Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials

Pittler M H, Schmidt K, Ernst E

CRD summary
This well-conducted review assessed the use of hawthorn extract to treat patients with chronic heart failure. The authors concluded that hawthorn extract has significant benefits, compared with placebo, as an adjunctive treatment for patients with chronic heart failure. The conclusions are reliable.

Authors’ objectives
To assess the efficacy of adjunctive treatment with hawthorn extract for patients with chronic heart failure (CHF).

Searching
MEDLINE, EMBASE, the Cochrane Library, CINAHL, CISCOM and AMED were each searched from inception to June 2002; the search terms were stated. Ten manufacturers of commercial hawthorn preparations and nine experts in the field were contacted for additional published and unpublished studies. Relevant medical journals, conference proceedings and the authors’ own files were handsearched. The references lists in identified papers were also checked. Studies in any language were included and non-English language papers were translated.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. One of the included RCTs was of a crossover design. The duration of the included studies ranged from 3 to 16 weeks.

Specific interventions included in the review
Studies that compared monopreparations of extract of hawthorn leaf plus flower with placebo were eligible for inclusion. The included studies used between 160 and 1,800 mg of hawthorn extract per day. All but one of the studies used the WS 1442 hawthorn formulation; the other study used the LI132 formulation. In most of the studies, the patients also received conventional medications such as angiotensin-converting enzymes inhibitors, calcium antagonists, diuretics, and blood-pressure and lipid lowering medications. Some studies excluded specified medications, while others did not make it clear whether any concomitant drugs were administered.

Participants included in the review
Studies of patients with CHF were eligible for inclusion. The participants in the included studies were classified as New York Heart Association I to III.

Outcomes assessed in the review
The inclusion criteria were not specified in terms of the outcomes. The primary outcome was the change in maximal workload. The included studies assessed maximal workload using bicycle ergometry. The review also assessed the pressure-heart rate product (systolic blood pressure in mmHg multiplied by the heart rate per minute, divided by 100), exercise tolerance, symptoms (e.g. dyspnoea, fatigue and symptoms assessed with the Zerssen symptom score) and adverse effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the identified papers for inclusion and selected studies. Any disagreements were resolved through discussion.

Assessment of study quality
Validity was assessed using the Jadad scale, which considers randomisation, blinding and withdrawals. Two reviewers independently assessed validity and resolved any disagreements through discussion.
Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. The mean difference and 95% confidence interval (CI) between hawthorn extract and placebo was calculated for the primary outcome for each study. Where the data were insufficient, the authors and manufacturers were contacted for additional information.

Methods of synthesis
How were the studies combined?
The overall effects of hawthorn on the maximal workload, pressure-heart rate product, exercise tolerance and Zerssen symptom score were estimated using the weighted mean difference (WMD) and 95% CI. Summary estimates of effect were calculated using a random-effects model. Where studies did not report sufficient information to calculate the variance of the change from baseline, the variance was input (the methods for this were described in the review). The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
For the meta-analysis of maximal workload, statistical heterogeneity was tested using the chi-squared statistic and a forest plot was presented. A sensitivity analysis was carried out for maximal workload by using data for the low-dose (900 mg) treatment arm instead of the high-dose arm (1800 mg) in one study, and by analysing separately data from studies that used hawthorn extract in combination with other medications and data from studies in which the use of concomitant medications was unclear.

Results of the review
Thirteen RCTs (997 patients) were included. Eight of these were used in the meta-analyses (632 patients).

The validity scores ranged from two to five out of a possible five points.

Maximal workload (4 RCTs, 310 patients): hawthorn extract significantly increased maximal workload compared with placebo; the WMD was 7 watts (W) (95% CI: 3, 11, P<0.01). No significant heterogeneity was detected (P=0.5). The inclusion of data from the low-dose instead of the high-dose treatment arm made little difference to the results; the WMD (311 patients) was 6 W (95% CI: -1, 14). The WMD for studies using hawthorn plus other medications (212 patients) was 5 W (95% CI: 0.2, 10). The WMD for studies in which the use of other medications was unclear (98 patients) was 12 W (95% CI: 4, 21).

There were too few studies to reach any conclusions about the possibility of publication bias.

Hawthorn extract significantly reduced the pressure-heart rate product; the WMD (6 RCTs, 264 patients) was -20 (95% CI: -32, -8).

Hawthorn extract improved exercise tolerance, but the increase was not statistically significant; the WMD (98 patients) was 117 W minutes (95% CI: -1, 235).

Four RCTs showed that hawthorn extract improved symptoms (dyspnoea and fatigue). A meta-analysis of two RCTs using the Zerssen symptom score showed that hawthorn extract significantly improved the score; the WMD (169 patients) was 6 (95% CI: -9, -2).

The most common adverse effect was dizziness or vertigo (reported in 8 patients). Five RCTs reported no adverse effects with hawthorn extract.

Authors’ conclusions
The authors concluded that the evidence suggests that adjunctive treatment with hawthorn extract is beneficial in patients with CHF. The results from studies on the effect of hawthorn extract on prognosis are awaited.
CRD commentary
This was a well-conducted and clearly presented review. The review question was clear in terms of the study design, intervention and participants. Several relevant sources were searched, the search terms were stated, studies in any language were eligible, and attempts were made to locate unpublished studies. Two reviewers independently selected the studies, assessed validity and extracted the data; this reduces the potential for bias and errors. Only double-blind RCTs were included and validity was assessed using appropriate criteria.

Some relevant data were extracted and tabulated, but reasons for drop-outs (rates ranged from 0 to 33%) were not reported. The data were appropriately combined using meta-analyses and statistical heterogeneity was assessed for the main outcome of the review. A sensitivity analysis was carried out to test the robustness of the results. The authors discussed some of the limitations of the evidence and the review. The evidence presented appears to support the authors' conclusions, but the robustness of the results would have been strengthened by an exploration of the influence of drop-outs on the results.

Implications of the review for practice and research
Practice: The authors stated that self-medication is not appropriate for patients with heart failure, and that such patients should be treated by a licensed physician.

Research: The authors stated that research is underway into the effect of hawthorn extract on the prognosis of patients with heart failure (see Other Publications of Related Interest).

Bibliographic details

PubMedID
12798455

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Crataegus; Double-Blind Method; Endpoint Determination; Exercise Test; Heart Failure /drug therapy; Humans; Phytotherapy; Plant Extracts /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.