not affected by pure adrenergic stimulation.

The effect of hawthorn on human coronary arteries smooth muscle action potential was studied *in vitro*. Coronary arteries were obtained from heart transplant patients suffering from dilated cardiomyopathy or extensive atherosclerosis. Both normal and atherosclerotic vessels were studied. Hawthorn extract caused an increase in the K<sup>+</sup> conduction and a hyperpolarization of the membrane potential. This hyperpolarization increases the L-type Ca<sup>2+</sup> channel in the closed position. The Ca<sup>2+</sup> inward current into vascular smooth muscle was decreased by 16.3%, causing a decrease in wall tension and dilation of the vessels.

*Comment*

Previous studies have shown that hawthorn increases intracellular cAMP, which in turn, activates protein kinase A. This study, in addition to the previously referenced study by Schussler *et al.*, demonstrates that the actions of hawthorn cannot be explained purely by adrenergic properties. Hawthorn may activate protein kinase A, but it also affects targets not phosphorylated by PK-A or other PK-A agonists. These *in vitro* data, demonstrating the ability of hawthorn to affect ion channels in the membrane of cardiac and smooth muscle cells may account for the decreased ventricular arrhythmias, the positive inotropic effect and the decrease in diastolic blood pressure seen in the *in vivo* studies referenced earlier.

Oxygen species scavenging activity of phenolic extracts from hawthorn fresh plant organs and pharmaceutical preparations.

Bahorun T, Gressier B, Trotin F, Brunet C, Dine T, Luyckx M, Vasseur J, Cazin M, Cazin JC, Pinkas M. *Arzneim.-Forsch./Drug Res* 1996; **46** (II).

Different extracts of hawthorn from fresh and dried flowers and pharmaceutical preparations were analysed for their antioxidant activity *in vitro*. These preparations were also analysed for their content of total phenols, total proanthocyanidin and total flavonoid. Antioxidant activity was determined by measuring scavenging ability of hydrogen peroxide, superoxide anion and hypochlorous acid. This study concluded that fresh young leaves, fresh floral buds and pharmaceutical preparations of dried flowers all exhibited *in vitro* antioxidant activities using all three models to measure antioxidant activity *in vitro*. The activity appeared to be bound to the total phenolic proanthocyanidin and flavonoid contents. The concentrations needed for the pharmaceutical preparations were slightly higher than those in the fresh preparation.

*Comment*

This study demonstrates *in vitro* antioxidant actions of hawthorn preparations. The role of free radicals in disease, including atherosclerosis, was reviewed by Trilling and Jaber.<sup>2</sup> The antioxidant effects of hawthorn theoretically may be cardioprotective by having anti-atherosclerotic actions, as well as decreasing reperfusion damage to an ischaemic myocardium. In addition to the effect of hawthorn on ion channel activity, antioxidant actions may be an additional component to its clinical effect.

Inhibition of thromboxane A2 biosynthesis *in vitro* by the main components of *Crataegus oxyacantha* (Hawthorn) flower heads.

Vibes J, Lasserre B, Gleye J, Declume C. *Prostaglandins Leukotrienes Essential Fatty Acids* 1994; **50**: 173–175.

The authors had previously demonstrated that hawthorn extracts inhibited thromboxane A2 *in vitro*. This study

analysed specific components of hawthorn flower heads for their ability to inhibit thromboxane A2. Vitexin-2''-o-rhamnoside, which is flavonoid (yellow pigmented), had an inhibitory effect on thromboxane A2 biosynthesis; vitexin was even more potent, but it is not a regular component of hawthorn; instead it forms over time. Catechin and epicatechin, which are flavans (uncoloured), are known to be present in hawthorn, but were not isolated by the authors' method of extraction. These compounds were tested and found to significantly inhibit thromboxane A2 biosynthesis.

*Comments*

The significance of inhibition of platelet adhesion in ischaemic heart disease has been well studied. This *in vitro* study demonstrates that components of hawthorn may inhibit platelet adhesion by decreasing thromboxane A2 biosynthesis.

**Conclusion**

Recent research has shown that hawthorn decreases total cholesterol, LDL cholesterol and triglycerides in humans. It also increases exercise capacity of patients with NYHA Class II congestive heart failure. Additional clinical studies are required with an increased number of patients in the trials, and including populations that are racially diverse and contain both men and women. Trials of hawthorn beyond 6–8 weeks are also needed.

The *in vitro* studies have shown an effect of hawthorn on ion channels, possible alteration of the hepatic LDL receptors and attenuation of thromboxane biosynthesis. These may account for the beneficial action of hawthorn on cardiovascular disease. Further clinical studies, *in vivo* studies and *in vitro* studies, are still required to elucidate the mechanisms by which hawthorn accomplishes these effects.

Some of the studies analysed individual components of hawthorn extracts to identify the active compounds. The beneficial effects of a herbal product may come from several different compounds acting synergistically; their interaction should therefore also be addressed. Much research has focused on flavonoids that are found in hawthorn. Flavonoids are a group of polyphenolic antioxidants which are found in some fruits, vegetables, teas and wine.

The study by Von Eiff *et al.* also reported side-effects in the patients given hawthorn. Two of the 19 patients had side-effects: one had dyspnoea, the other had fatigue, and a mild macular eruption on both hands which appeared during the last 10 days of the trial. Two of the 21 placebo control patients reported side-effects: one had heartburn and the other had oedema of the extremities.

It is also crucial to compare the composition of different methods of hawthorn extraction both at the clinical level and the chemical composition level to develop

an optimum method of extraction and standardization of the extract. The actions of individual components of hawthorn as well as their interaction, when looking for possible synergistic effects, must be analysed before one can determine the optimal extract. The interaction of hawthorn with pharmaceutical drugs must also be determined.

An article in the *Lancet* by Hertog *et al.*<sup>3</sup> analysed the diet of 805 men in The Netherlands between the ages of 65 and 84 years for the intake of flavonoid. The three main sources for flavonoids in their diet were black tea, onions, and apples. The men were followed for a 5-year period, and the flavonoid content of their diet was inversely associated with mortality from coronary heart disease. Although this study did not look at hawthorn in particular, an association appears to exist between flavonoid consumption and coronary heart disease mortality. The finding of this long-term study are in agreement with the short-term clinical studies of hawthorn.

There are still many questions that physicians have concerning hawthorn which need to be addressed in clinical and basic science research. However, these studies are encouraging, demonstrating a beneficial effect of hawthorn on the cardiovascular system acting by several different mechanisms, with few side-effects documented.

## References

- <sup>1</sup> Schmidt U, Kuhn U, Ploch M, Hubner WD. Wirksamkeit des Extraktes LI 132 (600 mg/Tag) bei achtwöchiger Therapie, Plazebokontrollierte Doppelblind-studie mit Weissdorn an 78 herzkranken Patienten im Stadium II nach NYHA. *Munch Med Wschr* 1994; **136 (Suppl 1)**: S13–S19.
- <sup>2</sup> Trilling JS, Jaber R. Selections from the current literature: the role of free radicals and antioxidants in disease. *Fam Pract* 1996; **13**: 322–326.
- <sup>3</sup> Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet* 1993; **342**: 1007–1011.