# Hawthorn extract for treating chronic heart failure (Review)

**Guo R, Pittler MH, Ernst E**


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**[Intervention Review]**

# Hawthorn extract for treating chronic heart failure

Ruoling Guo[1], Max H Pittler[2], Edzard Ernst[2]

[1]Complementary medicine, Peninsula Medical School, University of Exeter and Plymouth, Exeter, UK. [2]Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK

Contact address: Ruoling Guo, Complementary medicine, Peninsula Medical School, University of Exeter and Plymouth, 25 Victoria Park Road, Exeter, EX2 4NT, UK. ruoling.guo@pms.ac.uk.

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## ABSTRACT

### Background

Hawthorn extract is advocated as an oral treatment option for chronic heart failure. Also, the German Commission E approved the use of extracts of hawthorn leaf with flower in patients suffering from heart failure graded stage II according to the New York Heart Association.

### Objectives

To assess the benefits and harms as reported in double-blind randomised clinical trials of hawthorn extract compared with placebo for treating patients with chronic heart failure.

### Search methods

We searched CENTRAL on *The Cochrane Library* (issue 2, 2006), MEDLINE (1951 to June 2006), EMBASE (1974 to June 2006), CINAHL (1982 to June 2006) and AMED (1985 to June 2006). Experts and manufacturers were contacted. Language restrictions were not imposed.

### Selection criteria

To be included, studies were required to state that they were randomised, double-blind, and placebo controlled, and used hawthorn leaf and flower extract monopreparations.

### Data collection and analysis

Two reviewers independently performed the selection of studies, data extraction, and assessment of methodological quality. Data were entered into RevMan 4.2 software. Results from continuous data were reported as weighted mean difference (WMD) with 95% confidence interval (CI). Where data were suitable for combining, pooled results were calculated.

### Main results

Fourteen trials met all inclusion criteria and were included in this review. In most of the studies, hawthorn was used as an adjunct to conventional treatment. Ten trials including 855 patients with chronic heart failure (New York Heart Association classes I to III) provided data that were suitable for meta-analysis. For the physiologic outcome of maximal workload, treatment with hawthorn extract was more beneficial than placebo (WMD (Watt) 5.35, 95% CI 0.71 to 10.00, P < 0.02, n = 380). Exercise tolerance were significantly increased by hawthorn extract (WMD (Watt x min) 122.76, 95% CI 32.74 to 212.78, n = 98). The pressure-heart rate product,

an index of cardiac oxygen consumption, also showed a beneficial decrease with hawthorn treatment (WMD (mmHg/min) -19.22, 95% CI -30.46 to -7.98, n = 264). Symptoms such as shortness of breath and fatigue improved significantly with hawthorn treatment as compared with placebo (WMD -5.47, 95% CI -8.68 to -2.26, n = 239). No data on relevant mortality and morbidity such as cardiac events were reported, apart from one trial, which reported deaths (three in active, one in control) without providing further details. Reported adverse events were infrequent, mild, and transient; they included nausea, dizziness, and cardiac and gastrointestinal complaints.

**Authors' conclusions**

These results suggest that there is a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure.

## PLAIN LANGUAGE SUMMARY

**Hawthorn extract may be used as an oral treatment option for chronic heart failure**

Hawthorn extract (made from the dried leaves, flowers and fruits of the hawthorn bush) may be used as an oral treatment option for chronic heart failure. In this review, 14 double-blind, placebo controlled randomised clinical trials (RCTs) were found. They did not all measure the same outcomes and several did not explain what other heart failure treatments patients were receiving. Those trials that could be included in a meta-analysis showed improvements in heart failure symptoms and in the function of the heart. The results, therefore, are suggestive of a benefit from hawthorn extract used in addition to conventional treatments for chronic heart failure.

## BACKGROUND

Hawthorn extract is among the most popular herbal medicinal products in the US (Blumenthal 2001; Breevort 1998) and in Europe, where it is marketed in some countries as a prescription medicine (Ernst 2001). Preparations usually contain extract derived from the hawthorn bush (Latin name *Crataegus monogyna* or *Crataegus laevigata*). The cardiac properties of the extract have been investigated in pre-clinical experiments suggesting positive inotropic effects (ie.increase the strength of muscular contraction) and increases in coronary blood flow (Chang 2002; Loew 1997). Clinical studies report an increase in exercise tolerance, left ventricular ejection fraction and improvement in heart failure related symptoms (Eichstädt 2001; Fugh-Berman 2000; Kraft 2000; Kraft 2001). In most herbal reference texts, hawthorn extract is advocated as an oral treatment option for chronic heart failure (e.g. Ernst 2001, Fetrow 1999, Rotblatt 2002) and the German Commission E approved the use of extracts of hawthorn leaf with flower for stage II according to the New York Heart Association (NYHA) (Blumenthal 1998; Blumenthal 2000b). Trials reporting beneficial effects and trials showing no evidence of clinical benefit are available (Förster 1994; Schmidt 1994). To get a fair assessment of the evidence we performed a systematic review. Maximal workload in this context is defined as maximum energy output measured in Watt. Left ventricular ejection fraction is the fraction of blood pumped out of the left ventricle with each heart beat. Exercise tolerance is energy output per unit time.

## OBJECTIVES

To assess the benefits and harms of hawthorn extract compared with placebo for treating patients with chronic heart failure.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We only included randomised controlled trials (RCTs) which were described as placebo-controlled and double-blind. Studies that tested hawthorn extract as an adjunctive treatment were included.

#### Types of participants

Adult patients diagnosed with chronic heart failure and categorised according to the NYHA classification (Kelley 1992).

### Types of interventions

Oral preparations containing extract of hawthorn leaf and flower as the only component (mono-preparation). Studies assessing the effect of hawthorn extract in addition to other treatments for heart failure were included.

### Types of outcome measures

Trials assessing clinical outcome measures related to chronic heart failure (e.g. maximal workload) were included. Of primary interest is the change of baseline to post-treatment data, which was used to assess the difference compared with placebo. We specifically assessed the papers for data on mortality and morbidity such as cardiac events (e.g. heart attacks, angina). Data on the safety of hawthorn extract are described as they are reported in the reviewed trials.

## Search methods for identification of studies

All publications describing (or which might describe) double-blind, placebo-controlled RCTs of hawthorn extract for chronic heart failure were sought through electronic searches on the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (issue 2, 2006), MEDLINE (1951 to June 2006), EMBASE (1974 to June 2006), CINAHL (1982 to June 2006), AMED (1985 to June 2006), and Digital Dissertations. Additionally, manufacturers of hawthorn preparations and experts on the subject were contacted and asked to contribute published and unpublished material (McManus 1998). Handsearches were conducted in conference proceedings (*FACT - Focus on Alternative and Complementary Therapies* 1996 to 2005), our own collection of papers and medical journals (*Phytomedicine* 1994 to 2005, *Alternative and Complementary Therapies* 1995 - 2005 and *Forschende Komplementärmedizin Klassische Naturheilkunde* 1994 to 2005). The bibliographies of all papers located were searched for further trials. No restrictions regarding the language of publication were imposed. The following search strategy was used for all of the above databases:

#1 hawthorn
#2 crategus
#3 crataegus
#4 whitethorn
#5 weissdorn
#6 #1 or #2 or #3 or #4 or #5

## Data collection and analysis

### Trial selection

Two reviewers (MHP, RG) independently screened the title and abstracts from searches on electronic databases to identify those articles relevant to this systematic review. Full articles were retrieved for further assessment. All full text articles were read independently by two reviewers to make a decision on inclusion. Disagreements were resolved by discussion and by seeking the opinion of the third reviewer (EE).

### Quality assessment

Two reviewers (MHP, RG) independently assessed methodological quality of selected studies. Any differences of opinion was resolved by discussion and consensus reached by discussion with a third reviewer (EE).

***Method of treatment assignment or adequacy of the randomisation process***

We assessed whether the treatment was assigned by a process that was truly randomised:

A - adequate sequence generation reported (such as computer generated random numbers and random number tables, whilst inadequate approaches will included the use of alternation, case record numbers, birth dates or days of the week).

B - did not specify one of the adequate reported methods in (A) but mentioned randomisation method.

C - other methods of allocation that appear to be biased.

***Adequacy of the allocation concealment process***

A - adequate measures to conceal allocations. Concealment was deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following were used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients.

B - unclearly concealed trials, in which the authors either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A).

C - inadequately concealed trials, in which method of allocation was not concealed. Inadequate approaches included: the use of alternation, case record numbers, days of the week and open random number lists.

***Control of selection bias after treatment assignment***

We assessed if all patients entered in the trial and assigned to treatment were included in the analysis, any withdrawals from the trial were listed, and the results were analysed both by the original treatment assignment and by treatment received. We scored as follows:

A - studies where an intention to treat analysis is possible and few exclusions (with adequate reporting of these exclusions).

B - studies which reported exclusions as reported in (A), but exclusions were less than 10%.

C - no reporting of exclusions; exclusions of 10% or more or wide differences in exclusions between groups.

### Data extraction

A data extraction form was designed to include: design and methodological quality of the study, preparation used (including the concomitant medications), details of the participants (including the NYHA class), dosage and duration of intervention, out-

come measures as detailed above and adverse events. Data were extracted by two reviewers independently. Additional unpublished data were also obtained by contacting the authors of the paper and the manufactures of the products, who may also have funded the trials.

**Data analysis**

Quantitative analyses of outcomes were based on 'intention-to-treat' (ITT) analyses as reported by the authors of the original studies (that is, that data from all participants are analysed according to the original group assignment). For continuous data, where data are suitable for combining, pooled weighted mean differences (with 95% confidence intervals) were calculated, using a random-effects model. For homogeneous data we additionally used the fixe- effect model. Where standard deviations for the mean changes were not available, these data were estimated from the standard deviations for the pre-treatment and post-treatment measurements as recommended by Cochrane Collaboration, using a more conservative correlation coefficient (r = 0.4) (Follmann 1992; Higgins 2005). One three-arm trial (two dose levels and a placebo control) was treated as two individual trials (Tauchert 2002 (HD); Tauchert 2002 (LD)). The number of the participants in the control group was halved for each comparison to avoid a unit of analysis error. This was not planned in our original protocol but thought to be appropriate for this review.

**Heterogeneity**

Because trials found may not have been carried out according to a common protocol there will usually be variations in patient groups, clinical settings, concomitant care etc. Therefore we planned to assess heterogeneity between trial results: forest Plots were visually examined and the presence or absence of overlap in the confidence intervals was noted. Lack of overlap of confidence intervals may indicate heterogeneity. The chi-squared test for heterogeneity was performed. Trial data were considered to be heterogeneous if $P < 0.10$.

**Publication or other bias**

A funnel plot was carried out to test for the presence of publication bias based on the data for the primary outcome. Publication bias is usually detected by asymmetry of the funnel plot.

**Sensitivity analysis**

Sensitivity analysis were used to explore the influence on effect size: repeating analysis excluding trials using concomitant medication.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The literature searches identified 30 references that described 28 potentially relevant trials, including one unpublished study (Alexander 1995) and one conference abstract (Aaronson 2004). Thirteen publications were excluded because they were either not randomised and placebo controlled (Eichstädt 1989; Fischer 1994; Staiger 1987; Tauchert 1994; Weikl 1992; Weng 1984), did not use monopreparations of extracts of hawthorn leaf with flower (Czerny 1996; Degenring 2003; Eiff 1994; Rietbrock 2001; Schmidt 2000; Von 1994), assessed healthy volunteers (Hellenbrecht 1990). One was an ongoing trial (Holubarsch 2000). Sixteen references that described 14 trails involving 1110 patients met the inclusion criteria and were included in this review. These trials are described in the characteristics of included studies table. Two studies (O'Conolly 1986; O'Connolly 1987) were cross-over designs, the others were parallel. Trial size ranged from 30 to 209 participants. All trials administered standardised hawthorn extracts. Two brands of hawthorn extract (WS1442 and LI132) were used. Seven of eight trials used hawthorn extract WS 1442, which was standardized to 18.8% oligomeric procyanidins. The daily dose used in these trials ranged between 160 mg to 1800 mg. Reported outcomes included maximal workload, exercise tolerance, pressure-heart rate product, 6-min walk test and left ventricular ejection fraction (LVEF%). Ten trials provided data for meta-analysis. In most of the studies, hawthorn was used as an adjunct to conventional treatment for chronic heart failure. All trials used the NYHA classification to categorise patients. In most trials (n = 9), patients of NYHA II were included. In other trials, patients of NYHA I - II (n = 2), II to III (n=2) or III (n = 1) were included. Mean age of the included patients in each trial ranged from 50 to 74, with a higher overall proportion of female patients (62%). Reported co-morbidities included previous myocardial infarction, hypertension, hyperlipidemia, coronary heart disease, myocarditis and diabetes mellitus. Ten trials reported the use of concomitant drugs. Diuretics were allowed in four trials and ACE inhibitors were allowed in three trials. Length of the treatment range from 3 to 16 weeks and the longest follow up was 26 weeks.

## Risk of bias in included studies

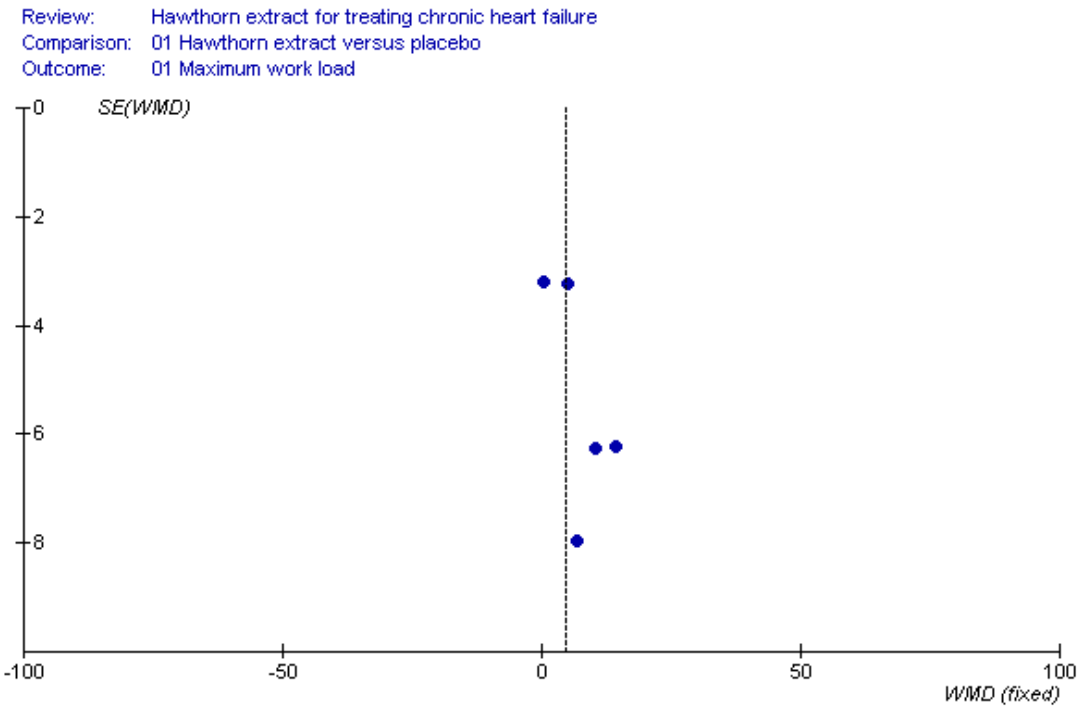
As described in the method section, we assessed the methodological quality of included studies in three aspects, i.e. randomisation, allocation concealment and control of selection bias after treatment assignment. Details can be found in Table 1. The overall methodological quality varies among studies. Six of 14 trials reported adequate sequence generation, the others only mentioned randomisation in the text. Adequate allocation concealment was reported in only three trials. No allocation concealment approach was reported in the other 11 trials. Four studies used intension-to-treat analysis and had few exclusions. Three trials provided no information on exclusion. The other seven trials reported less than 10% exclusions with reasons for exclusion given.

## Effects of interventions

Of the 14 included trials, maximal workload was the outcome most frequently used. The meta-analysis of trials which reported data on maximal workload (Bödigheimer 1994; Hanak 1983; Tauchert 2002 (HD); Tauchert 2002 (LD); Zapfe 2001), indicated a significant increase in this outcome in patients receiving hawthorn extract compared with patients receiving placebo WMD (Watt) 5.35 (95% CI 0.71 to 10.00, P < 0.02, n = 380). There was no evidence of heterogeneity among the studies (P = 0.27). Results calculated using a fixed-effect model were almost identical to those obtained using a random-effects model. All trials assessed maximal workload using bicycle ergometry with an increase of 25 Watt every 2 minutes until the patients had to stop.
Visual inspection of the funnel plot (Figure 1) showed a degree of asymmetry, but there are too few studies to make any conclusions about publication bias.

Sensitivity analyses were performed to test the robustness of the main analysis. We assessed trials in which hawthorn extract was administered in addition to other medications (WMD (Watt) 2.9, 95% CI -1.38 to 7.18, n = 282) and trials in which it was unclear whether the patients received any other medications (WMD (Watt) 12.36, 95% CI 3.72 to 21.00, n = 98).

**Figure 1. Funnel plot to examine publication bias**




Additional outcome data were available in five other trials (Leuchtgens 1993; O'Connolly 1987; O'Conolly 1986; Weikl 1996; Zapfe 2001) for the pressure-heart rate product (systolic blood pressure in mm Hg times heart rate per minute and divided by 100) and two trials for exercise tolerance (Hanak 1983; Zapfe 2001). The meta-analysis of these data suggests a reduction of the pressure-heart rate product (WMD (mmHg/min) -19.22, 95% CI -30.46 to -7.98, n=264) and an increase in exercise tolerance (WMD (Watt x min) 122.76, 95% CI 32.74 to 212.78, n = 98). Patients receiving hawthorn extract had an improvement in symptoms such as dyspnoea and fatigue (Leuchtgens 1993; Tauchert 2002 (HD); Tauchert 2002 (LD); Schmidt 1994; Iwamoto 1981). The symptom score developed by von Zerssen (Von Zerssen 1971) was used in two trials (Leuchtgens 1993; Tauchert 2002 (HD); Tauchert 2002 (LD)). Data from these two studies suggest a sig-

nificant differential effect in favour of hawthorn extract (WMD -5.47, 95% CI -8.68 to -2.26, n = 239).

Two single trials (Aaronson 2004; Eichstädt 2001) reported analysable data on left ventricular ejection fraction (LVEF) and 6-min walk test. One trial (Eichstädt 2001) found significant inter-group difference in LVEF% (WMD (%) 1.70, 95% CI 0.88 to 2.52, n = 40). However, LVEF% correlates only weakly with exercise tolerance and is often regarded as a surrogate outcome measure. Clinical outcomes were not available. The other trial (Aaronson 2004) found no significant difference in 6-min walk test between the two groups (WMD (min) -8.00, 95% CI -34.49 to 18.49, n = 113).

We also specifically looked for data on mortality and morbidity such as cardiac events, but only one trial reported deaths (three in active group versus one in control) without further details. The most common adverse event was dizziness/vertigo (n = 8) and gastrointestinal complaints (n = 5) (see Table 2 for further details of reported adverse events). Five trials reported no adverse events in patients receiving hawthorn extract.

## DISCUSSION

Our results suggest that, compared with placebo, hawthorn extract increases the maximal workload in patients with chronic heart failure. This conclusion, however, is based on small numbers of studies and patients. Nevertheless, the secondary outcome measures support the findings and suggest that hawthorn extract is superior to placebo as an adjunctive treatment for patients with chronic heart failure.

As described in the characteristics of included studies table, in seven trials most patients were also treated with conventional medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists. In the other trials, it was not clear whether patients received other medications. Thus, there is a degree of uncertainty whether the benefit can be ascribed to hawthorn extract alone. Many effective and established conventional treatments are available for chronic heart failure (ACC/AHA 1995; ESC 2001). Weight control, dietary measures, smoking cessation,and pharmacological interventions are generally regarded as first-line treatment approaches for most patients (ACC/AHA 1995; Dargie 1994; Millane 2000). Diuretics (Faris 2006) and digitalis (Hood 2004) lead to an improvement of heart failure-related symptoms, whereas beta-blockers and ACE inhibitors also improve survival (Doughty 1997; Lonn 2000; Tsuyuki 2000). ACE inhibitors have been reported to increase parameters of physical performance, such as exercise tolerance, by approximately 20% (Kiowski 1996). A meta-analysis of ACE inhibitors reported an average improvement of exercise duration by 19% in the treatment group, compared with 7% in the placebo group (Narang 1996). The results of our meta-analysis suggest an improvement of maximal workload of about 9% above placebo. In a direct comparison of 900 mg of hawthorn extract (LI 132) daily with 37.5 mg of captopril daily in 132 patients (Tauchert 1994), both groups increased their maximal workload significantly, without differences between the two treatments. Thus, these data suggest that hawthorn improves physical performance measures to a smaller yet clinically meaningful degree compared with ACE inhibitors.

Changes in physical performance due to drug effects do not correlate well with changes in mortality (Swedberg 1994), but currently there are no rigorous trials that have assessed important long-term clinical outcomes such as cardiac death, non-fatal myocardial infarction, and hospitalisation. One such large-scale study was recently completed (personal contact), which compares 900 mg of standardised hawthorn extract WS 1442 with placebo during a 24-month treatment period (Holubarsch 2000).

It has been suggested that hawthorn extract has positive inotropic effects, decreases atrioventricular conduction time, and increases coronary blood flow. These effects seem similar to those of phosphodiesterase inhibitors such as amrinone and milrinone. Hawthorn extract, however, increases the refractory period (Joseph 1995), which may explain why it seems to be associated with antiarrhythmic activity (Chang 2002; Loew 1997), whereas phosphodiesterase inhibitors and most other inotropic agents have proarrhythmic effects. Hawthorn extract blocks repolarising potassium currents in ventricular myocytes, an effect that is similar to the action of class III antiarrhythmic drugs (Müller 1999). In addition, the positive inotropic effect is similar to the action of cardiac glycosides (Schwinger 2000).

Whether or not hawthorn, like phosphodiesterase inhibitors, has adverse effects on the prognosis of patients with chronic heart failure is not known, but may be answered by the ongoing trial (Holubarsch 2000). The pharmacologic profile of hawthorn is similar to digoxin (Joseph 1995). Because of a relatively small therapeutic window, digoxin is associated with a risk of intoxication, particularly in elderly patients and those with impaired renal function (ACC/AHA 1995; Kernan 1994). In contrast, patients with NYHA class III were treated with 1800 mg of hawthorn extract daily for 16 weeks (Tauchert 2002 (HD)), an increase of 100% over the standard dose. Patients reported only mild and infrequent adverse events which were not different from those reported by patients taking 900 mg of hawthorn extract and fewer than with placebo. These were (cases) dizziness/vertigo (4), bronchitis (4), back pain (5), flu-like syndrome (4), headache (2), arthritis (1), flatulence (1) and gastroenteritis (1).

Postmarketing surveillance studies report only mild and infrequent adverse events in patients receiving hawthorn extract. In a study of 1011 patients, 14 adverse events (1.4%) occurred after the administration of 900 mg of hawthorn extract for 24 weeks. In 2 of these patients, a causal relation with hawthorn was suspected, but regarded by the treating doctors as unlikely (Tauchert

1999). In another postmarketing surveillance study of 3664 patients who were treated with 900 mg of hawthorn extract for 8 weeks (Schmidt 1998), 48 patients (1.3%) reported adverse events, including hot flushes, stomach complaints, palpitations, dizziness, dyspnoea, headache, and epistaxis. In 19 patients, this resulted in the discontinuation of the treatment. Although these data suggest that hawthorn extract is relatively safe, self-medication is inappropriate among patients with heart failure, who should be treated by a licensed clinician. Self-medication might also increase the risk of adverse events through herb-drug interactions (Barnes 1998; Eisenberg 1998). Based primarily on animal experiments, hawthorn extracts may interact with anticoagulants, antihypertensives, and cardiac glycosides (Ernst 2000; Herr 2002). In a preliminary report presented in abstract form, there was no interaction between hawthorn extract and digoxin in healthy volunteers (Tankanow 2002). Nevertheless, we believe that hawthorn extracts are not ideal candidates for the over-the-counter market.

Limitations of our systematic review and indeed systematic reviews in general, pertain to the potential incompleteness of the reviewed evidence. We aimed to identify all RCTs on the topic. However, only a few studies provided data on our primary outcome variable. The distorting effects on systematic reviews arising from publication bias and location bias are well-documented (Dickersin 1990; Easterbrook 1991; Egger 1998). This includes suggestions that positive findings may be overrepresented in complementary medicine journals (Ernst 1997; Schmidt 2001) and that these journals favour positive conclusions at the expense of methodological quality (Pittler 2000). In addition, there is evidence that positive findings tend to be published in English-language journals (Egger 1997), whereas some European journals are not indexed in major medical databases (Nieminen 1999). Thus, treatment effects may be exaggerated, especially for herbal medicinal products because much of the evidence originates from European countries. We did not restrict our searches by publication language, and are therefore confident that our strategy minimised bias. We only included data from clinical trials that were randomised, double-blind, and placebo controlled. Nevertheless, the extent of methodological rigour varied among trials.

## AUTHORS' CONCLUSIONS

### Implications for practice

The best evidence that is available suggests that hawthorn extract has significant benefits, compared with placebo, as an adjunctive treatment for patients with chronic heart failure. Reported adverse events were infrequent, mild, and transient.

### Implications for research

Whether hawthorn extract affects the prognosis of patients with chronic heart failure requires further investigation. Future trials should report clinical as well as physiological outcomes.

## ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Aaronson 2004**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, parallel trial |
| Participants | 113 patients were included in the analysis, mean age 54 (hawthorn group), 58 (placebo group); no details of male and female proportion; NYHA II to III, LVEF < 40%, 6-min walk test distance of 150 to 450 meters, treated with ACE inhibitors, angiotensin receptor blocker and beta-blocker unless contraindicated |
| Interventions | WS1442, 450 mg per day. Duration of the treatment 6 weeks and follow up for 26 weeks |
| Outcomes | Primary outcome: 6-min walk test<br>Secondary outcome: LVEF, Patient global assessment of quality of life, MLWHFQ (Minnesota living with heart failure questionnaire) |
| Notes | Identified as an abstract presented at the Heart Failure Society of America annual meeting 2006 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Alexander 1995**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 73 patients, all completed the study, mean age 49.4 (hawthorn group), 53.1 (placebo group); male 48%; NYHA II, treated with diuretics; 42% in test group and 50% in placebo group suffered from myocarditis in history, 29% and 34% were diagnosed as coronary heart disease and 8% from each group also had hypertension |
| Interventions | WS1442, 900 mg per day. Duration of the treatment: 4 weeks; follow up for 8 weeks |
| Outcomes | Primary outcome: excercise tolerance<br>Secondary outcome: pressure-heart rate product |
| Notes | Dr Med dissertation |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Bödigheimer 1994**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 85 patients, 73 completed the study, mean age 61.1 (hawthorn group), 62.1 (placebo group); 30% male NYHA II; treated with Ca-antagonists and ACE inhibitors |
| Interventions | LI132, 300 mg per day. Duration of the treatment: 4 weeks. |
| Outcomes | Primary outcomes: maximum workload<br>Secondary outcomes: clinical assessment; symptom score |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Eichstädt 2001**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 40 patients, all completed the study, mean age 65.3 (hawthorn group), 66.3 (placebo group); 70% male; NYHA II; LVEF < 55%; all diagnosed with coronary heart disease; 12.5% and 17.9% also suffered from diabetes mellitus or hyper-cholesterol respectively; concomitant medication included aspirin, nitrates, Ca-antagonists, antidiabetics, lipid-lowering medications or ACE inhibitors |
| Interventions | WS1442, 480 mg per day. Duration of the treatment: 4 weeks |
| Outcomes | Primary outcomes: LVEF<br>Secondary outcomes: end systolic volume, end diastolic volume, blood pressure and heart rate |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Förster 1994**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 72 patients, 69 completed the study, mean age 49.8 (hawthorn group), 52.0 (placebo group); 43.5% male; NYHA II; treated with diuretics; average LVEF at baseline were 51%; most of the patients have had myocarditis and some may also suffer from coronary heart disease or hypertension |

**Förster 1994** (*Continued*)

| | |
|---|---|
| Interventions | LI132, 900 mg per day. Duration of the treatment: 8 weeks |
| Outcomes | Primary outcomes: exercise tolerance<br>Secondary outcomes: oxygen uptake |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Hanak 1983**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 60 patients, 58 completed the study, mean age 55.4 (hawthorn group), 55.2 (placebo group); 55% male; NYHA I to II |
| Interventions | WS1442, 180 mg per day. Duration of the treatment: 3 weeks |
| Outcomes | Primary outcomes: maximum workload<br>Secondary outcomes: exercise tolerance |
| Notes | Concomitant treatments: balneotherapy |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Iwamoto 1981**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 102 patients, 80 completed the study, mean age 61 (hawthorn group), 66 (placebo group); 37% male; NYHA II to III, patients may also suffer from Ischaemic or hypertensive heart disease |
| Interventions | WS1442, 180 - 270 mg per day. Duration of the treatment: 6 weeks |
| Outcomes | Primary outcomes: pressure-heart rate products;<br>Secondary outcomes: symptoms |
| Notes | Concomitant medication: not specified |

**Iwamoto 1981** (*Continued*)

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

**Leuchtgens 1993**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 30 patients, all completed the study, mean age: hawthorn group, 67.9 (male), 66.0 (female); placebo group, 66.8 (male), 61.6 (female); 60% male |
| Interventions | WS1442, 160 mg per day. Duration of the treatment: ?? weeks. |
| Outcomes | Primary outcomes: pressure-heart rate product<br>Secondary outcomes: symptom score |
| Notes | Concomitant medication: not specified |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**O'Connolly 1987**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled cross-over trial |
| Participants | 36 patients, 31 completed the study, mean age 74.0 (Hawthorn group), 74.0 (placebo group); 25% male; NYHA I to II with multi-morbidity (hypertension, emphysema, diabetes, myocardia infarction, glaucoma and dementia); concomitant medication: diuretics, lipid lowering drugs, antidiabetics, antirheumatics |
| Interventions | WS1442, 180 mg per day. Duration of the treatment: 6 weeks. |
| Outcomes | Primary outcomes: pressure-heart rate product<br>Secondary outcomes: psychiatric status |
| Notes | |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |

**O'Connolly 1987** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**O'Conolly 1986**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled cross-over trial |
| Participants | 36 patients, 34 completed the study, age range from 62 to 84, 28% male; NYHA I to II with multi-morbidity (not specified) |
| Interventions | WS 1442, 180 mg per day. Duration of the treatment: 6 weeks |
| Outcomes | Primary outcomes: pressure-heart rate product<br>Secondary outcomes: psychiatric status |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Schmidt 1994**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 78 patients, 70 completed the study, age range from 45 to 73, 38% male; NYHA II; exercise capacity < 100 watts; diuretics were allowed during the study period |
| Interventions | LI132, 600 mg per day. Duration of the treatment: 8 weeks |
| Outcomes | Primary outcomes: maximum workload<br>Secondary outcomes: pressure-heart rate product; symptom score |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Tauchert 2002 (HD)**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, three-arm parallel trial |
| Participants | 209 patients, 197 completed the study, mean age 67.1 (hawthorn HD group), 67.4 (hawthorn LD group) , 68.4 (placebo group); 32% male;NYHA III; known for at least 6 months; previous untreated or treated with a diuretic and/or with a low dose ACE inhibitor, exercise capacity < 75 watts; during study period, only triamterene and hydrochlorothiazide were allowed |
| Interventions | HD: 1800 mg per day. LD: 900 mg per day. Duration of the treatment: 16 weeks |
| Outcomes | Primary outcomes: maximum workload<br>Secondary outcomes: symptom score |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Tauchert 2002 (LD)**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, three-arm parallel trial |
| Participants | 209 patients, 197 completed the study, mean age 67.1 (hawthorn HD group), 67.4 (hawthorn LD group) , 68.4 (placebo group); 32% male; NYHA III; known for at least 6 months; previous untreated or treated with a diuretic and/or with a low dose ACE inhibitor, exercise capacity < 75 watts; during study period, only triamterene and hydrochlorothiazide were allowed |
| Interventions | HD: 1800 mg per day. LD: 900 mg per day. Duration of the treatment: 16 weeks |
| Outcomes | Primary outcomes: maximum workload<br>Secondary outcomes: symptom score |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Weikl 1996**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 136 patients, 129 completed the study, mean age 65.5 (hawthorn group), 65.3 (placebo group); 28% male; NYHA II; concomitant medication included Ca-antagonists and/or ACE inhibitors |
| Interventions | WS1442, 160 mg per day. Duration of the treatment: 8 weeks |
| Outcomes | Primary outcomes: pressure-heart rate product<br>Secondary outcomes: quality of life |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Zapfe 2001**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled parallel trial |
| Participants | 40 patients, 39 completed the study, mean age 58.2 (hawthorn group), 66.5 (placebo group); 28% male; NYHA II, concomitant medication was not allowed, these included cardiac glycosides, diuretics, calcium antagonists, ACE inhibitors and other hawthorn preparations |
| Interventions | WS1442, 240 mg per day. Duration of the treatment: 12 weeks |
| Outcomes | Primary outcomes: maximum workload (exercise tolerance)<br>Secondary outcomes: pressure-heart rate product |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

LVEF= left ventricular ejection fraction
NYHA=New York Heart Association

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Czerny 1996 | Did not use monopreparations of hawthorn leaf with flower |
| Degenring 2003 | Did not use extract of hawthorn leaf with flower |
| Eichstädt 1989 | Not randomised, placebo-controlled |
| Eiff 1994 | Did not use monopreparations of hawthorn leaf with flower |
| Fischer 1994 | Not randomised, placebo-controlled |
| Hellenbrecht 1990 | Participants being healthy volunteers |
| Rietbrock 2001 | Did not use monopreparations of hawthorn leaf with flower |
| Schmidt 2000 | Did not use monopreparations of hawthorn leaf with flower |
| Staiger 1987 | Not randomised, placebo-controlled |
| Tauchert 1994 | Not randomised, placebo-controlled |
| Von 1994 | Did not use monopreparations of hawthorn leaf with flower |
| Weikl 1992 | Not randomised, placebo-controlled |
| Weng 1984 | Not randomised, placebo-controlled |

## Characteristics of ongoing studies *[ordered by study ID]*

**Holubarsch 2000**

| | |
|---|---|
| Trial name or title | |
| Methods | |
| Participants | Patients with chronic heart failure |
| Interventions | Hawthorn extract preparation (WS1422) |
| Outcomes | Time to first cardiac event |
| Starting date | |
| Contact information | |

**Holubarsch 2000** (*Continued*)

| Notes | |
|---|---|

## DATA AND ANALYSES

### Comparison 1. Hawthorn extract versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximum work load | 5 | 380 | Mean Difference (IV, Random, 95% CI) | 5.35 [0.71, 10.00] |
| 2 Exercise tolerance (Watt min) | 2 | 98 | Mean Difference (IV, Random, 95% CI) | 122.76 [32.74, 212.78] |
| 3 Pressure-heart rate product | 5 | 329 | Mean Difference (IV, Random, 95% CI) | -19.22 [-30.46, -7.98] |
| 4 Symptom scores according to v Zerssen | 3 | 239 | Mean Difference (IV, Random, 95% CI) | -5.47 [-8.68, -2.26] |
| 5 6-min walk test | 1 | 111 | Mean Difference (IV, Random, 95% CI) | -8.0 [-34.49, 18.49] |
| 6 LVEF% | 1 | 40 | Mean Difference (IV, Random, 95% CI) | 1.7 [0.88, 2.52] |

### Comparison 2. Sensitivity test

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Maximal workload (Watt) - with additional medication | 3 | 282 | Mean Difference (IV, Random, 95% CI) | 2.90 [-1.38, 7.18] |
| 1.1 Hawthorn administered in addition to other medication | 3 | 282 | Mean Difference (IV, Random, 95% CI) | 2.90 [-1.38, 7.18] |
| 2 Maximal workload (Watt) - use of additional medication unclear | 2 | 98 | Mean Difference (IV, Random, 95% CI) | 12.36 [3.72, 21.00] |
| 2.1 Use of concomitant medication unclear | 2 | 98 | Mean Difference (IV, Random, 95% CI) | 12.36 [3.72, 21.00] |

### Analysis 1.1. Comparison 1 Hawthorn extract versus placebo, Outcome 1 Maximum work load.

Review: Hawthorn extract for treating chronic heart failure

Comparison: 1 Hawthorn extract versus placebo

Outcome: 1 Maximum work load

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Bödigheimer 1994 | 36 | 15.7 (35.8) | 37 | 8.8 (32) | | 8.1 % | 6.90 [ -8.69, 22.49 ] |
| Hanak 1983 | 29 | 9.7 (22.1) | 29 | -0.8 (25.4) | | 12.3 % | 10.50 [ -1.75, 22.75 ] |
| Tauchert 2002 (HD) | 69 | 9.8 (15.5) | 35 | 4.9 (15.6) | | 33.4 % | 4.90 [ -1.43, 11.23 ] |
| Tauchert 2002 (LD) | 70 | 5.2 (15.1) | 35 | 4.9 (15.6) | | 33.8 % | 0.30 [ -5.96, 6.56 ] |
| Zapfe 2001 | 20 | 5.6 (17.9) | 20 | -8.6 (21.3) | | 12.4 % | 14.20 [ 2.01, 26.39 ] |
| **Total (95% CI)** | **224** | | **156** | | | **100.0 %** | **5.35 [ 0.71, 10.00 ]** |

Heterogeneity: $Tau^2 = 6.38$; $Chi^2 = 5.17$, df = 4 (P = 0.27); $I^2 = 23\%$

Test for overall effect: Z = 2.26 (P = 0.024)


### Analysis 1.2. Comparison 1 Hawthorn extract versus placebo, Outcome 2 Exercise tolerance (Watt min).

Review: Hawthorn extract for treating chronic heart failure

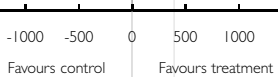
Comparison: 1 Hawthorn extract versus placebo

Outcome: 2 Exercise tolerance (Watt min)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Hanak 1983 | 29 | 100.1 (180.2) | 29 | -1.5 (247.7) | | 65.2 % | 101.60 [ -9.88, 213.08 ] |
| Zapfe 2001 | 20 | 66.2 (202.8) | 20 | -96.2 (283) | | 34.8 % | 162.40 [ 9.81, 314.99 ] |
| **Total (95% CI)** | **49** | | **49** | | | **100.0 %** | **122.76 [ 32.74, 212.78 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.67 (P = 0.0075)



### Analysis 1.3. Comparison 1 Hawthorn extract versus placebo, Outcome 3 Pressure-heart rate product.

Review: Hawthorn extract for treating chronic heart failure

Comparison: 1 Hawthorn extract versus placebo

Outcome: 3 Pressure-heart rate product

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Leuchtgens 1993 | 15 | -9.9 (14) | 15 | -1.5 (8.9) | | 22.7 % | -8.40 [ -16.80, 0.00 ] |
| O'Connolly 1987 | 31 | -29.2 (27.5) | 31 | 7.1 (30.8) | | 18.1 % | -36.30 [ -50.84, -21.76 ] |
| O'Conolly 1986 | 34 | -22.4 (22.7) | 34 | 8.2 (20.5) | | 21.3 % | -30.60 [ -40.88, -20.32 ] |
| Weikl 1996 | 63 | -5.6 (23.5) | 66 | 4.2 (26.8) | | 22.5 % | -9.80 [ -18.49, -1.11 ] |
| Zapfe 2001 | 20 | -14.4 (29.3) | 20 | -1.3 (29.1) | | 15.5 % | -13.10 [ -31.20, 5.00 ] |
| **Total (95% CI)** | **163** | | **166** | | | **100.0 %** | **-19.22 [ -30.46, -7.98 ]** |

Heterogeneity: $Tau^2$ = 126.79; $Chi^2$ = 20.34, df = 4 (P = 0.00043); $I^2$ =80%

Test for overall effect: Z = 3.35 (P = 0.00080)

### Analysis 1.4. Comparison 1 Hawthorn extract versus placebo, Outcome 4 Symptom scores according to v Zerssen.

Review: Hawthorn extract for treating chronic heart failure

Comparison: 1 Hawthorn extract versus placebo

Outcome: 4 Symptom scores according to v Zerssen

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Leuchtgens 1993 | 15 | -12 (8.1) | 15 | -4.7 (9.7) | | 25.2 % | -7.30 [ -13.70, -0.90 ] |
| Tauchert 2002 (HD) | 69 | -11.3 (13.7) | 35 | -6.3 (12.5) | | 37.3 % | -5.00 [ -10.25, 0.25 ] |
| Tauchert 2002 (LD) | 70 | -11 (13.7) | 35 | -6.3 (12.5) | | 37.5 % | -4.70 [ -9.94, 0.54 ] |
| **Total (95% CI)** | **154** | | **85** | | | **100.0 %** | **-5.47 [ -8.68, -2.26 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.43$, df = 2 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 3.34 (P = 0.00084)


### Analysis 1.5. Comparison 1 Hawthorn extract versus placebo, Outcome 5 6-min walk test.

Review: Hawthorn extract for treating chronic heart failure

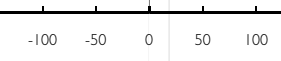
Comparison: 1 Hawthorn extract versus placebo

Outcome: 5 6-min walk test

| Study or subgroup | Control N | Mean(SD) | Treatment N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Aaronson 2004 | 54 | 6 (57.52) | 57 | 14 (83.2) | | 100.0 % | -8.00 [ -34.49, 18.49 ] |
| **Total (95% CI)** | **54** | | **57** | | | **100.0 %** | **-8.00 [ -34.49, 18.49 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.59 (P = 0.55)



### Analysis 1.6. Comparison 1 Hawthorn extract versus placebo, Outcome 6 LVEF%.

Review: Hawthorn extract for treating chronic heart failure

Comparison: 1 Hawthorn extract versus placebo

Outcome: 6 LVEF%

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Eichstädt 2001 | 20 | 1.5 (1.1) | 20 | -0.2 (1.5) | | 100.0 % | 1.70 [ 0.88, 2.52 ] |
| **Total (95% CI)** | **20** | | **20** | | | **100.0 %** | **1.70 [ 0.88, 2.52 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 4.09 (P = 0.000044)


### Analysis 2.1. Comparison 2 Sensitivity test, Outcome 1 Maximal workload (Watt) - with additional medication.

Review: Hawthorn extract for treating chronic heart failure

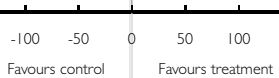
Comparison: 2 Sensitivity test

Outcome: 1 Maximal workload (Watt) - with additional medication

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hawthorn administered in addition to other medication | | | | | | | |
| Bödigheimer 1994 | 36 | 15.7 (35.8) | 37 | 8.8 (32) | | 7.5 % | 6.90 [ -8.69, 22.49 ] |
| Tauchert 2002 (HD) | 69 | 9.8 (15.5) | 35 | 4.9 (15.6) | | 45.7 % | 4.90 [ -1.43, 11.23 ] |
| Tauchert 2002 (LD) | 70 | 5.2 (15.1) | 35 | 4.9 (15.6) | | 46.7 % | 0.30 [ -5.96, 6.56 ] |
| **Total (95% CI)** | **175** | | **107** | | | **100.0 %** | **2.90 [ -1.38, 7.18 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.30$, df = 2 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 1.33 (P = 0.18)

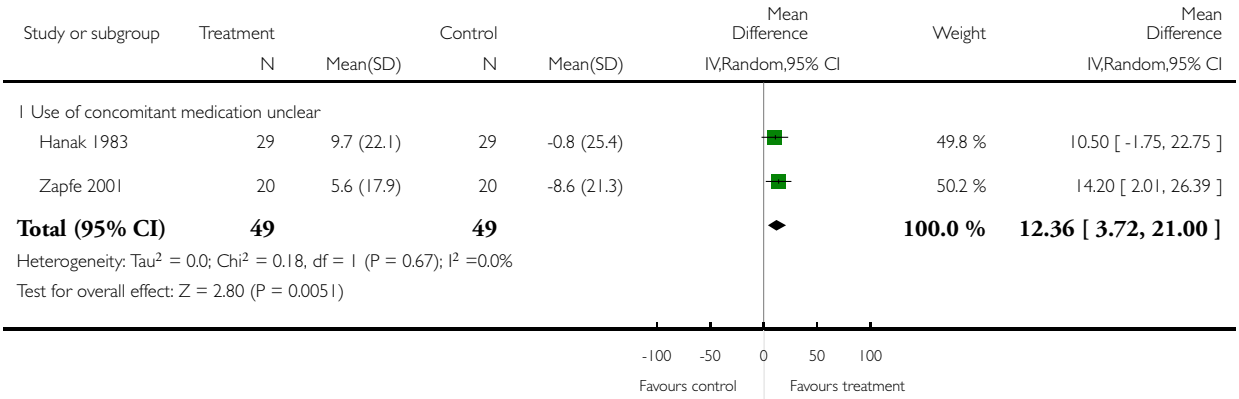


**Analysis 2.2. Comparison 2 Sensitivity test, Outcome 2 Maximal workload (Watt) - use of additional medication unclear.**

Review: Hawthorn extract for treating chronic heart failure

Comparison: 2 Sensitivity test

Outcome: 2 Maximal workload (Watt) - use of additional medication unclear




## ADDITIONAL TABLES

**Table 1. Methodological quality assessment of included studies**

| Study ID | Randomisation | Allocation | Drop-outs handling |
|---|---|---|---|
| Aaronson 2004 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | C - No reporting of exclusion |
| Alexander 1995 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | B - Exclusions were adequately reported and less than 10% |
| Bödigheimer 1994 | A - Adequate sequence generation is reported | B - Unclear | B - Exclusions were adequately reported and less than 10% |
| Eichstädt 2001 | A - Adequate sequence generation is reported | B - Unclear | A - Intend to treat analysis used and few exclusions with adequate reporting of these exclusions |
| Förster 1994 | A - Adequate sequence generation is reported | A - Adequate | B - Exclusions were adequately reported and less than 10% |

**Table 1. Methodological quality assessment of included studies** (*Continued*)

| | | | |
|---|---|---|---|
| Hanak 1983 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | B - Exclusions were adequately reported and less than 10% |
| Iwamoto 1981 | A - Adequate sequence generation is reported | A - Adequate | B - Exclusions were adequately reported and less than 10% |
| Leuchtgens 1993 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | C - No reporting of exclusion |
| O'Connolly 1987 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | B - Exclusions were adequately reported and less than 10% |
| O'Conolly 1986 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | B - Exclusions were adequately reported and less than 10% |
| Schmidt 1994 | A - Adequate sequence generation is reported | A - Adequate | C - No reporting of exclusion |
| Tauchert 2002 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | A - Intension to treat analysis used and few exclusions with adequate reporting of these exclusions |
| Weikl 1996 | B - Mentioned randomisation, but did not specify one of the adequate reported methods | B - Unclear | A - Intension to treat analysis used and few exclusions with adequate reporting of these exclusions |
| Zapfe 2001 | A - Adequate sequence generation is reported | B - Unclear | A - Intension to treat analysis used and few exclusions with adequate reporting of these exclusions |

**Table 2. Adverse events observed in hawthorn extract group**

| Study ID | Extracts and doses | Adverse events |
|---|---|---|
| Aaronson 2004 | WS1442, 450 mg | Not reported |
| Alexander 1995 | WS1442, 900 mg | Nervousness (1); heart pain (2); sleeplessness (2); hand tremor (1); cardiac complaints (1) |
| Bödigheimer 1994 | LI132, 300 mg | Dyspnoea (1); restlessness (1); stomach complaint (1); tachycardiac (1) ; dizziness (1) |
| Eichstädt 2001 | WS1442, 480 mg | None |

**Table 2. Adverse events observed in hawthorn extract group** (*Continued*)

| | | |
|---|---|---|
| Förster 1994 | LI132, 900 mg | None |
| Hanak 1983 | WS1442, 180 mg | Not reported |
| Iwamoto 1981 | WS1442, 180 mg | Nausea (1) |
| Leuchtgens 1993 | WS1442, 160 mg | None |
| O'Connolly 1987 | WS1442, 180 mg | Dizziness (3) |
| O'Conolly 1986 | WS1442, 180 mg | None |
| Schmidt 1994 | LI132, 600 mg | Nausea (1); cardiac complaints (1) |
| Tauchert 2002 | WS1442, HD 1800 mg, LD 900 mg | Dizziness/vertigo (4); bronchitis (4); back pain (5); flu-like syndrome (4); headache (2); arthritis (1); flatulence (1); gastroenteritis (2) |
| Weikl 1996 | WS1442, 160 mg | Migraine (1); nausea (1); flatulence (1); palpitations (1) |
| Zapfe 2001 | WS1442, 240 mg | None |

## WHAT'S NEW

Last assessed as up-to-date: 18 September 2007.

| Date | Event | Description |
|---|---|---|
| 8 September 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 1, 2008

| Date | Event | Description |
|---|---|---|
| 19 September 2007 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

Max H Pittler, Edzard Ernst: Conception and design, analysis

Max H Pittler, Ruoling Guo, Edzard Ernst: interpretation of data, drafting of manuscript and revising for important intellectual content, final approval of the manuscript

Edzard Ernst is guarantor of the review

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT


### Internal sources

- Complementary Medicine, Peninsula Medical School, Exeter, UK.

### External sources

- Videns- og forsknings- center for alternativ behandling, Denmark.


## INDEX TERMS

### Medical Subject Headings (MeSH)

*Crataegus; *Phytotherapy; Chronic Disease; Heart Failure [*drug therapy]; Randomized Controlled Trials as Topic

### MeSH check words

Humans