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Major Therapeutic Activity of Hawthorn Leaf & Flower

A number of species have been used as hawthorn for medicinal use, mostly *Crataegus monogyna* and *C. laevigata* (synonym *C. oxyacantha*) in the Western herbal tradition. Crataegus is in the rose family (Rosaceae).

Traditional Use

The traditional use of hawthorn berries is well known, less so the leaf and/or flower.

Since the 14th century, hawthorn flower has been described in herbal texts, but not with cardiac applications.[1] Henri Leclerc in his *Précis de Phytothérapie* notes a 17th century reference that suggests a recommendation for use in high blood pressure: hawthorn relieves the cause of blood vessel distension and increased blood flow with high pulse rate. The plant part was undefined and there is much further discussion about clinicians who used hawthorn for their patients in the late 1800s and early 1900s, at least some of who were using berries, but at the end of his monograph he provides dosage information: *"On peut prescrire l'aubépine sous forme d'infusion (1 cuillerée à café de fleurs pour 1 tasse d'eau bouillante, 2 ou 3 fois par jour), de poudre (2 à 5 g)* ..." ["We can prescribe hawthorn in the form of infusion (1 teaspoon of flowers to 1 cup of boiling water, 2 or 3 times per day), powder (2 to 5 g) ..."].[2]

Other traditional and/or folk use in Europe, probably dating from the early 20th century, of hawthorn includes:

- excitability in adults, such as palpitations in the absence of heart disease; neurotonic states in adults and children, especially minor sleep disorders (flower/flowering tops; France);[3,4]
- to improve circulation (flower; southern Italy and Spain);[5,6]
- insomnia (flower; northern Italy).[7]

The Eclectics, a group of practitioners who were prominent around the late 19th and early 20th centuries in the United States used hawthorn leaf as a tonic.[8]

Clinical Studies

Constituents

The main constituents of leaf and flower are flavonoids (particularly the flavone C-glycosides including vitexin-2"-rhamnoside), procyanidins (including oligomeric procyanidins), triterpenes, hydroxycinnamic acid derivatives, amines and polysaccharides. The flavone C-glycosides and oligomeric procyanidins (OPCs) are regarded as the active compounds.[3,9] Over several decades, clinical studies have used extracts with claimed levels of these flavonoids and OPCs, but there is doubt that the OPCs levels were accurate. Analysis to determine the quantity of procyanidins that use (older) colourimetric methods will at best indicate the content but give no information about the procyanidin profile (oligomeric/polymeric procyanidins). (OPCs consist of 2 to 6 units of epicatechin/catechin units; polymeric procyanidins are larger, with a greater number of units.) To date, chromatographic determination, such as with the use of HPLC, has also had problems.[9] Given the recently identified questions concerning the accuracy of OPC quantification methods, and this relates to procyanidins generally, not just in relation to those in hawthorn,[9] the OPC dosage is not outlined in the following clinical data.

Heart Failure

The clinical efficacy of concentrated, standardised extracts of hawthorn leaf and flower in the treatment chronic heart failure is well established – a 2008 meta-analysis illustrates this. Of the randomised, double-blind, placebo-controlled trials reviewed, 14 met the inclusion criteria and 10 trials were suitable for meta-analysis. In most of the studies, hawthorn was used as an adjunct to conventional drug treatment. In all trials, adult patients were diagnosed with chronic heart failure and categorised according to the New York Heart Association (NYHA) classification (classes I to III – as the class increases, physical activity is increasingly limited). Length of the treatment ranged from 3 to 16 weeks. A summary of the major results is outlined in Table 1.[10] To be included, studies were required to have used hawthorn leaf and flower extract, however, closer scrutiny of the primary references indicates that several of the trials did not administer extracts containing only leaf

and flower – on the basis of their trade names, they contained berry with flower and/or leaf.[11,12]

Of the eight trials with results outlined in Table 1, four trials with verified product contents, prescribed a daily dosage of extract equivalent to about 0.8-9.5 g of dried leaf and flower (and standardised for OPC content). Another commonly available extract was used, it was standardised for flavonoids.

Compared to those receiving placebo, treatment with hawthorn produced a significant:

- increase in maximal workload§ (4 trials*)
- increase in exercise tolerance (2 trials*)
- decrease in pressure-heart rate product† (5 trials^)
- improvement in symptoms such as shortness of breath and fatigue, as measured by the von Zerssen score (2 trials)

Table 1. Major results of meta-analysis of randomised controlled trials of concentrated hawthorn extract for heart failure.

Notes: § about 9% above placebo; * one trial used an extract containing leaf + flower + berry; † this parameter is an index of cardiac oxygen consumption; ^ at least one, possibly two trials, used extract containing leaf + fruit.

Another pooled analysis has been conducted. It included 8 of the trials covered in the above 2008 meta-analysis and an additional two trials (one open design, the other randomised and controlled). Results were also compared with observations in a 3-year cohort study. Of the trials, 7 used the same concentrated leaf and flower extract, standardised for OPCs, as did the cohort study. Unsurprisingly the analysis confirmed the findings of the 2008 meta-analysis, but the individual patient data was investigated for the impact of baseline severity. **Stronger effects were apparent in patients who had more severe baseline conditions**: those with high pressure-heart rate product values and/or low maximal workload values showed greater improvement when treated with hawthorn. Results from the 3-year cohort study were also in line with the results of the pooled analysis.[13]

Several trials have been published since the 2008 meta-analysis. In each of these trials, concentrated leaf and flower extract, standardised for OPCs was administered in patients with chronic heart failure, providing a daily dosage equivalent to about 4.8 g of dried leaf and flower. No benefit was found for physical function,[14] average time to first cardiac event or cardiac mortality,[15] although in those with left ventricular ejection fraction between 25 and 35% (i.e. with less severe heart failure), hawthorn significantly decreased sudden cardiac death.[15] The authors noted that the lower sudden cardiac death rate in this subgroup of patients, and in a trial where the prevalence of implantable cardioverter defibrillator therapy was very low, suggests that hawthorn provided an antiarrhythmic effect. (Patients in this trial were taking conventional medications such as beta-blockers, digoxin, ACE inhibitors and diuretics, but not class I antiarrhythmics.)[15] In an open trial of short duration (8 weeks), addition of hawthorn increased the improved physical function and quality of life results obtained by doing exercise training.[16]

In a postmarketing surveillance study, published in the late 1990s, involving patients with heart failure NYHA stage I and II, the incidence of arrhythmias was drastically reduced. The reduction was independent of the severity of heart failure. Hawthorn leaf and flower extract, providing 19.8 mg/day of flavonoids was taken for 8 weeks.[17,18]

Mechanism of Action

The results of experimental (*in vitro* and *in vivo* animal) studies suggest that hawthorn preparations improve the strength of cardiac muscle contractions and increase coronary blood flow.[10]

Other Conditions

A hypotensive effect was observed in patients with type 2 diabetes taking hypoglycaemic and/or hypotensive drugs. Treatment with hawthorn resulted in a significant **reduction in diastolic blood pressure** compared to the reduction in the placebo group. The daily dosage of extract was equivalent to 6 g of dried leaf and flower, and provided 26.4 mg of flavonoids.[19] A controlled, crossover study investigated a potential hypotensive mechanism by investigating the effect of hawthorn on brachial artery flow mediated dilation, which is an indirect measure of nitric oxide release. Prehypertensive and mildly hypertensive adults received placebo and three doses of concentrated leaf and flower extract, each for a period of 3.5 days with a washout of 4 days. The daily dosage of extract was equivalent to 4, 6 and 10 g of dried leaf and flower (and standardised for OPC content). Hawthorn had no effect on flow mediated dilation or blood pressure. If hawthorn has a hypotensive effect, it is not likely to be mediated via release of nitric oxide.[20]

A double-blind trial found that hawthorn leaf and flower extract taken for 6 months significantly decreased plasma levels of neutrophil elastase (which is important in the development and **progression of atherosclerosis**) compared to placebo, in diabetics with chronic coronary heart disease. In addition, treatment with hawthorn resulted in a trend towards significantly lower LDL-cholesterol levels. Patients remained on their conventional medications. The daily dose of extract provided 26.4 mg of flavonoids, of which 17 mg was vitexin-2-rhamnoside. It was also standardised for OPCs.[21]

Safety

The 2008 meta-analysis found that adverse effects from hawthorn were infrequent, mild and transient. Five trials reported no adverse events in those receiving hawthorn extract.[10] Other reviews note that hawthorn is well tolerated overall and rarely associated with serious

adverse effects, with vertigo and dizziness the most common adverse effects observed.[22,23] Although adverse effects are not generally anticipated (as evidenced from the trials of conventional drug-medicated heart failure patients), modification of dosages may be required in patients taking cardioactive and hypotensive drugs.[3,24]

A randomised, cross-over trial verified that standardised extract of hawthorn leaf and flower did not demonstrate an antiplatelet effect in healthy volunteers. The effect of 15-days intake of hawthorn was compared to that of aspirin, separated by a washout period of 2 weeks. The daily dose of hawthorn extract provided 50 mg of flavonoids. It was also standardised for OPCs.[25]

Actions

Heart tonic, possibly antiatherosclerotic.

Indications

- Cardiovascular and circulatory diseases.
- May provide support for insomnia and nervous conditions.

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